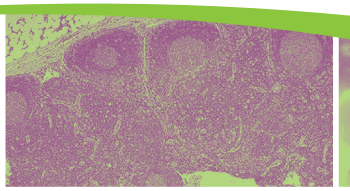
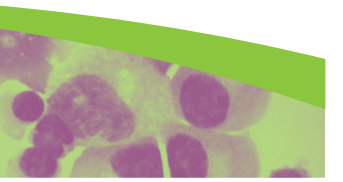
FINAL PROGRAM AND PRESENTATIONS

Imedex®

Lymphoma & Myeloma 2011

An International Congress on Hematologic Malignancies





A comprehensive forum presenting the most recent developments in lymphocytic and plasma cell neoplasms

October 20-22, 2011 I New York, New York
The Waldorf=Astoria



Congress Chairs

Chair
Morton Coleman, MD
Center for Lymphoma and Myeloma
Weill Cornell Medical College
NewYork Presbyterian Hospital/
Weill Cornell Medical Center
New York, New York

Co-Chair, Lymphoma Session
John P. Leonard, MD
Center for Lymphoma and Myeloma
Weill Cornell Medical College
NewYork Presbyterian Hospital/
Weill Cornell Medical Center
New York, New York

Co-Chair, Myeloma Session
Ruben Niesvizky, MD
Center for Lymphoma and Myeloma
Weill Cornell Medical College
NewYork Presbyterian Hospital/
Weill Cornell Medical Center
New York, New York

Co-Chair, Leukemia Session
Richard R. Furman, MD
Center for Lymphoma and Myeloma
Weill Cornell Medical College
NewYork Presbyterian Hospital/
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Lymphoma & Myeloma 2011

An International Congress on Hematologic Malignancies

Schedule of Events

Registration and all Congress activities are located in The Waldorf=Astoria hotel.

Event	Location
Registration	East Foyer, Grand Ballroom, 3rd Floor
General Session	Grand Ballroom, 3rd Floor
Exhibition	Rooms Jade and Astor, 3rd Floor
Luncheon Symposia	Starlight Roof, 18th Floor
Abstracts	Basildon Room (Thursday only)

Thursday, October 20, 2011

7:00 am - 4:50 pm	Registration	East Foyer, Grand Ballroom
7:00 am	Breakfast	Rooms Jade and Astor
8:00 am	General Session	Grand Ballroom
9:25 am	Break	Rooms Jade and Astor
9:45 am	General Session	Grand Ballroom
11:20 am	Luncheon Symposium	Starlight Roof, 18th floor
	Supported by: Celgene Corporation and Genentech BioOncology	
1:20 pm	General Session	Grand Ballroom
3:15 pm	Break	Rooms Jade and Astor
2:40 pm	General Session	Grand Ballroom
4:50 pm	Adjourn	
5:00 pm	Abstract Reception	Vanderbilt Room
	Supported by: Imedex, LLC	
7:00 pm	Adjourn	

Friday, October 21, 2011

7:30 am - 4:55 pm	Registration	East Foyer, Grand Ballroom
7:00 am	Breakfast	Rooms Jade and Astor
8:00 am	General Session	Grand Ballroom
9:00 am	Break	Rooms Jade and Astor
9:30 am	General Session	Grand Ballroom
11:10 am	Luncheon Symposium	Starlight Roof, 18th floor
	Supported by: Celgene Corporation	
2:00 pm	General Session	Grand Ballroom
3:00 pm	Break	Rooms Jade and Astor
3:20 pm	General Session	Grand Ballroom
4:45 pm	Adjourn	

Saturday, October 22, 2011

7:30 am - 4:50 pm	Registration	East Foyer, Grand Ballroom
7:00 am	Breakfast	Rooms Jade and Astor
8:00 am	General Session	Grand Ballroom
10:05 am	Break	Rooms Jade and Astor
10:25 am	General Session	Grand Ballroom
11:40 am	Luncheon	Starlight Roof, 18th floor
1:40 pm	General Session	Grand Ballroom
4:55 pm	Adjourn	



Lymphoma & Myeloma 2011

An International Congress on Hematologic Malignancies

General Information

Continuing Medical Education

Imedex®, LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Imedex, LLC designates this live educational activity for a maximum 18.5 of *AMA PRA Category 1 Credits™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Who Should Attend:

This educational activity is specifically designed for hematologists, oncologists, and other physicians, clinicians, physicians-in-training, and healthcare professionals involved and/or interested in the therapeutic management of patients with lymphoproliferative and other plasma cell disorders.

Objectives

Upon completion of this activity, participants should be able to:

① Have increased awareness/knowledge regarding:

- Biological pathways in hematological malignances and their therapeutic implications
- The biology of bone disease in myeloma and the evolving role of bisphosphonates and other anti-RANK agents in patient care
- The implications of recent clinical investigations in improving standard therapy for lymphoma and other hematological malignancies
- Novel therapies on the horizon, including HDAC inhibitors, new generation IMiDs, and proteasome inhibitors, and how to best use them in lymphoma and myeloma

② Have increased confidence in their ability to:

- Address challenging issues surrounding the use of transplantation including determining which patients it would benefit, optimal timing, and whether it is necessary as frontline therapy in myeloma
- Adequately evaluate clinical situations in which maintenance therapy should be used in myeloma and lymphoma
- Create optimal therapeutic plans for younger and elderly patients with CLL
- Evaluate the potential of new treatment strategies for relapsed aggressive lymphoma for recent clinical investigations for both transplant-eligible and ineligible patients

③ Increased their planned (compared with current) frequency of use of:

- Enrollment in clinical trials of promising novel agents for hematologic malignancies

Registration Fee Inclusions

Registration fees include admittance to all scientific sessions, conference materials, processing of certificates of attendance or continuing medical education, and all event functions as specified in the agenda.

Congress Location

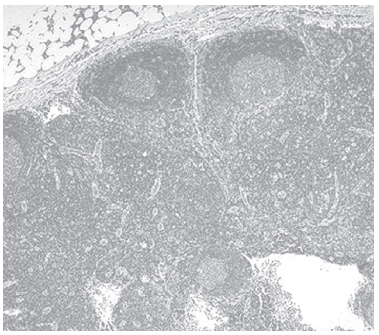
The Waldorf=Astoria
301 Park Avenue
New York, New York 10022, USA
Tel.: +1 (800) 925 3673
Fax: +1 (212) 872 7272
www.waldorf.com

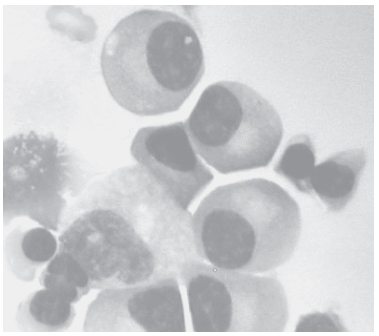
The Registration and Information Desk will be staffed:

Thursday, October 20, 2011:
7:00 am – 4:50 pm

Friday, October 21, 2011:
7:30 am – 4:55 pm

Saturday, October 22, 2011:
7:30 am – 4:50 pm





Faculty

Edwin Alyea, MD
Harvard Medical School
Dana-Farber Cancer Institute
Boston, Massachusetts

Kenneth C. Anderson, MD
Harvard Medical School
Dana-Farber Cancer Institute
Boston, Massachusetts

Stephen M. Ansell, MD, PhD
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Rochester, Minnesota

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The Sass Foundation
New York, New York

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Little Rock, Arkansas

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Cancer Research
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Washington, District of Columbia

Bertrand Coiffier, MD
Hospices Civils de Lyon
Lyon, France

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Sundar Jagannath, MD
St. Vincent's Comprehensive
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Peter Johnson, MD
Cancer Research UK Center
South Hampton, United Kingdom

Brad Kahl, MD
University of Wisconsin
Carbone Comprehensive
Cancer Center
Madison, Wisconsin

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Mayo Clinic
Rochester, Minnesota

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MD Anderson Cancer Center
Houston, Texas

Thomas J. Kipps, MD, PhD
University of California, San Diego
Moores Cancer Center
LaJolla, California

Suzanne Lentzsch, MD, PhD
University of Pittsburgh
School of Medicine and
Cancer Institute
Pittsburgh, Pennsylvania

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Kanti Rai, MD
North Shore Long Island Jewish
Medical Center
New Hyde Park, New York

Noopur S. Raje, MD
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Paul G. Richardson, MD
Harvard Medical School
Dana-Farber Cancer Institute
Boston, Massachusetts

Lisa M. Rimsza, MD
University of Arizona
Tucson, Arizona

Ritz Shaknovich, MD
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New York, New York

David H. Vesole, MD, PhD, FACS
Hackensack University
Medical Center
Hackensack, New Jersey



Lymphoma & Myeloma 2011

An International Congress on Hematologic Malignancies

Support

The following companies have provided an educational grant in support of this Congress:

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SILVER

Cephalon Oncology

Onyx Pharmaceuticals

BRONZE

Abbott

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NOVARTIS ONCOLOGY

Commercial Exhibition

As part of the Congress, companies and organizations may display their products and services. The exhibition is located in the Astor and Jade Rooms. Exhibitions should not be construed as an endorsement of a product or the manufacturer's claims by Imedex.

The following companies are exhibitors at this Congress:

ALLOS THERAPEUTICS

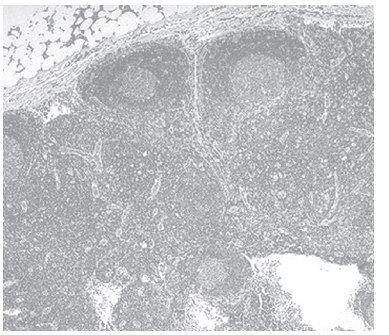
Allos Therapeutics is a biopharmaceutical company committed to the development and commercialization of innovative anti-cancer therapeutics. Allos is currently focused on the development and commercialization of a folate analogue metabolic inhibitor that has been approved in the United States for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). Allos is currently pursuing regulatory approval to market this therapeutic in the European Union for relapsed or refractory PTCL and exploring its potential in other indications.

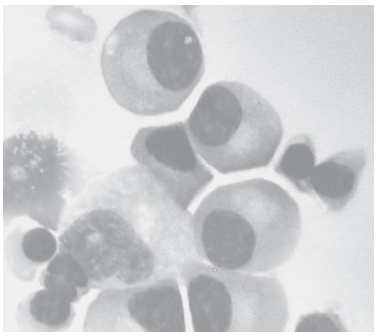
Binding Site

The Binding Site produces serum free Kappa and Lambda light chain assays as an aid in the diagnosis and monitoring of multiple myeloma, AL amylodosis and Light Chain disease. The assay is more sensitive than current electrophoretic methods and is fully quantitative and automated on routine clinical analyzers. The assay is recommended to be used in the initial diagnostic work up for Myeloma by the both the NCCN and the International Myeloma Working Group Guidelines. Many patients who were previously classified as non- secretory myeloma can also now be diagnosed and monitored with this assay.

Celgene

Celgene Corporation (Nasdaq:CELG) is a global biopharmaceutical company that is helping healthcare providers turn incurable cancers into chronic, manageable diseases through innovative therapies. This dedication to medical progress goes hand-in-hand with our industry-leading patient support and access programs. Together, these aspects form the core of our commitment to patients worldwide. For more information, visit www.celgene.com.





Commercial Exhibition

Cephalon Oncology

Cephalon Oncology is committed to enhancing the lives of cancer patients through the discovery, development and commercialization of innovative medicines, providing therapeutic solutions enhancing the quality and length of life. Cephalon Oncology has an extensive portfolio of products in hematology, solid tumors and supportive care. www.cephalon.com

Diplomat Specialty Pharmacy

Diplomat Specialty Pharmacy, an independently held healthcare company dedicated to being a customer focused and innovative partner, provides medication management, disease management, and clinical services in a caring, supportive environment. Stop by our booth to see our innovative solutions today.

Genentech
A Member of the Roche Group

We are leaders in the discovery, development, and delivery of innovative cancer therapeutics. At Genentech BioOncology, our goal is to fundamentally transform the way cancer is treated. Our commitment to this goal has enabled us to make significant contributions to the understanding of cancer and to translate this understanding into targeted and biologic-based therapies. We are dedicated to defining the molecular basis of cancer and investigating multiple approaches to treating the disease and improving patients' lives.

GILEAD

Gilead Sciences is a biopharmaceutical company that discovers, develops and commercializes innovative therapeutics in areas of unmet medical need. The company's mission is to advance the care of patients suffering from life-threatening diseases worldwide. Headquartered in Foster City, California, Gilead has operations in North America, Europe and Asia Pacific.

gsk GlaxoSmithKline

GlaxoSmithKline is a leading research-based pharmaceutical company with a powerful combination of skills to discover and deliver innovative medicines. We offer a number of program resources to support effective health management strategies and improve patient care. Please visit our exhibit to learn more about our products and resources.

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

The mission of The Leukemia & Lymphoma Society (LLS) is: Cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families. LLS is the world's largest voluntary health agency dedicated to blood cancer. LLS funds lifesaving blood cancer research around the world and provides free information and support services.

LLS provides educational, emotional, and financial support to patients and families touched by blood cancers. We provide education and resources for healthcare professionals, and advocate for public policies that affect our cancer community.

To connect with your local LLS chapter, please call (800) 955-4572 or email infocenter@lls.org.

LYMPHOMA
RESEARCH • FOUNDATION

The Lymphoma Research Foundation (LRF) is the nation's largest non-profit organization devoted exclusively to funding innovative lymphoma research and providing people with lymphoma and healthcare professionals with up-to-date information about this type of cancer. LRF's mission is to eradicate lymphoma and serve those touched by this disease.

LRF's goal is to change the future for everyone whose life has been affected by a lymphoma diagnosis. LRF is dedicated to funding biomedical research focused on the origins, treatment and identification of a cure for lymphoma; to raising public awareness of the disease; and providing support and services to people with lymphoma, their families and caregivers.



Commercial Exhibition

Medtronic

At Medtronic (www.medtronic.com), we're committed to Innovating for life by pushing the boundaries of medical technology and changing the way the world treats chronic disease. To do that, we're thinking beyond products and beyond the status quo - to continually find more ways to help people live better, longer.

Takeda MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Millennium: The Takeda Oncology Company, a leading biopharmaceutical company based in Cambridge, Massachusetts, markets a novel therapy for patients with blood cancer and has a robust clinical development pipeline. Millennium strives to become a top three global oncology company by 2020. Additional information is available through the Company's website, www.millennium.com.

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

NewYork-Presbyterian Hospital is one of the foremost academic medical centers in the world, with leading specialists in every field of medicine and a staff dedicated to the care of its patients.

NewYork-Presbyterian enjoys a unique affiliation with two of the nation's leading Ivy League medical schools: Columbia University College of Physicians and Surgeons and Weill Cornell Medical College. With its academic partners, the Hospital shares a commitment to pursuing clinical excellence, engaging in groundbreaking biomedical research, offering outstanding medical education, and providing prevention and wellness services to the community.

Onyx Pharmaceuticals

Onyx Pharmaceuticals, Inc. is a global biopharmaceutical company engaged in the development and commercialization of innovative therapies for improving the lives of people with cancer and other serious diseases. The company is focused on developing novel medicines that target key molecular pathways, to transform the treatment of life-threatening diseases. Onyx today has three major areas of focus: an approved tyrosine kinase inhibitor, an emerging proteasome inhibitor franchise, and an earlier stage pipeline. For more information about Onyx, visit the company's website at www.onyx-pharm.com.

SeattleGenetics

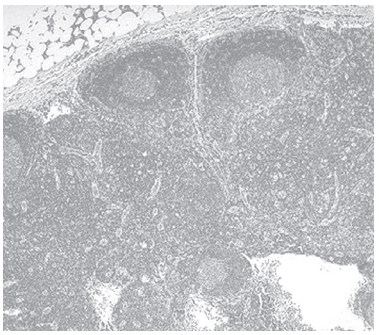
Seattle Genetics is a biotechnology company focused on the development and commercialization of monoclonal antibody-based therapies for the treatment of cancer. The company's first product, brentuximab vedotin, was approved by the FDA on August 19, 2011 for two indications. In addition to brentuximab vedotin, Seattle Genetics has three other clinical-stage antibody-drug conjugate (ADC) programs: SGN-75, ASG-5ME and ASG-22ME. Seattle Genetics has collaborations and co-development agreements for its ADC technology with a number of leading biotechnology and pharmaceutical companies. Find more information at www.seattlegenetics.com.

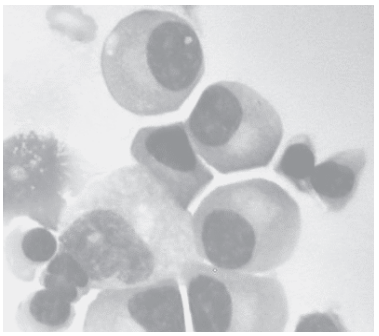
sigma-tau
PHARMACEUTICALS, INC.

Sigma-Tau Pharmaceuticals, Inc. is a rare corporation dedicated to creating novel medicines for the unmet needs of patients with rare diseases. Truly unique in its field, Sigma-Tau places its considerable scientific resources behind the discovery and commercialization of compounds that benefit the few. At Sigma-Tau there is no difference between a disease that affects 300 and 300,000,000.

SPECTRUM
PHARMACEUTICALS

Spectrum Pharmaceuticals is a commercial-stage biotechnology company with a focus in oncology. The Company's strategy is comprised of acquiring and developing a broad and diverse pipeline of late-stage clinical and commercial products; establishing a commercial organization for its approved drugs; continuing to build a team with people who have demonstrated skills, passion, commitment and have a track record of success in its areas of focus; and, leveraging the expertise of partners around the world to assist it in the execution of its strategy.





Scientific Agenda

Thursday, October 20, 2011

8:00 am Welcome and audience survey
Morton Coleman, MD

MYELOMA SESSION

8:05 am Introduction to myeloma session
Ruben Niesvizky, MD

Session I: Translational science impacting the clinic
Moderator: Scott A. Ely, MD, MPH

8:10 am Understanding the genetics and epigenetics of myeloma and their therapeutic potential
Faith E. Davies, MBBBch, MD, MRCP, FRCPath

8:30 am Understanding the cell cycle of myeloma and the therapeutic opportunities
Selina Chen-Kiang, MD

8:50 am Understanding the biologic pathways in myeloma and their therapeutic implications
Constantine S. Mitsiades, MD, PhD

9:10 am Panel discussion and questions

9:25 am Coffee break

Session II: Bone disease in myeloma
Moderator: Roger N. Pearse, MD, PhD

9:45 am Pre-session audience survey

9:55 am The biology of bone disease: How important are "markers"
Noopur S. Raje, MD

10:15 am A role of denosumab and other new agents in myeloma
James E. Berenson, MD

10:35 am Imaging techniques in myeloma: How best to use them
Meletios-Athanasios Dimopoulos, MD

10:55 am Post-session audience survey

11:05 am Panel discussion and questions

11:20 am Break for lunch symposium:
How I Manage Distinct Clinical Scenarios Across Lymphoma: A Case-Based, Rapid Fire Panel Discussion
Supported by Celgene Corporation and Genentech BioOncology

Session III: Special considerations in myeloma
Moderator: Morton Coleman, MD

1:20 pm Pre-session audience survey

1:30 pm "High-risk" myeloma: Definition and treatment
Rafael Fonseca, MD

1:50 pm Plasma cell leukemia:
Should it be treated differently?
Joan Bladé, MD

2:10 pm If and when should an allogeneic transplant be done?
Sergio A. Giralt, MD

2:30 pm Post-session audience survey

2:40 pm Panel discussion and questions

2:55 pm Coffee break

Session IV: Special lectures
Moderator: Morton Coleman, MD

3:15 pm Presentation of the best myeloma abstract
Myeloma-initiating cells are enriched in CD138+/CD38high cells and can be eliminated through an anti-CD47 antibody therapy
Dongkyoon Kim, PhD

3:25 pm The SASS Foundation for Medical Research Award Ceremony
Francis P. Arena, MD - President & Director of Research for the SASS Foundation
Presentation: Joseph Michaeli Award for Contributions to Myeloma Research
Recipient: *Brian G. M. Durie, MD*

3:30 pm "Consensus" on the standards of treatment in the 21st century: How should we treat transplant-eligible, transplant-ineligible, and relapsed patients
Brian G. M. Durie, MD



Scientific Agenda

Session V: Myeloma treatment I
Facilitator: Sergio A. Giralt, MD

3:55 pm Pre-debate audience survey
Debate: Is maintenance therapy necessary?
Yes: *Antonio Palambo, MD*
No: *David Vesole, MD*
Post-debate audience survey

4:35 pm Panel discussion and questions

4:50 pm Adjourn for abstract reception

Friday, October 21, 2011

8:00 am Welcome and audience survey
Morton Coleman, MD

Session VI: Myeloma treatment II
Facilitator: Ruben Niesvizky, MD

8:05 am Pre-debate audience survey
Debate: Are transplants necessary as frontline therapy?
Yes: *Bart Barlogie, MD, PhD*
No: *Sundar Jagannath, MD*
Post-debate audience survey

8:45 am Panel discussion and questions

9:00 am Coffee break

Session VII: New treatments and how best to use them in lymphoma and myeloma
Moderator: Tomer Mark, MD

9:30 am Carfilzomib
Ruben Niesvizky, MD

9:50 am Pomalidomide
Tomer Mark, MD

10:10 am Elotuzumab
Paul G. Richardson, MD

10:30 am HDAC inhibitors
Kenneth C. Anderson MD

10:50 am Bendamustine
Suzanne Lentzsch, MD, PhD

11:10 am Break for lunch symposium:
Prolonging Survival in Multiple Myeloma: Balancing the Efficacy of Maintenance Therapy with Long-Term Safety A Case-Based, Roundtable Discussion
Supported by Celgene Corporation

CLL SESSION

1:10 pm Introduction to CLL session
Richard Furman, MD

Session VIII: Treatment approaches I
Moderator: Richard Furman, MD

1:15 pm Pre-session audience survey

1:25 pm Introduction to The Prince Family Lecture

1:30 pm The Prince Family lecture: Is a cure on the horizon?
Michael J. Keating, MD

1:55 pm Molecular pathogenesis and therapy of CLL
Thomas J. Kipps, MD, PhD

2:15 pm Transplantation in CLL: How major a role?
Edwin Alyea, MD

2:35 pm Post-session audience survey

2:45 pm Panel discussion and questions

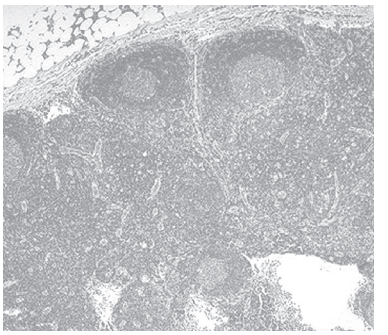
3:00 pm Coffee break

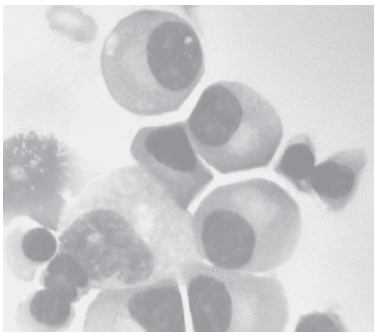
Session IX: Treatment approaches II
Moderator: Kanti Rai, MD

3:20 pm Pre-session audience survey

3:30 pm Treatment of the elderly:
How gentle should it be?
Neil E. Kay, MD

3:50 pm Non-chemotherapeutic approaches: Can we avoid alkylators and purine analogues?
Susan O'Brien, MD





Scientific Agenda

4:10 pm Novel approaches to CLL: Exciting new agents
Richard Furman, MD

4:30 pm Post-session audience survey

4:40 pm Panel discussion and questions

4:55 pm Adjourn

Saturday, October 22, 2011

8:00 am Welcome and audience survey
Morton Coleman, MD

LYMPHOMA SESSION

8:05 am Introduction to lymphoma session
John P. Leonard, MD

Session X: Lymphoma biology
Moderator: Rita Shaknovich, MD

8:10 am New molecular targets in large cell lymphoma
Lisa M. Rimsza, MD

8:25 am BCL-6: A regulator of lymphomagenesis
Ari Melnick, MD

8:40 am Panel discussion and questions

Session XI: Hodgkin's disease
Moderator: Rebecca Elstrom, MD

8:50 am Limited treatment for limited disease?
Volker Diehl, MD

9:10 am Emerging new agents in Hodgkin's and lymphoma
Jonathan Friedberg, MD

9:30 am Is there a role for consolidation radiation in limited and advanced Hodgkin's disease in the era of PET scan?
Peter Johnson, MD

9:50 am Panel discussion and questions

10:05 am Coffee break

Session XII: Special lectures in lymphoma
Moderator: Morton Coleman, MD

10:25 am Presentation of best lymphoma abstract
Synchronous non-Hodgkin lymphoma and pregnancy: A single institution long-term experience
Thomas Haberman, MD

10:35 am The SASS Foundation for Medical Research Award Ceremony
Francis P. Arena, MD - President & Director of Research for the SASS Foundation

Presentation: John Ultmann Award for Contributions to Lymphoma Research
Presenters: *Morton Coleman, MD and John P. Leonard, MD*
Recipient: *Bertrand Coiffier, MD*

10:40 am Is R-CHOP-21 still the standard for all patients or is there a role for CHOP-14, ABVCP, EPOCH, etc?
Bertrand Coiffier, MD

11:00 am The Bruce Waterfall Memorial Lecture in Waldenstrom's Macroglobulinemia
Presenter: Morton Coleman, MD
Moderator: Peter Martin, MD

Treatment approaches for untreated and relapsed disease
Stephen M. Ansell, MD, PhD

11:25 am Panel discussion and questions

11:40 am Break for lunch

Session XIII: Follicular lymphoma
Moderator: John Leonard, MD

1:40 pm Pre-debate audience survey
Debate: Should everyone receive maintenance rituximab?
Yes: *David Maloney, MD, PhD*
No: *Bruce E. Cheson, MD*
Post-debate audience survey

Session XIII continued on next page.



Scientific Agenda

2:20 pm Pre-debate audience survey
Debate: Is "watch and wait" passé in asymptomatic follicular lymphoma?
Yes: *John P. Leonard, MD*
No: *Myron Czuczman, MD*
Post-debate audience survey

3:00 pm Panel discussion and questions

Session XIV: Aggressive lymphoma
Moderator: Peter Martin, MD

3:15 pm Pre-session audience survey

3:25 pm Relapsed aggressive lymphoma: what approaches are applicable for transplant eligible and ineligible patients? What has the CORAL study taught us?
Craig Moskowitz, MD

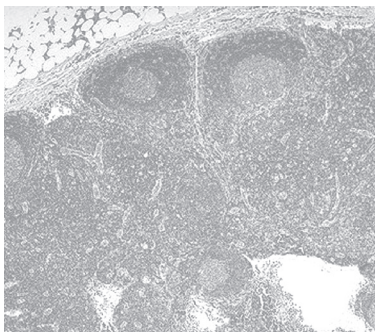
3:45 pm Mantle cell lymphoma: How best to approach and treatment: Is there a role for maintenance?
Brad Kahl, MD

4:05 pm Double hit aggressive lymphoma
Kieron Dunleavy, MD

4:25 pm Post-session audience survey

4:35 pm Panel discussion and questions

4:50 pm Adjourn



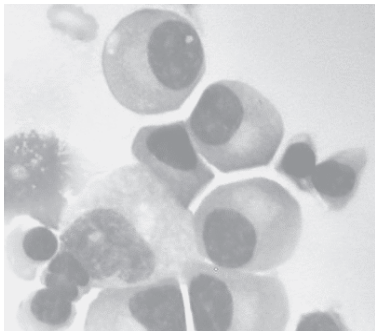


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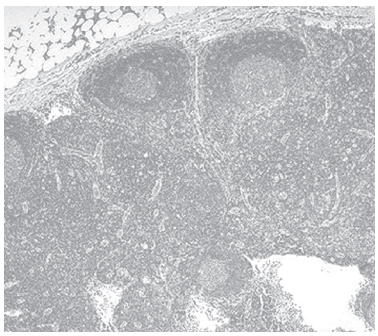
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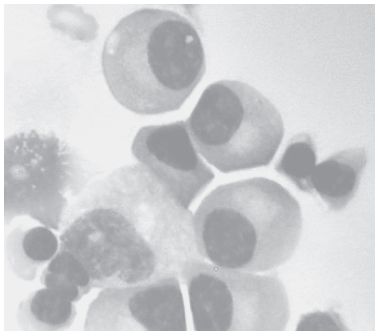
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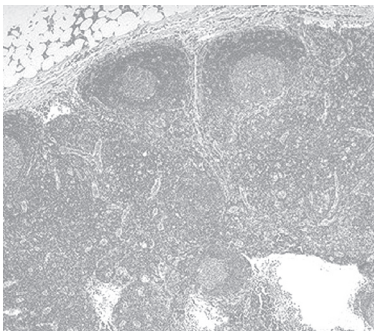
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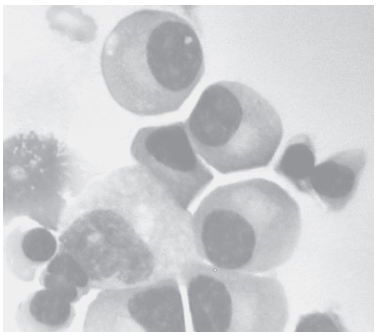
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Lymphoma & Myeloma 2011
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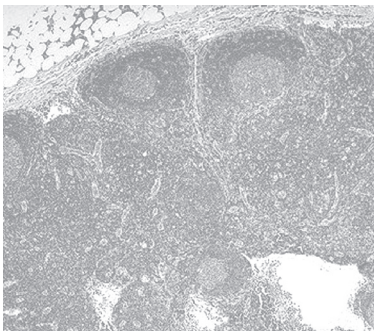


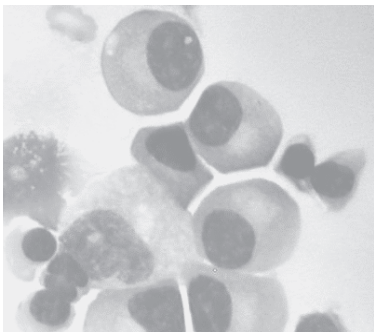


Understanding the genetics and epigenetics of myeloma and their therapeutic potential

Faith E. Davies, MBBBch, MD, MRCP, FRCPath

Lymphoma & Myeloma 2011
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Understanding the cell cycle of myeloma and the therapeutic opportunities

Selina Chen-Kiang, MD

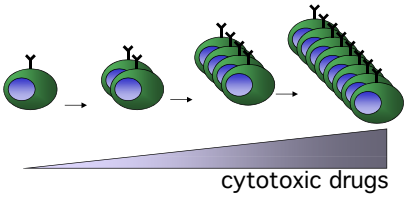
Targeting CDK4/CDK6 in Myeloma and Mantle Cell Lymphoma

Mechanism and Therapy

Selina Chen-Kiang

Weill Cornell Medical College

Targeting the Cell Cycle in Cancer

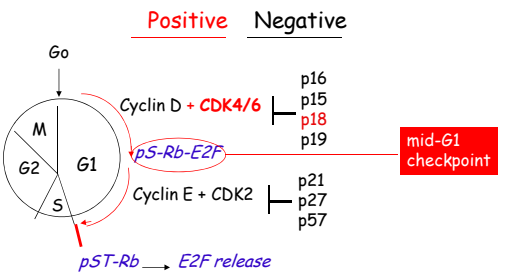


Goals

To inhibit tumor cell proliferation
To sensitize them for cytotoxic killing
To advance rational design of combination therapy

Success in targeting the cell cycle in cancer with broad-Spectrum CDK inhibitors has been modest due to a lack of specificity and high toxicity.

The Cell Cycle



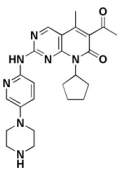
CDK: Cyclin-Dependent Kinase
$p18^{INK4c}$ (*CDKN2C*)

Why Targeting CDK4 and CDK6 ?

- Cell cycle control by CDK4/CDK6 is essential for homeostasis in B cell immunity
  Tourigney et al, 2002, Immunity; Bretz et al, 2011, Blood;
- Dysregulation of CDK4 and CDK6 is one of the most common genomic abnormalities in human cancer
  - *Myeloma, Lymphoma, Leukemia*
    Ely et al, 2005, Cancer Res; Baughn et al, 2006, Cancer Res
  - *Breast Cancer*
    Landis et al, 2006, Cancer Cell; Yu et al, 2006, Cancer Cell, Pei et al, 2009 Cancer cell
  - *Metastatic lung adenocarcinoma*
    Weir et al, 2007, Nature
  - *Glioblastoma*
    Wiedemeyer et al, 2008, Cancer Cell

Targeting CDK4/6 with PD 0332991

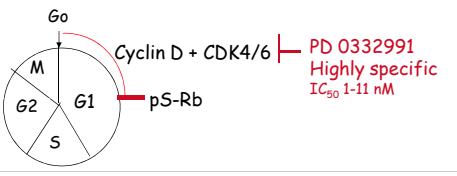
- Only known effective CDK4/CDK6-specific inhibitor (IC_{50} 11 nM)
- Induces early G1 arrest
- Reversible
- Orally bioavailable pyridopyrimidine
- Low in toxicity



- Selectively and potently inhibits CDK4/6 phosphorylation of Rb in primary human myeloma cells (IC_{50} 60 nM)
- Inhibits tumor growth in the NOD-SCID human myeloma xenograft models and the immune-competent mouse 5T models

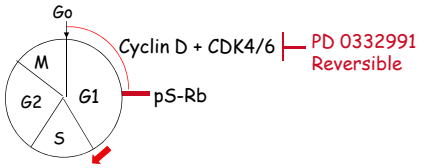
Fry et al., 2004, Mol Cancer Ther
Baughn et al., 2006, Cancer Research
Menu et al., 2008, Cancer Research

Hypothesis



Prolonged inhibition of CDK4/6
↓
Halts the gene expression program in early G1
depletes expression of genes in other cell cycle phases
↓
Sensitizes tumor cells to cytotoxic killing

Hypothesis



Release of early G1 block

↓

Cell cycle synchronization
incomplete restoration of scheduled gene expression

↓

Further sensitizes tumor cells to cytotoxic killing

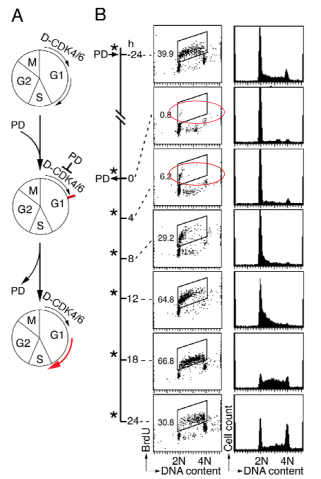
PD inhibition of CDK4/6

↓

- early G1 arrest

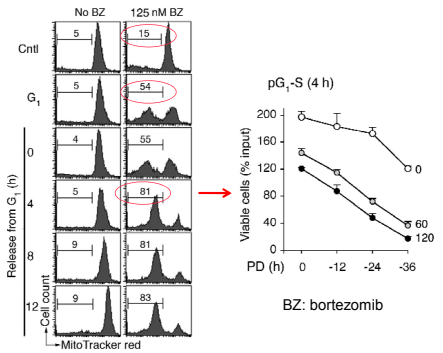
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- synchronous cell cycle progression upon release of the G1 block



Huang and Di Liberto

Prolonged early G1 arrest sensitizes MM cells to cytotoxic killing, greater in S phase synchronization and proportional to time of G1 arrest



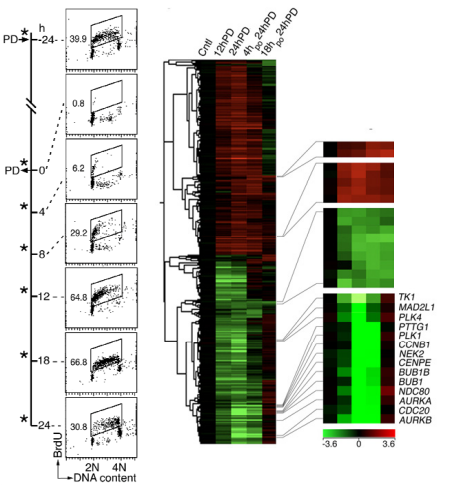
Huang and Di Liberto

Inhibition of CDK4/CDK6

↑ Early G1 genes

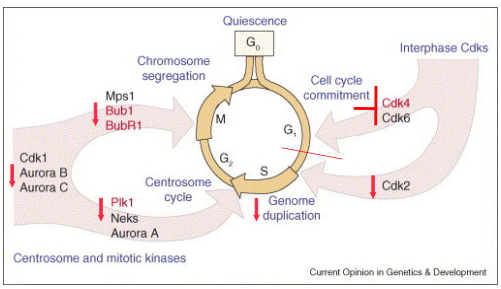
↓

↓ Late G2, S, G2/M genes



Huang
Di Liberto
Bretz

Prolonged inhibition of CDK4/6
Halts the gene expression program in early G1
Depletes expression of genes in late G1, S and G2/M



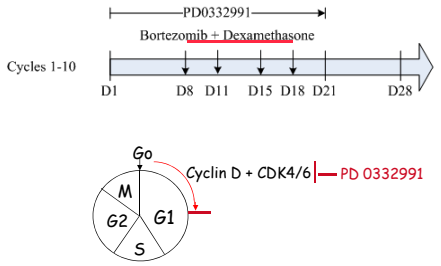
Release of early G1 block
Cell cycle synchronization
Incomplete restoration of scheduled gene expression

Next steps:

- Clinical application
  1. *Targeting CDK4/CDK6 with PD 0332991 in combination with bortezomib and dexamethasone in myeloma (Ruben Niesvizky, Tomer Mark)*
  2. *Targeting CDK4/CDK6 with PD 0332991 in combination with borteomib in mantle cell lymphoma (John Leonard, Peter Martin)*
- Mechanism
  1. *Genome- scale sensitizing shRNA lentivirus lethal suppression screen for genes mediating cell cycle sensitization to cytotoxic killing*
  2. *Discovery of molecular biomarkers by RNA-Seq of serial biopsies of patients participating in the two clinical studies*

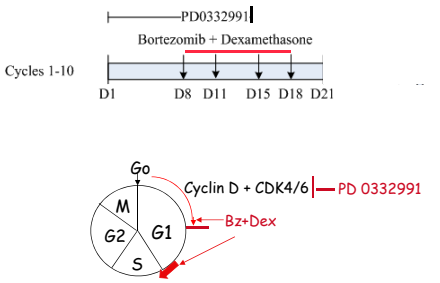
Phase I/II clinical trial of PD 0332991-bortezomib-dexamethasone combination therapy in MM

Schedule A

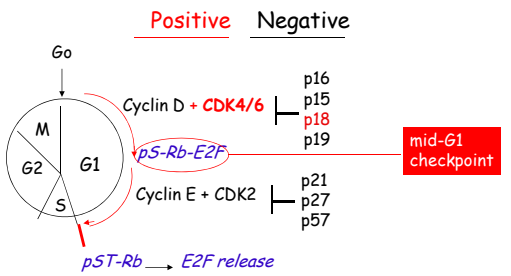


Phase I/II clinical trial of PD 0332991-bortezomib-dexamethasone combination therapy in MM

Schedule B

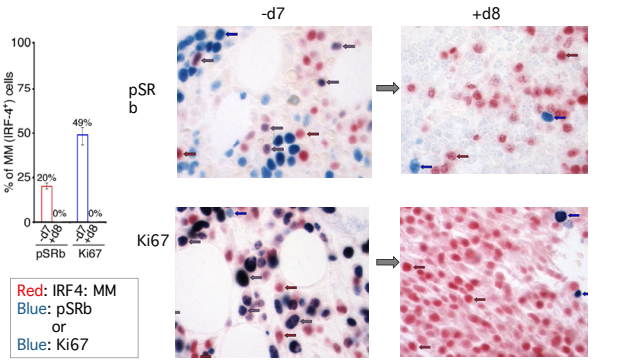


The Cell Cycle



CDK: Cyclin-Dependent Kinase
p18^{INK4c} (*CDKN2C*)

PD 0332991 potently inhibits tumor cell proliferation by preferential inhibition of CDK4 and CDK6 in MM



Ely, DiLiberto, Huang, Niesvizky

Phase I/II PD 0332991 sequential combination therapy clinical trial in relapsed refractory MM

- First clinical study to target CDK4/6 in sequential combination therapy in human cancer
- PD preferentially and completely inhibits CDK4/6 in MM patients (n=16)
- Inhibition of the cell cycle by PD *in vivo* is reversible
- PD is generally well tolerated, with neutropenia as the most common adverse event
- 1 VGPR, 1 PR and 3 stable disease in these heavily pretreated myeloma patients

  Phase II in progress (Ruben Niesvizky, Tomar Mark)

Mantle Cell Lymphoma (MCL)

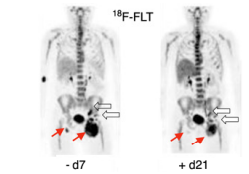
Non-Hodgkin's lymphoma with an overall poor prognosis.

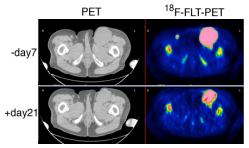
Incurable due to the eventual development of drug resistance

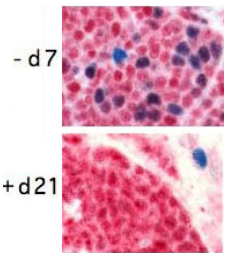
Constitutive cyclin D1 expression due to chromosomal t(11;14) translocation and mutations

Overexpression of CDK4

PD 0332991 inhibits CDK4/CDK6 in MCL cells and induces tumor regression







Red: Pax5: MCL cells
Blue: CDK4/6 phosphorylation of Rb

Leonard, Ely, Goldsmith and Chen-Kiang

Targeting CDK4/CDK6 in MCL

Single agent Phase I study (2007--)

- Inhibition of CDK4/CDK6 by PD 0332991 leads to prolonged G1 arrest and increased tumor-specific cell death in MCL (n=16)
- PD is generally well tolerated with neutropenia, fatigue and diarrhea as the most common adverse events
- 1 CR > 3 years; 1 near CR > 2 years; 1 PR > 2 years; 7 stable disease

Combination therapy 2010-- (John Leonard and Peter Martin)

RNA-sequencing

RNA abundance, variant, indel

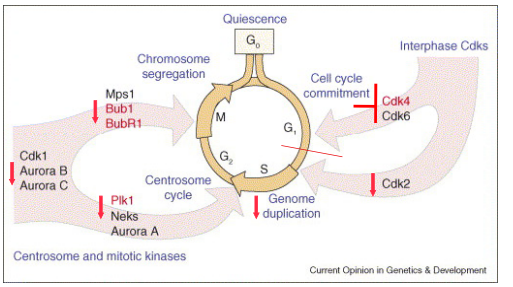
50x50 paired-end RNA sequencing on a HiSeq2000, 76 million reads per sample

Used the Burrow-Wheeler Aligner to align reads to the genome (Building 37)

SAMtools and Genome Analysis Toolkit to call non-reference variants.

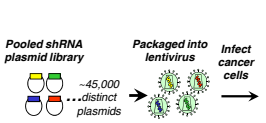
X. Huang, M. DiLibiberto, D. Chiron, C. Mason

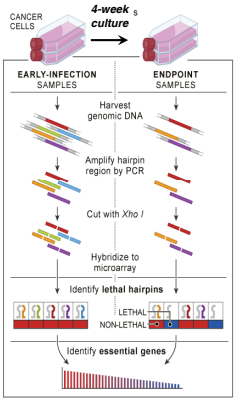
Prolonged inhibition of CDK4/6
Halts the gene expression program in early G1
Depletes expression of genes in late G1, S and G2/M



Release of early G1 block
Cell cycle synchronization

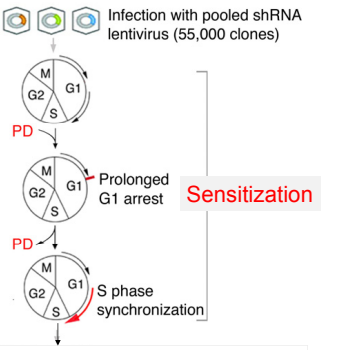
Genome scale pooled shRNA barcode screens





Biao Luo
Tony Cheung
Aravind Subramanian
David Root

Sensitizing Lethal Suppression genome scale pooled shRNA lentivirus screen for genes required for cell cycle sensitization



Complete killing by CFZ (MM) or Ara C (AML)

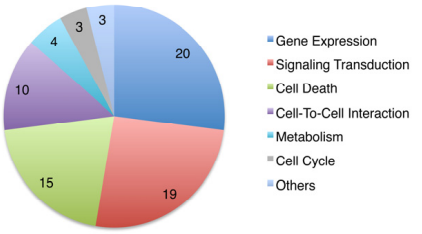
Rescued cells

Identification of genes by deep sequencing of shRNA

X. Huang, M. Diliberto, C. Yang, J, Hannah, A. Schinzel

Ranking Candidate Cell Cycle Sensitizing (CCS) Genes

- Responsiveness to CDK4/CDK6 inhibition in its absence
- High frequency
- Common to the 4 replica of each cell line
  3 myeloma cell lines, 2 AML cell lines
- Common to the cell lines used in the screen



Huang , Di Liberto. D. Chiron, C. Yang, J. Hannah

Validation of CCS genes in MM

- Functional validation in >3 independent shRNA clones
- Mutations identified by WGS in MM (*Chapmen et al, Nature, 2011*) --8/20 top ranking genes
- Therapy specificity (PD+CFZ vs PD+ Ara C)
- Disease specificity (MM, lymphoma, AML)
- Validation in patient's MM cells from phase I/II clinical trial
  Signal Transduction
  Metabolism
  Cell Death
  Ubiquitin-proteasome machinery

Huang , C. Chiron, Di Liberto.

Targeting CDK4/CDK6 in Cancer

- **Both inhibits the cell cycle in tumor cells and sensitizes them to cytotoxic killing**
  metabolic imbalance
- **Mechanism-based combination therapy**
  bortezomib, carfilzomib, lenalidomide, Ara-C
  MM, Mantle Cell lymphoma, AML,
- **Sensitizing genome-scale pooled shRNA screen**
  cell cycle sensitizing genes (CCS)
- **RNA-Sequencing of patient's serial biopsies from clinical trials of PD+bortezomib in MM and MCL**
  validation of reversible CDK4/6 inhibition and CCS

Targeting CDK4/CDK6 in combination therapy



Weill-Cornell

Mantle cell lymphoma	*Phase I single drug study (2007-10 Multi-Center)*
Multiple Myeloma	*Phase I/II combination therapy (2008-Multi-Center)*
Mantle cell lymphoma	*Phase I combination therapy (8/2010--)*
Acute myeloid Leukemia	*Preclinical*
Advanced Solid tumors	*Phase I single agent (2006, completed)*
Breast cancer	*Phase I/II front line combination therapy (2009-*
Metastatic liposarcoma	*Phase I single agent (9/2010--*
Glioblastoma	*Phase I single agent (10/2010--*
Non-small cell lung carcinoma	*Phase I single agent (2/2011--*

Acknowledgements

Weill-Cornell

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Jamie Bretz
David Jayabalan
Linda Baughn
Josefina Garcia

Chris Mason
Scott Ely

Ruben Niesvizky
Tomer Mark
Morten Coleman
John Leonard
Peter Martin

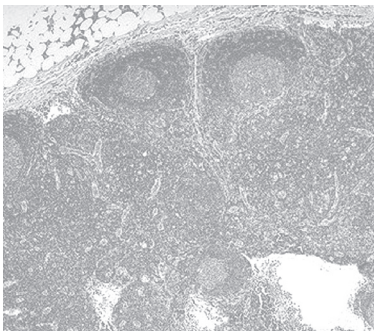
Broad
William Hahn
Anna Schinzel

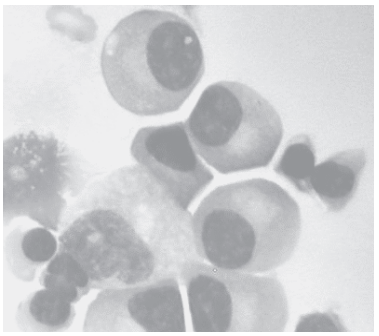
MSKCC
Malcolm Moore

Patients

Starr Cancer Consortium
NIH/NCI
Lymphoma Research Foundation
Leukemia and Lymphoma Society

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Understanding the biologic pathways in myeloma and their therapeutic implications

Constantine S. Mitsiades, MD, PhD

DANA-FARBER CANCER INSTITUTE

Understanding the biologic pathways in myeloma and their therapeutic implications

Constantine S Mitsiades, M.D., Ph.D.
Div. of Molecular and Cellular Oncology, Dept. of Medical Oncology,
Center for Novel Experimental Therapeutics
Dana-Farber Cancer Institute, Harvard Medical School
Boston MA

Lymphoma & Myeloma 2011 Conference

October 19th, 2011

Disclosure Information

Constantine S. Mitsiades, MD, PhD.

I have the following financial relationships to disclose:

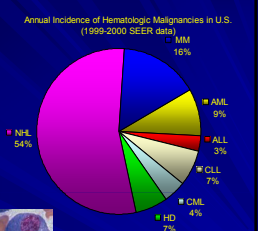
Consultant for:	**Millennium, Novartis, Bristol-Myers Squibb, Merck &Co., Kosan, Pharmion, Centocor**
Speaker's Bureau for:	**n/a**
Grant/Research support:	**OSI Pharm., Amgen, AVEO Pharma, EMD Serono, Sunesis, Gloucester Pharm., Genzyme, J&J**
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Honoraria from:	**Millennium, Novartis, Bristol-Myers Squibb, Merck &Co., Kosan, Pharmion, Centocor, Celgene, Amnis Therapeutics**
Employee of:	**n/a**
Advisory Board:	**Axios Biosciences (pro bono)**

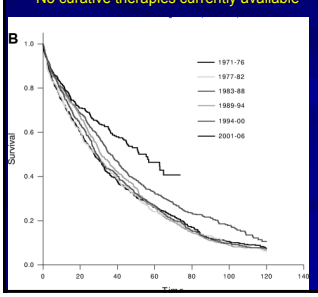
- and -

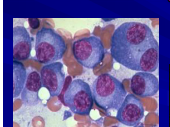
I will not discuss off label use and/or investigational clinical use in my presentation.

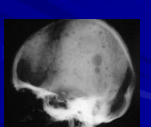
Multiple Myeloma (MM)

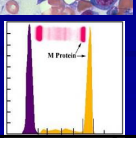
- 2nd most commonly diagnosed hematologic malignancy
- Plasma cell neoplasia producing monoclonal Ig (or fragment of it) secreted in serum and/or urine
- Extensive skeletal involvement
  - osteolytic lesions, spontaneous fractures
  - hypercalcemia
  - Renal impairement
- No curative therapies currently available











Impact of novel therapies on clinical outcome in MM

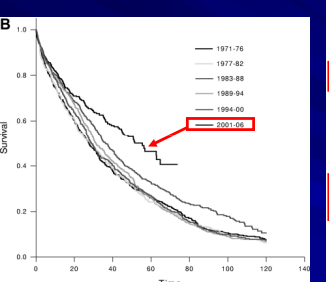


Table 4 Survival according to prognostic factors

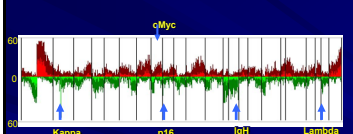
	Median survival (months)		P-value
	Started treatment before novel agents	Started treatment after novel agents	
Male	37.5	40.5	0.062
Female	36	59	0.001
Age < 70	39	74	< 0.001
Age > 70	26	32.5	0.270
Performance status			
0 or 1	43	64	0.006
> 1	25	36	0.007
Hemoglobin			
< 10 g/100 ml	25	34	0.002
> 10 g/100 ml	43	70	0.004
ISS stage			
I	58	Not reached	0.017
II	41	66	0.067
III	19	31.5	0.006
Creatinine			
< 2 mg/100 ml	40.7	51	0.009
≥ 2 mg/100 ml	20.5	31.5	0.03
LDH			
< 300 IU/l	40	51	0.001
≥ 300 IU/l	14	21	0.048
Bone marrow plasma cells			
≤ 40%	47	73	0.012
> 40%	30	37	0.001

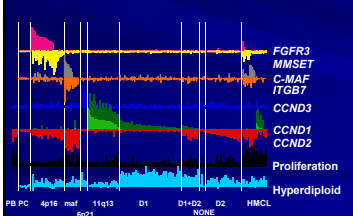
Abbreviations: ISS, international staging system; LDH, lactate dehydrogenase.

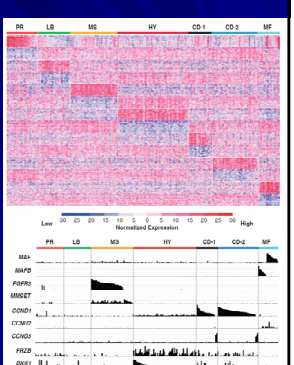
Kumar S. et al Blood. 2008; 111(5): 2516–2520.

Kastritis E. et al Leukemia. 2009 Jun;23(6):1152-7

Complexity and molecular heterogeneity of molecular lesions in tumor cells of MM patients



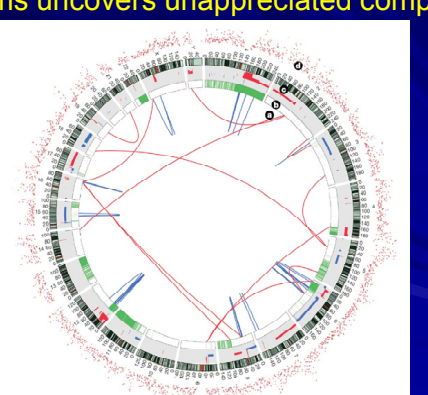




Bergsagel et al. Blood. 2005 Jul 1;106(1):296-303

Zhou Y et al Leukemia. 2009 Nov;23(11):1941-56.

Increased sensitivity of molecular profiling platforms uncovers unappreciated complexity



Lee W Nature. 2010 May 27;465(7297):473-7.

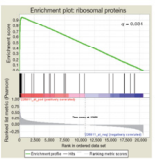
Initial genome sequencing and analysis of primary multiple myeloma cells

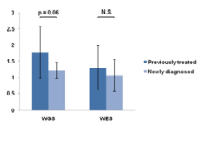
Table 1 | Statistically significant protein-coding mutations in multiple myeloma

Gene	N	n	Untreated n	CpG transition	Other C:G transition	C:G transversion	A:T mutation	Indel/ null	P-value	q-value
NRAS	20,711	9	3	0	0	3	6	0	$<1.0 \times 10^{-11}$	$<1.0 \times 10^{-6}$
KRAS	25,728	10	6	0	5	1	4	0	$<1.0 \times 10^{-11}$	$<1.0 \times 10^{-6}$
FAM46C	39,661	5	3	0	0	2	1	2	1.8×10^{-10}	1.0×10^{-6}
DIS3	89,758	4	1	0	1	1	2	0	2.4×10^{-6}	0.011
TP53	32,585	3	1	0	0	1	1	1	5.1×10^{-6}	0.019
CCND1	12,899	2	1	0	0	0	2	0	0.000027	0.086
PNKC1	19,621	2	2	0	1	0	0	1	0.000039	0.094
ALOX12B	40,369	3	0	1	0	1	1	0	0.000042	0.094
HLA-A	18,635	2	0	0	0	0	2	0	0.000045	0.094
MAGED1	53,950	2	1	0	0	0	0	2	0.000053	0.10

Territory (*N*) refers to total covered territory in base pairs across 38 sequenced samples. Total numbers of mutations (*n*) and numbers of mutations occurring in therapy-naive disease (Untreated *n*) are shown for each gene.

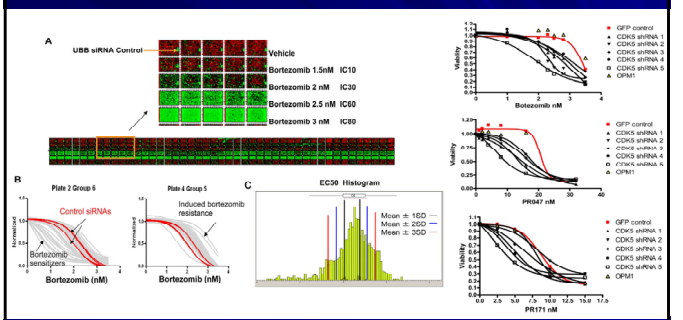
- RNA processing and protein homeostasis mutations
- NF-kB pathway
- Histone modifying enzymes
- Clinically actionable (?) mutations in BRAF





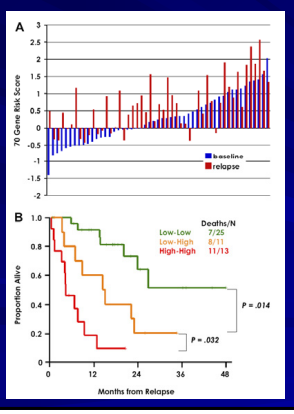
Chapman MA et al. Nature. 2011 Mar 24;471(7339):467-72

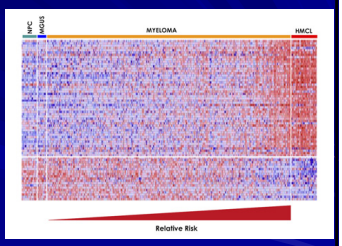
RNAi screens to identify modulators of sensitivity to proteasome inhibitors: CDK5 as candidate target



Zhu YX, et al. Blood. 2011 Apr 7;117(14):3847-57.

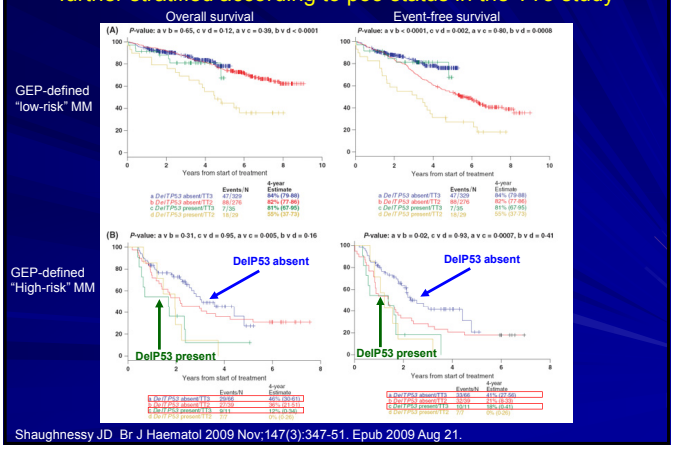
Gene-expression based "high-risk" score progressively with disease progression and trends towards the scores for MM cell lines





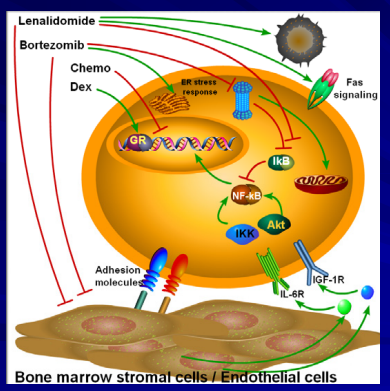
Shaughnessy JD Jr, et al. Blood. 2007;109:2276-2284.

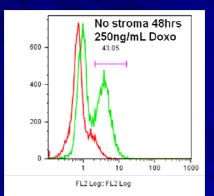
Myeloma patients with "high-risk" gene expression profiles can be further stratified according to p53 status in the TT3 study

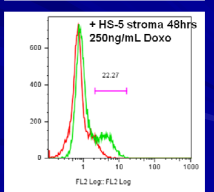


Shaughnessy JD Br J Haematol 2009 Nov;147(3):347-51. Epub 2009 Aug 21.

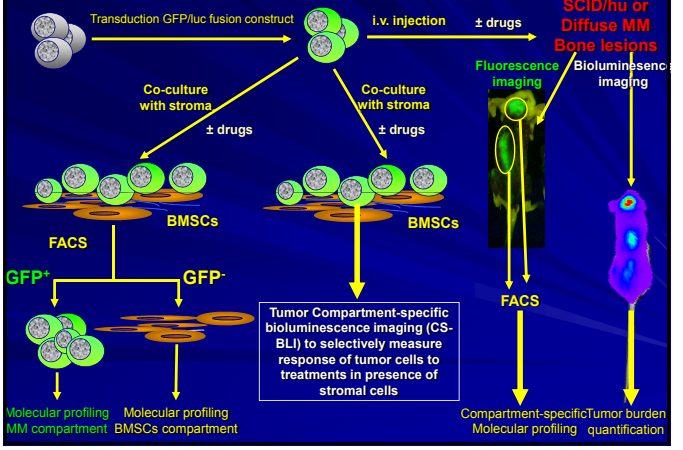
The role of the tumor microenvironment in modulating response to therapies



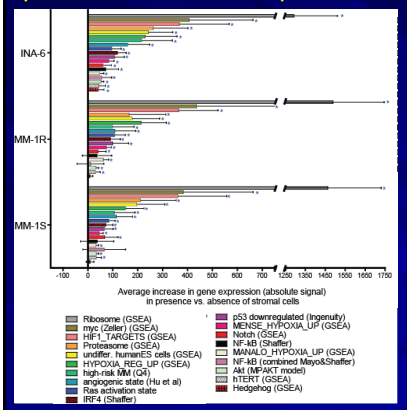




Compartment-specific models for tumor-microenvironment interactions



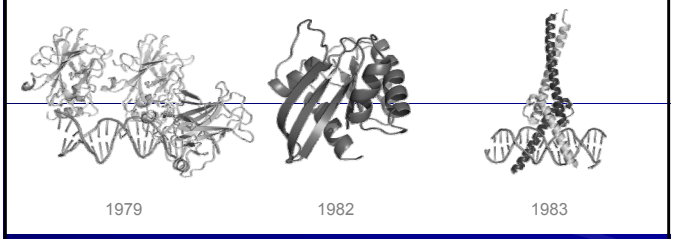
Pathway activation status analysis of gene expression profiles of MM cells in presence vs absence of BMSCs



- Akt, Ras, NF-κB
- ubiquitin/proteasome
- ribosomal signature
- Signatures of "stemness"/ self renewal in NML and/or cancer stem cells
- myc
- IRF4
- hTERT
- Hedgehog
- Notch
- genes ↓ by p53 function
- transcriptional signature of "high-risk" MM
- HIF-1a / hypoxia target genes

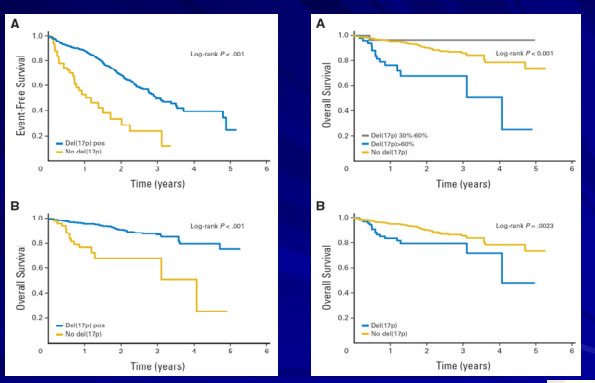
McMillin et al. Nat Med. 2010 Apr;16(4):483-9.

P53 loss – Ras mutation – MYC: elusive targets



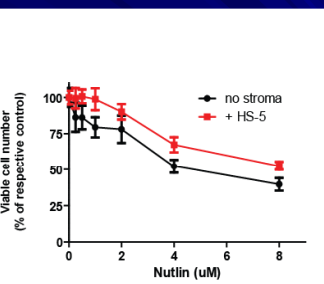
Slide courtesy of J. Bradner

Del(17p) with Bortezomib+Dex induction

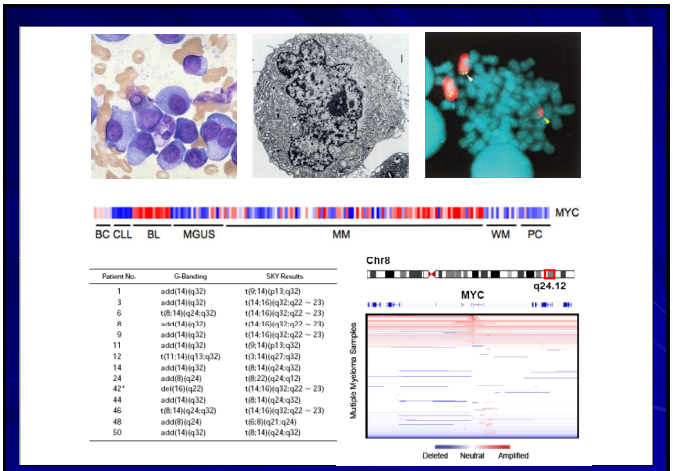


Avet-Loiseau, JCO in press 2010 (10.1200/JCO.2010.28.3945)

Preclinical p53 activation by the small molecule inhibitor nultin

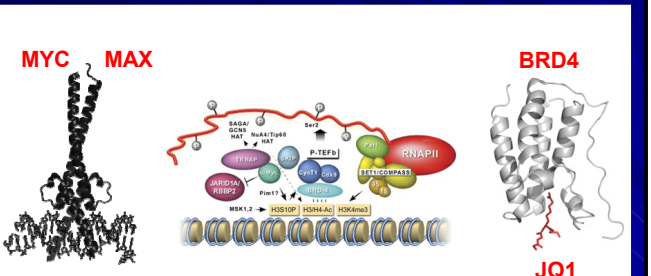


Ooi M.G., Hayden P. et al, Clin Cancer Res, Dec 2009



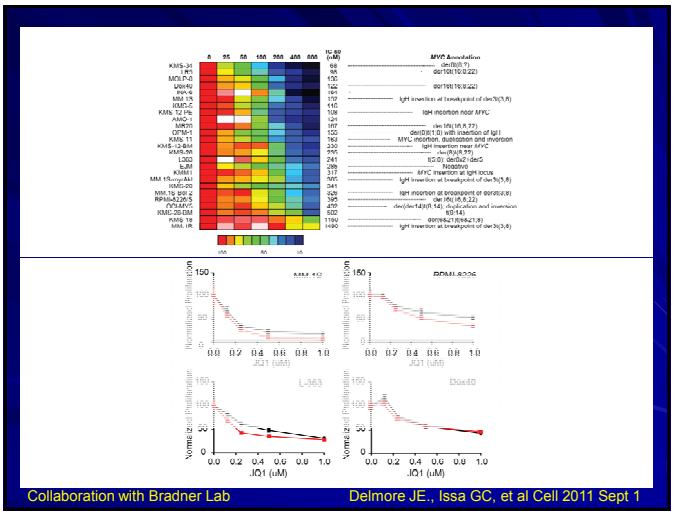
Gazdar, Blood (1996)
Kuehl, *PNAS* (2000)
Barlogie, Blood (1998)
www.broadinstitute.org/mmgp
Bergsagel and Chesi, *Cancer Cell* (2008)

BET bromodomain proteins are regulators of MYC expression and function

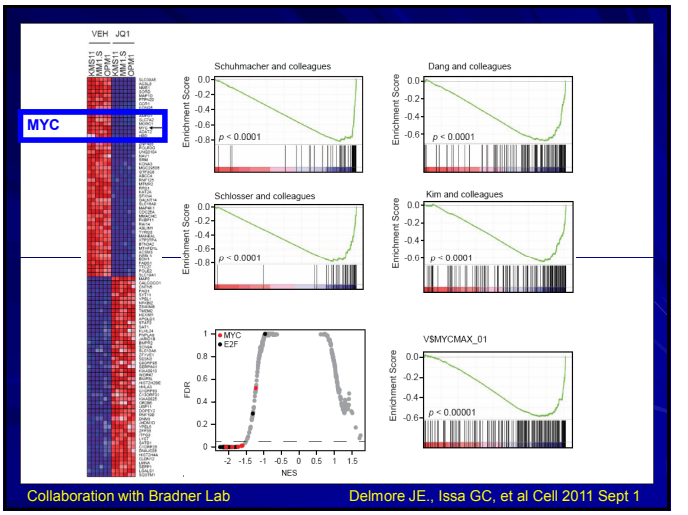


Brès V. Curr Opin Cell Biol. 2008 Jun;20(3):334-40

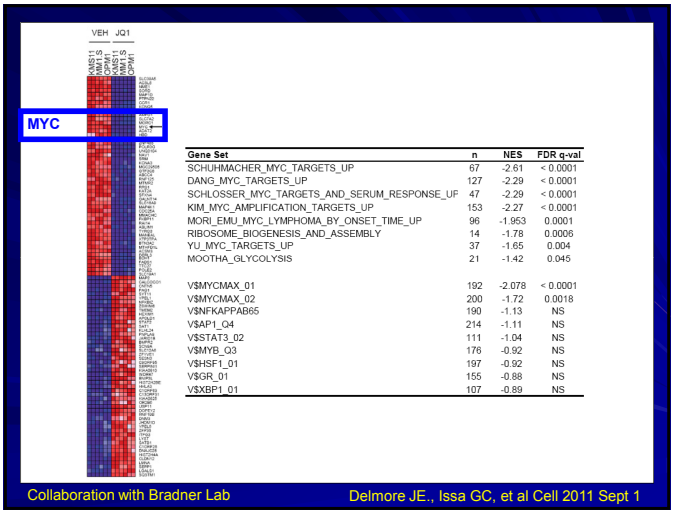
Filipakopoulos P., Qi J et al. Nature (2010)



Collaboration with Bradner Lab Delmore JE., Issa GC, et al Cell 2011 Sept 1

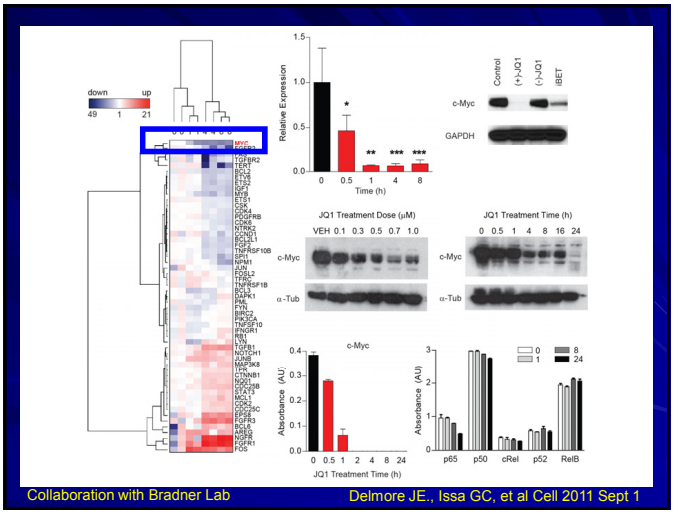


Collaboration with Bradner Lab Delmore JE., Issa GC, et al Cell 2011 Sept 1

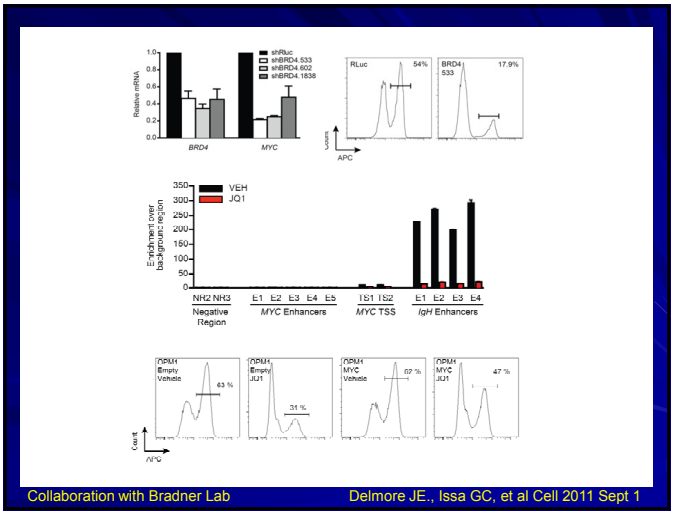


Gene Set	n	NES	FDR q-val
SCHUHMACHER_MYC_TARGETS_UP	67	-2.61	< 0.0001
DANG_MYC_TARGETS_UP	127	-2.29	< 0.0001
SCHLOSSER_MYC_TARGETS_AND_SERUM_RESPONSE_UP	47	-2.29	< 0.0001
KIM_MYC_AMPLIFICATION_TARGETS_UP	153	-2.27	< 0.0001
MORI_EMU_MYC_LYMPHOMA_BY_ONSET_TIME_UP	96	-1.953	0.0001
RIBOSOME_BIOGENESIS_AND_ASSEMBLY	14	-1.78	0.0006
YU_MYC_TARGETS_UP	37	-1.65	0.004
MOOTHA_GLYCOLYSIS	21	-1.42	0.045
V$MYCMAX_01	192	-2.078	< 0.0001
V$MYCMAX_02	200	-1.72	0.0018
V$NFKAPPAB65	190	-1.13	NS
V$AP1_C4	214	-1.11	NS
V$STAT3_02	111	-1.04	NS
V$MYB_Q3	176	-0.92	NS
V$HSF1_01	197	-0.92	NS
V$GR_01	155	-0.88	NS
V$XBP1_01	107	-0.89	NS

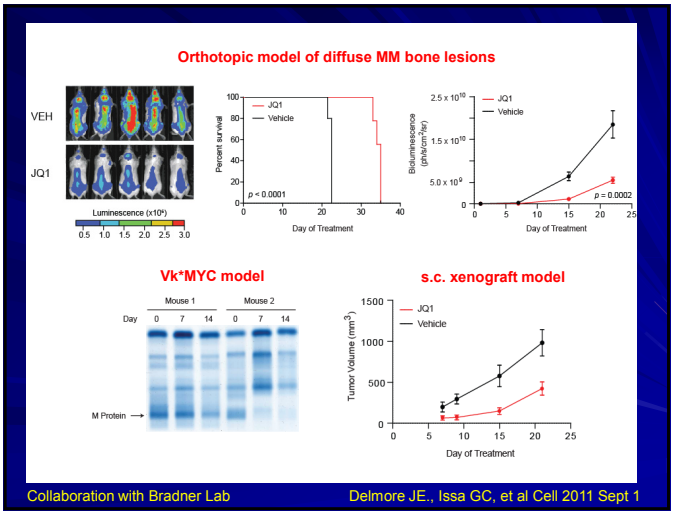
Collaboration with Bradner Lab Delmore JE., Issa GC, et al Cell 2011 Sept 1



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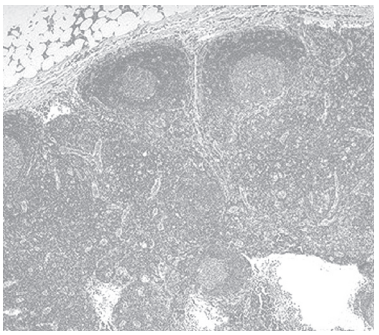
Collaboration with Bradner Lab Delmore JE., Issa GC, et al Cell 2011 Sept 1

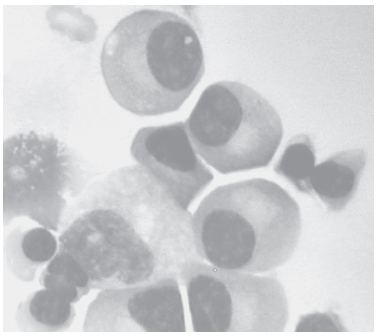


Collaboration with Bradner Lab Delmore JE., Issa GC, et al Cell 2011 Sept 1


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Acknowledgments
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Myeloma Center Nursing staff / CRCs
Jun Qi, PhD / J. Bradner MD
A. Letai MD, PhD / Triona Chonghaile
Nathaniel Gray, PhD
Sara Buhrlage, PhD
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Multiple Myeloma Research Foundation
Leukemia & Lymphoma Society
Lauri Strauss Leukemia Foundation
June 2011

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies

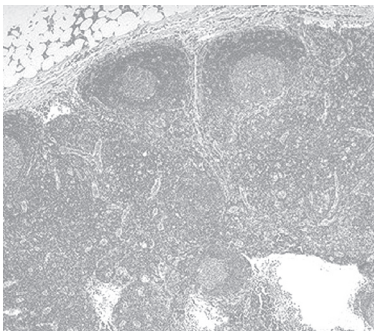


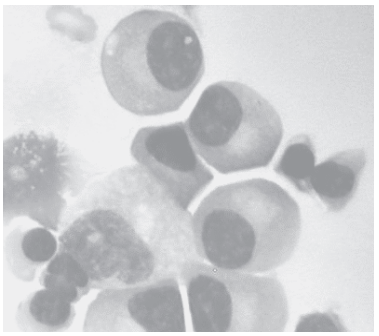


The biology of bone disease: How important are "markers"

Noopur S. Raje, MD

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





A role of denosumab and other new agents in myeloma

James E. Berenson, MD

New Advances in the Management of Myeloma Bone Disease

James R. Berenson, MD

Medical & Scientific Director
Institute for Myeloma & Bone Cancer Research
Los Angeles, CA

New Advances in the Management of Myeloma Bone Disease

- Surgical- Results of a randomized trial involving balloon kyphoplasty for cancer patients w/ VCFs
- Medical management
  - Bisphosphonates
    - Anti-MM effects in the lab and clinic
    - Recent reports of new side effects w/ long term use
  - Anti-bone resorptive effects of currently available anti-MM drugs
  - Denosumab- anti-RANKL antibody
  - Agents in early clinical development
    - ACE-011- Activin A inhibitor
    - BHQ880- anti-DKK-1 antibody
  - New therapeutic targets
    - MIP1α and its receptor CCR1
    - TRAF6

Clinical Consequences of Myeloma Bone Disease

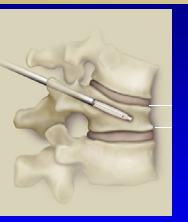
- Pathological fractures
  - Non-vertebral
  - Vertebral compression
    - Most common site
- Spinal cord compression/collapse
- Radiation therapy
- Surgery to bone
- Hypercalcemia

*SREs

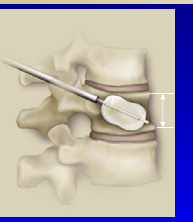
- Bone pain
- Use of analgesics
- Quality-of-life effects
- Survival

*SREs- skeletal-related events

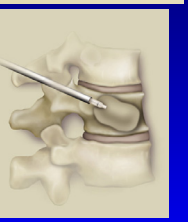
Kyphoplasty: A Minimally Invasive Fracture Reduction Procedure for Treatment of VCFs



KyphX Introducer Tool Kit:
- Allows precise, minimally invasive access to the vertebral body.
- Provides working channel.



KyphX IBT inflation:
- Reduces the fracture.
- Compacts the bone.
- May elevate endplates.



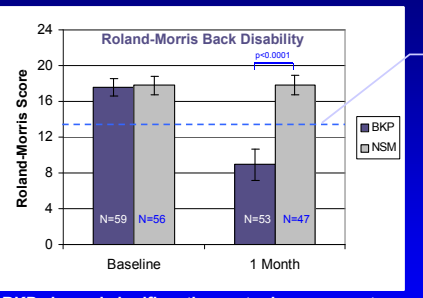
KyphX IBT Removal:
- Leaves a defined cavity and trabecular dam that can be filled with an approved bone void filler of the physician's choice.

Balloon Kyphoplasty Improves Both Disability Scores and Pain Among Cancer Patients with Vertebral Compression Fractures

- The CAFÉ trial: A randomized trial of balloon kyphoplasty vs. non-surgical management (NSM) in cancer patients with symptomatic vertebral compression fractures (VCFs)
- Patients enrolled within 3 months of diagnosis of VCF
- 1 year follow-up, optional crossover at 1 month patients randomized to NSM

Berenson JR et al. Lancet Oncology 2011

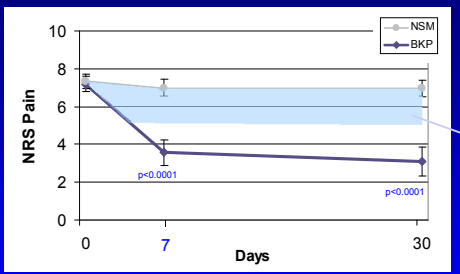
Roland-Morris Back Disability Scores Improved w/ Balloon Kyphoplasty



- BKP showed significantly greater improvement
  - Mean improvement from baseline, -8.3 points (95%CI -6.2, -10.5; p<0.0001)
  - Change exceeded the 2.5 point minimally clinically important difference
- No significant change with the control group
  - Mean improvement from (-0.1 points, 95%CI 0.9, -1.0)

Berenson et al. Lancet Oncol 2011

Back Pain (VAS) Improved within 7 Days of Balloon Kyphoplasty

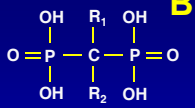


Level for the 2-point MCID from baseline

- BKP provided statistically significant reduction of pain within 7 days
  - Mean improvement from baseline, -4.1 points (95%CI -3.2, -4.9; p<0.0001) at 1 month
  - Change exceeded the 2-point minimally clinically important difference
- Pain scores in control patients did not improve
  - Mean improvement from baseline, -0.5 points (95%CI 0.04, -1.0) at 1 month

Berenson et al. Lancet Oncol 2011

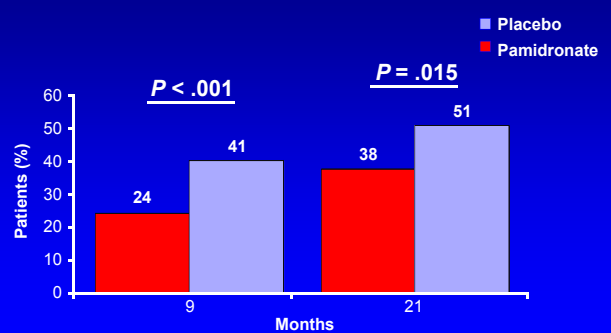
Bisphosphonates



- inhibitors of bone loss
- potency varies greatly depending upon R1 & R2 side chains

	R_1	R_2		Relative potency
Etidronate	OH	$-CH_3$	no N	1
Clodronate	Cl	$-Cl$	no N	10
Tiludronate	H	$-S-\bigcirc-Cl$	no N	10
Pamidronate	OH	$-(CH_2)_2-NH_2$	N	100
Alendronate	OH	$-(CH_2)_3-NH_2$	N	1,000
Risedronate	H	$-CH_2-\bigcirc^{N}$	N	5,000
Ibandronate	OH	$(CH_2)_2$-N-$(CH_2)_4$-CH_3 (CH3)	N	10,000
Zoledronic acid	OH	$-N\bigcirc N$	N	100,000

Monthly Pamidronate Decreases SREs in Patients With Myeloma



Berenson JR, et al. N Engl J Med. 1996;334:488-493. Berenson JR, et al. J Clin Oncol. 1998;16:593-602.

Bisphosphonates: Anti-Tumor Effects in MM

- Direct
  - Induces apoptosis
  - Prevents prenylation of GTPases
- Indirect
  - Reduces anti-apoptotic and growth factors
  - Anti-angiogenic
    - Decreases angiogenic factors
    - Prevents endothelial cell development
    - Inhibits angioattraction
  - Prevents adhesion of MM cells to stroma
- Synergizes w/ other anti-MM drugs
- Immune stimulatory effects-
  - Increases γ9δ2 T cells

MRC Myeloma IX: Trial Design for Monthly IV Zoledronic Acid vs Daily Oral Clodronate for Newly Diagnosed MM

N = 1,960
Patients with newly diagnosed MM (stage I, II, III)

RANDOMIZATION

- Zoledronic acid (4 mg[a] IV q 3-4 wk) + intensive or non-intensive chemotherapy (n = 981)
- Clodronate (1600 mg/d PO) + intensive or non-intensive chemotherapy (n = 979)

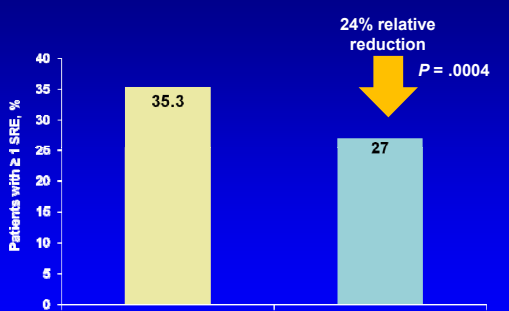
Treatment continued at least until disease progression

- Endpoints (ZOL vs CLO)
  - Primary: PFS, OS, and ORR
  - Secondary: Time to first SRE, SRE incidence, and safety

Abbreviations: CLO, clodronate; IV, intravenous; MM, multiple myeloma; ORR, overall response rate; OS, overall survival, PFS, progression-free survival; PO, oral; SRE, skeletal-related event; ZOL, zoledronic acid.
[a] Dose-adjusted for patients with impaired renal function, per the prescribing information.

Morgan G, et al. Lancet. 2010;376:1989-1999.

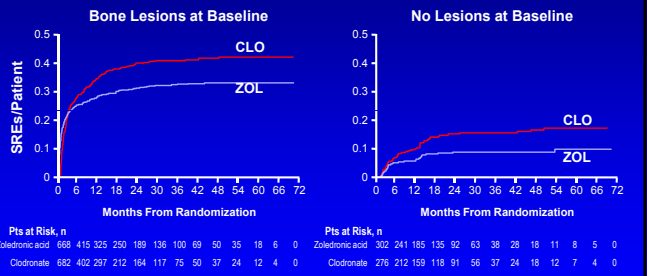
MRC Myeloma IX: ZOL Significantly Reduced SREs vs CLO[a]



[a] SREs were defined as vertebral fractures, other fractures, spinal cord compression, and the requirement for radiation or surgery to bone lesions or the appearance of new osteolytic bone lesions.

Morgan G, et al. Lancet. 2010;376:1989-1999.

MRC Myeloma IX: ZOL Reduces SREs* vs CLO Regardless of Bone Lesions at Baseline

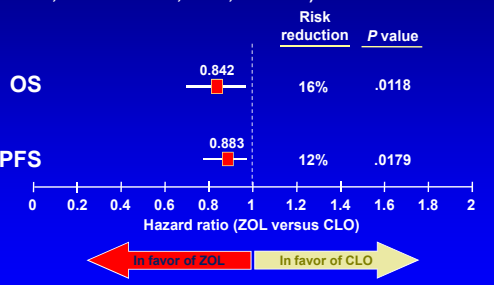


Highlights the importance of treating all patients regardless of skeletal morbidity at presentation

Morgan GJ, et al. ASH 2010. Abstract 311. Reprinted with permission.
Morgan G, et al. Lancet. 2010;376:1989-1999.

MRC Myeloma IX: ZOL Improved OS and PFS vs CLO[a]

- ZOL significantly reduced the relative risk of death by 16% vs CLO (HR = 0.842; 95% CI = 0.736, 0.963; *P* = .0118)



[a] Cox model adjusted for chemotherapy, and minimization factors.

Morgan G, et al. Lancet. 2010;376:1989-1999.

MRC Myeloma IX: Adverse Events (Safety Population)

	Patients, n (%)					
	Intensive Pathway			Non-Intensive Pathway		
	ZOL (*n* = 555)	CLO (*n* = 550)	*P*[a]	ZOL (*n* = 428)	CLO (*n* = 423)	*P*[a]
Acute renal failure	29 (5.2%)	33 (5.9%)	.70	28 (6.5%)	27 (6.4%)	1.0
ONJ[b]	21 (3.8)	2 (0.4)	< .0001	14 (3.3)	1 (0.2)	.0009
Thromboembolic	104 (18.7)	82 (14.7)	.08	53 (12.4)	35 (8.3)	.06
Infection SAE	52 (9.4)	62 (11.2)	.37	16 (3.7)	28 (6.6)	.06

[a] Statistical significance determined by Fisher's exact test.
[b] ONJ cases were confirmed by an independent adjudication committee.

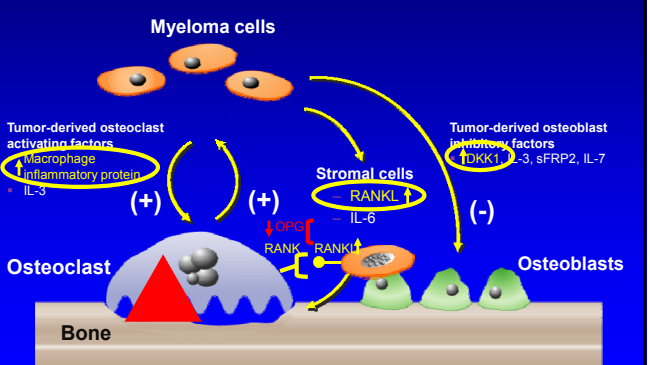
Morgan G, et al. Lancet. 2010;376:1989-1999.

Bisphosphonates (BPs): Newer Complications from Long term Treatment

- Proteninuria w/ long term use of ZOL; improves when drug is held
- Atraumatic Fractures
  - Transverse fractures of the femur
    - –First reported w/ oral BPs
    - –Recently observed w/ long term use of IV BPs in cancer pts
    - – Two of our MM patients w/ long term use (> 10 y) and used both pamidronate (PAM) and zoledronic acid (ZOL)
  - Metatarsal stress fractures in 6 MM patients w/ long term use (median 8.1 y, range 5.5-13 y)
    - – 4 PAM & ZA; 1 only PAM; 1 only ZA
    - –12% of our pts receiving > 5.5 y of IV BPs!
    - –Two patients showed bilateral fractures
    - –All resolved symptoms w/ continued BP use
      - » 2 showed continued non-union on X-rays

Waterman et al J Bone Joint Surg 2011

Pathophysiology of Myeloma Bone Disease



Derived and adapted from Roodman GD. N Engl J Med. 2004;32:290-292.

Denosumab: Inhibiting RANK Signaling to Prevent Bone Loss

- High-affinity human monoclonal antibody that binds RANKL
  - – Prevents RANKL from binding RANK
  - – Inhibits formation and activation of osteoclasts
- Administered via subcutaneous injection
- Specific: does not bind to TNF-α, TNF-β, TRAIL, or CD40L

Denosumab vs Zoledronic Acid

- Phase III trial in 1776 patients with solid tumors (n=1586; not breast or prostate) or myeloma (n=190)
  - Primary endpoint: median time to first SRE
- Randomized to monthly denosumab 120 mg SC vs zoledronic acid 4 mg IV
- Overall, denosumab was noninferior to zoledronic acid in delaying time to first on-study SRE (HR: 0.84; 95% CI: 0.71-0.98; *P* = .0007)

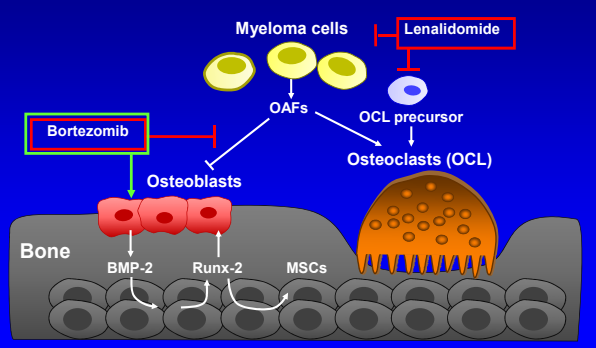
Henry D, et al. J Clin Oncol. 2011;29:1125-1132.

Denosumab vs Zoledronic in MM

- However, among the 190 myeloma patients
  - More than twice as many deaths in the denosumab arm
  - Overall survival was INFERIOR in denosumab-treated patients (HR2.26, 95% CI, 1.13 to 4.50)
  - No difference in SREs
- *Does this represent*
  - *Subset analysis?*
  - *Anti-tumor effects of zoledronic acid? (MRC Myeloma IX trial results)*
  - *Unknown negative effects of denosumab?*
- Randomized trial starting in MM (1,500 pts)
- Denosumab is NOT recommended for MM

Henry D, et al. J Clin Oncol. 2011;29:1125-1132.

Mechanisms through which Bortezomib & Lenalidomide Prevent Myeloma Bone Disease



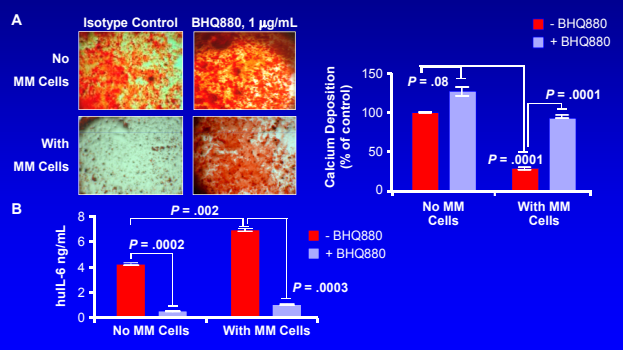
Roodman GD. J Clin Invest. 2008;118:462-464.

DKK1 and sFRP-2 in Myeloma Bone Disease

- Inhibitors of the WNT signaling pathway
- WNT signaling critical to osteoblast (OBL) differentiation
- Secreted by myeloma cells
- Marrow plasma from patients with high levels of DKK1 or sFRP-2 inhibit murine OBL differentiation
- DKK1 gene expression levels correlated with MM bone disease

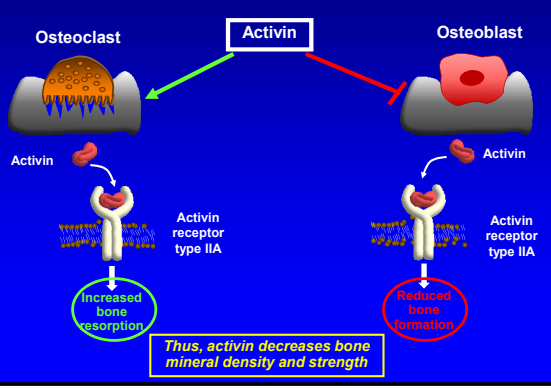
Tian E, et al. N Engl J Med. 2003;349:2483-2489. Oshima T, et al. Blood. 2005;106:3160-3165.

Anti-DKK1 Antibody BHQ880 Reverses Inhibitory Effect of MM Cells on Osteoblastogenesis

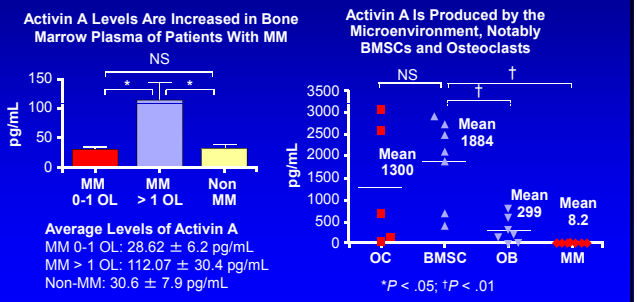


This research was originally published in Blood. Fulciniti M, et al. Anti-DKK1 mAb (BHQ880) as a potential therapeutic agent for multiple myeloma. 2009;114:371-379. © the American Society of Hematology.

Activin and Bone Growth



Activin A Levels Are Elevated in Patients With MM and Osteolytic Disease



Average Levels of Activin A
MM 0-1 OL: 28.62 ± 6.2 pg/mL
MM > 1 OL: 112.07 ± 30.4 pg/mL
Non-MM: 30.6 ± 7.9 pg/mL

Vallet S, et al. Proc Natl Acad Sci U S A. 2010;107:5124-5129. Copyright 2010 National Academy of Sciences, U.S.A.

Phase II Study of hActRIIA-IgG1 in Patients With Osteolytic Lesions of MM

- Randomized, double blind, placebo controlled
- Dose ranging, multiple dose, parallel assignment
- N = 30
- All patients receiving backbone MPT regimen

0.1 mg/kg ACE-011, **SQ** monthly x 4 (n = 8)

0.3 mg/kg ACE-011, **SQ** monthly x 4 (n = 8)

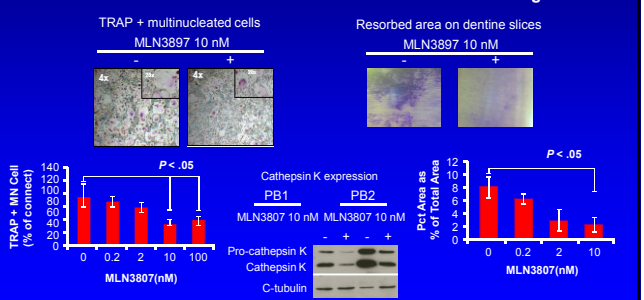
0.5 mg/kg ACE-011, **SQ** monthly x 4 (n = 8)

Placebo, **SQ** monthly x 4 (n = 6)

ClinicalTrials.gov. NCT00747123.

Inhibiting CCR1, a Receptor for MIP1α, Decreases Osteoclastogenesis

CCR1 and Osteoclastogenesis/Osteoclasts Function
Menu: On Murine OC BX4471 Is a Potent Inhibitor of Osteoclastogenesis

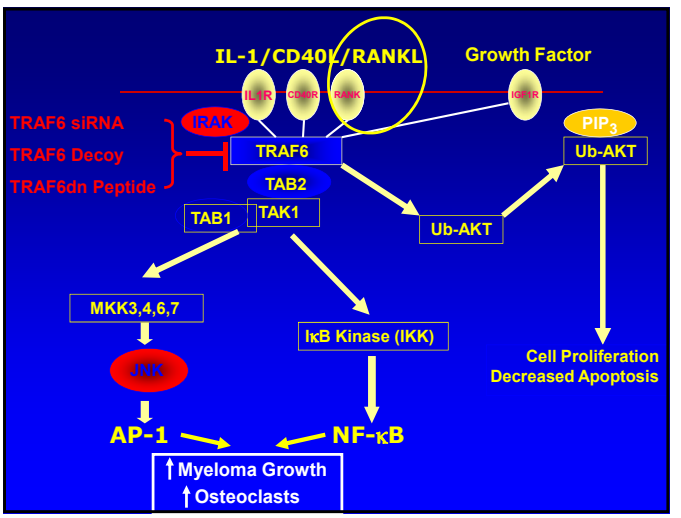


This research was originally published in Blood. Vallet S, et al. MLN3897, a novel CCR1 inhibitor, impairs osteoclastogenesis and inhibits the interaction of multiple myeloma cells and osteoclasts. 2007 Nov 15;110(10):3744-52. © the American Society of Hematology.

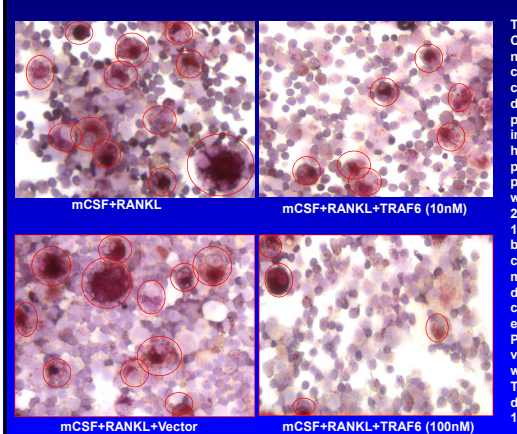
Tumor necrosis factor receptor (TNF)-associated factor 6 (TRAF6)

- Is over-expressed in bone marrow from myeloma patients
- Blockage of TRAF6
  - Inhibits MM tumor cell growth
  - Reduces osteoclast formation
  - Decreases bone resorption

Chen et al. Oncogene 2006; Chen et al. ASH 2009 & 2011

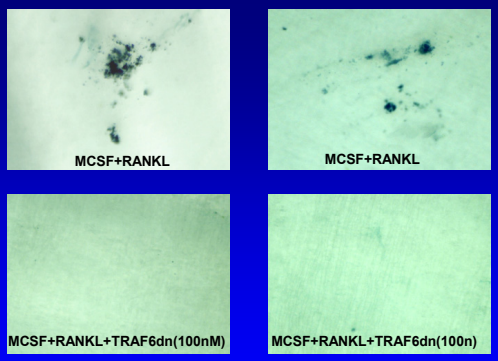


Inhibition of Osteoclast Cell Formation by TRAF6dn (1)



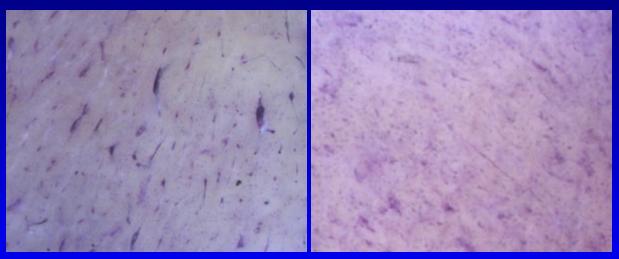
TRAP-staining assay: CD14+ cells from normal PBMC were cultured on slide-culture dishes at a density of 2x105 cells per well. The cells infected by pLenti6.2-hTRAF6dn or by pLenti6.2h vector, pLenti6.2/GW/EmGFP were treated with 20ng/ml RANKL and 10ng/ml mCSF at the beginning of the culture and during a medium change on 3 days. In some wells, cells were also exposed to the PLenti6.2hTRAF6dn or vector alone. The cells were fixed and TRAP-staining determined at day 14das.

Toluidine Blue Staining of Dentin for Pit Formation Assay



Dentin pit bone resorption assay: Monocytes in the presence of MCSF and RANKL were cultured on dentin bone slides at a density of $4x10^5$ cells per slide, respectively. TRAF6dn expressed from the pLenti6.2-hPLenti6.2hTRAF6dn significantly inhibited bone resorption by osteoclasts.

TRAF6dn Peptide Inhibits Bone Resorption



Bone pit resorption assay: Monocytes in the presence of MCSF and RANKL were cultured on dentin bone slides at a density of $4x10^5$ cells per slide with and without TRAF6dn peptide for 28 days, respectively.

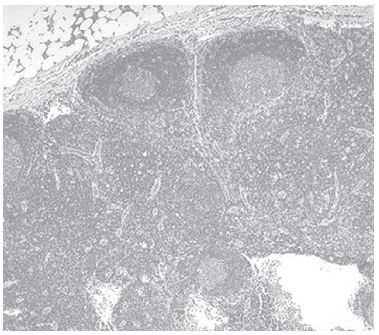
New Advances in the Management of Myeloma Bone Disease

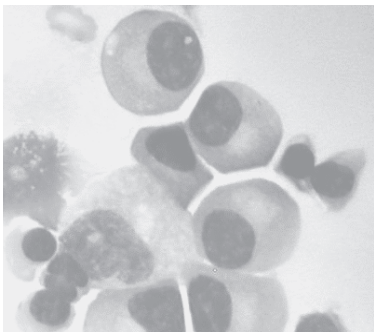
- Surgical- CAFÉ trial results show advantage of balloon kyphoplasty compared to nonsurgical management for cancer patients with VCFs
- Medical management
  - Bisphosphonates
    - Anti-tumor effects
      - Preclinical
      - Clinical- randomized trial showing overall survival advantage with monthly zoledronic acid compared to daily oral clodronate (MRC Myeloma IX trial)
    - New side effects w/ long term IV BP use
      - Renal- proteinuria w/ zoledronic acid
      - Atraumatic fractures
        - » Femoral fractures
        - » Stress metatarsal foot fractures

New Advances in the Management of Myeloma Bone Disease

- Anti-bone resorptive effects of currently available anti-MM drugs
  - Bortezomib
  - IMiDs- thalidomide and lenalidomide
- Denosumab- anti-RANKL antibody
  - Among MM patients, increased deaths compared to zoledronic acid-treated pts
- Agents in clinical development
  - ACE-011- Activin A inhibitor
  - BHQ880- anti-DKK-1 antibody
- New therapeutic targets
  - MIP1α and its receptor CCR1
  - TRAF6

Lymphoma & Myeloma 2011
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Imaging techniques in myeloma: How best to use them

Meletios-Athanasios Dimopoulos, MD

Imaging Techniques in Myeloma: How Best to Use Them

Meletios A. Dimopoulos, MD
Department of Clinical Therapeutics,
University of Athens School of Medicine,
Athens, Greece

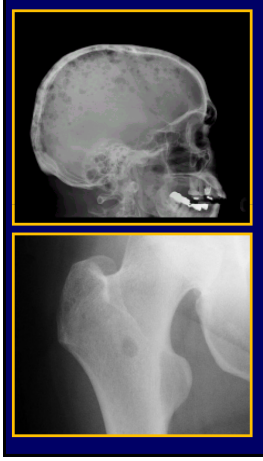
Disclosures (M. A. Dimopoulos)

In compliance with accreditation, we require the following disclosures to the session audience:

Research Support/P.I.	No
Employee	No
Consultant	No
Major Stockholder	No
Speakers Bureau	No
Honoraria	No
Scientific Advisory Board	No

Presentation includes discussion of the following off- label use of a drug or medical device: N/A

Bone Lesions in Conventional Radiography



- Present up to 80% of patients at diagnosis.
- Lytic lesions on plain X-rays are typically punched-out lesions with absent reactive sclerosis of the surrounding bone in the flat bones of the skull and pelvis.
- In the long bones, there is a range of appearances from endosteal scalloping, to discrete small (<1 cm) lytic lesions, to mottled areas of multiple small lesions, to large destructive lesions

Dimopoulos et al. Leukemia 2009;23:1545-56

Imaging for Myeloma Bone Disease



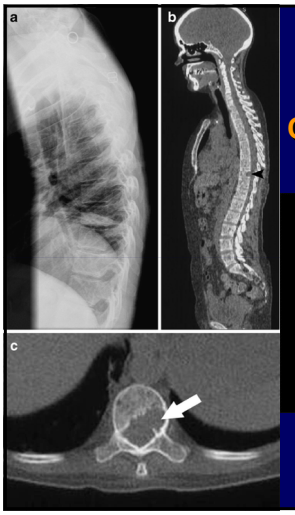
- As part of the staging procedures of newly diagnosed myeloma, the skeletal survey is mandatory
  - a posteroanterior view of the chest
  - antero-posterior and lateral views of the cervical spine (including an open mouth view), thoracic spine, lumbar spine
  - antero-posterior and lateral views of humeri and femora
  - antero-posterior and lateral views of the skull and antero-posterior view of the pelvis
- At diagnosis lytic lesions:
  - vertebrae in 65% of patients
  - ribs in 45%
  - skull in 40%
  - shoulders in 40%
  - pelvis in 30% & long bones in 25%

Dimopoulos et al. Leukemia 2009;23:1545-56

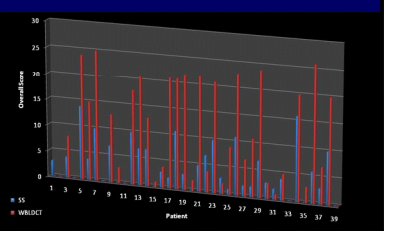
Disadvantages of Conventional Radiography

- Reveals lytic disease when over 30% of the trabecular bone has been lost; ~20% of patients at diagnosis have normal skeletal survey.
- Cannot be used for the assessment of response to therapy as the lytic bone lesions seldom show evidence of healing, while new compression vertebral fractures do not always indicate disease progression.
- Lack of accurate visualization of some areas.
- Reduced specificity versus benign causes of osteopenia.
- Observer dependency.
- Lengthy period on the examination table.
- Poor tolerance by patients with severe pain and extensive lytic disease.

Dimopoulos et al. Leukemia 2009;23:1545-56
Dimopoulos et al. Blood 2011; in press



Whole-Body Low-Dose Multi-Detector CT: More Sensitive than Conventional Radiography



Gleeson et al. Skeletal Radiol 2009;38:225-36

Advantages of CT and of WBLDMD CT Over Conventional Radiography

- superior diagnostic sensitivity in revealing more osteolytic lesions, mainly in areas that cannot be accurately visualized by plain radiography, e.g. scapulae, rib or sternum
- superiority in estimating fracture risk and instability
- duration of the examination, which is practically three times less than that of standard radiography
- complete diagnostic evaluation in a single examination without having to reposition the patients
- demonstration of other unsuspected pathological processes, especially those involving the lungs and
- superiority in planning the radiation therapy or the surgical intervention

Terpos et al. J Clin Oncol 2011;in press

But……

Typical effective dose (mSv)

Conventional X-ray	
Chest (single PA film)	0.02
Pelvis	0.7
Abdomen	1.0
Computed tomography	
Chest	8
Pelvis	10
Abdomen	10

Other disadvantages of CT:

•non-specificity for the evaluation of osteopenia or osteoporosis

•caution is needed regarding the use of intravenous contrast

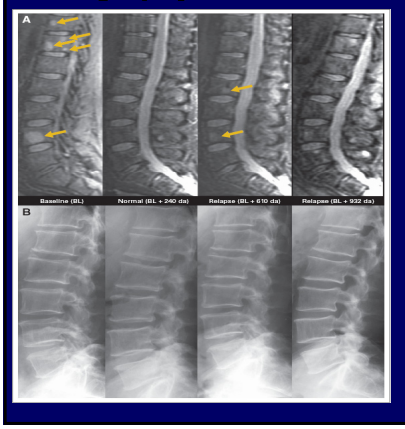
Valentin. Ann ICRP 2000;30:7-67
Dimopoulos et al. Leukemia 2009;23:1545-56

Magnetic Resonance Imaging



- Magnetic resonance imaging is a non-invasive technique which provides detailed information about bone marrow involvement and its pattern (focal, diffuse, variegated)
- MRI is useful for the assessment of the extent and nature of soft tissue disease arising from bone lesions, and can detect unsuspected, asymptomatic lesions
- An MRI of the spine and pelvis is mandatory in all patients with a presumed diagnosis of solitary plasmacytoma and in patients with smoledring myeloma.

MRI: More Sensitive than Conventional Radiography



- Detection of Focal Lesions:
  - MRI: 74%
  - Con. Rad.: 56%
- 52% of 267 patients with normal skeletal survey had focal lesions on MRI
- MRI better in the spine, sternum and pelvis

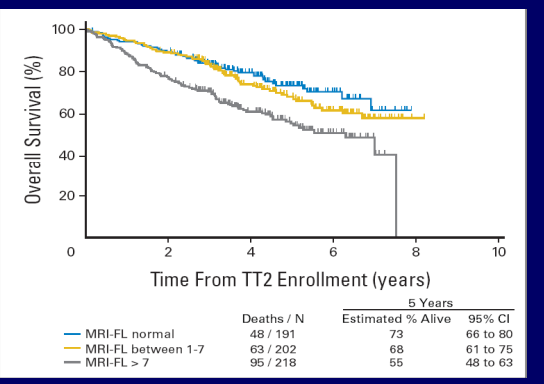
Walker et al. J Clin Oncol 2007;25:1121-8

Advantages of MRI against Conventional Radiography

- excellent imaging of the axial skeleton due to the greater sensitivity of the method
- discrimination of myeloma from normal marrow
- accurate illustration of spinal cord and/or nerve root compression, soft tissue extension, head and neck plasmacytomas, avascular necrosis of the femoral head
- better evaluation of cardiac amyloidosis and/or soft tissue amyloid deposits

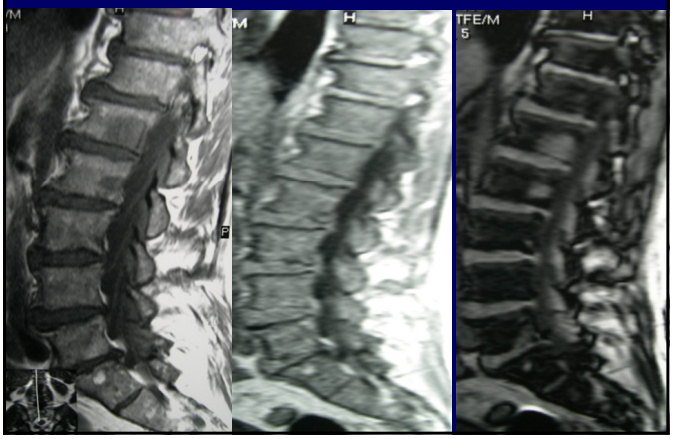
Dimopoulos et al. Leukemia 2009;23:1545-56

Focal Lesions in MRI of Symptomatic MM Predicts for Overall survival

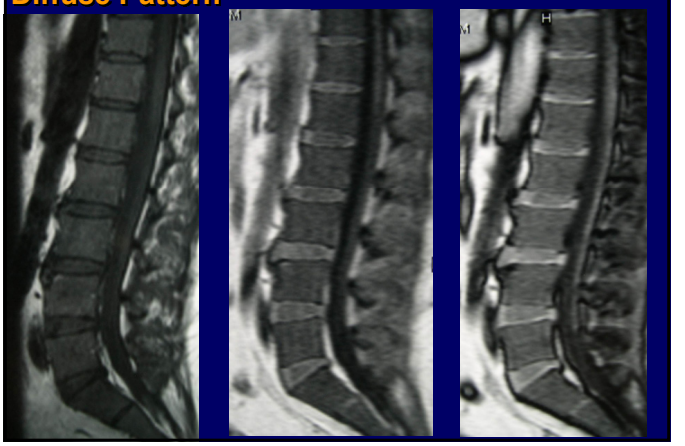


Walker et al. J Clin Oncol 2007;25:1121-8

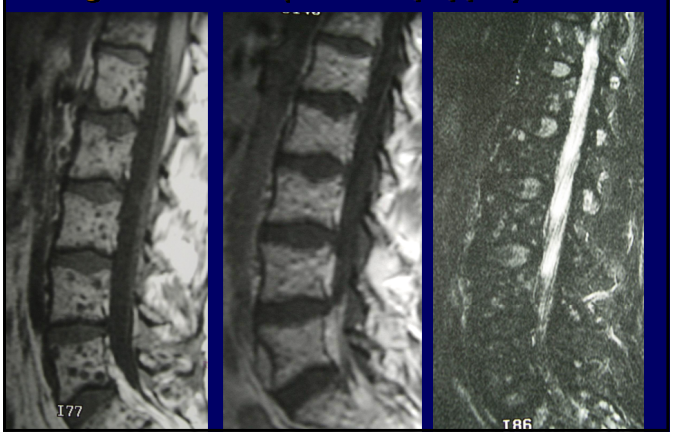
MRI Patterns of Marrow Involvement in MM: Focal Pattern



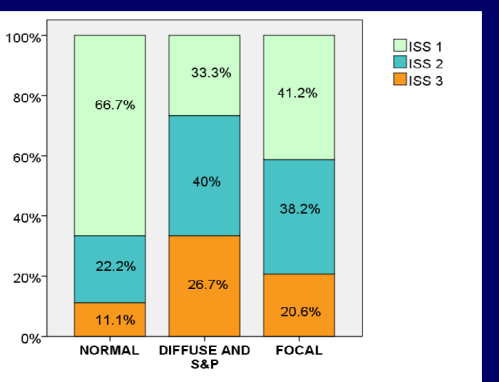
MRI patterns of marrow involvement in MM: Diffuse Pattern



MRI patterns of marrow involvement in MM: Variegated Pattern (salt-and-pepper)

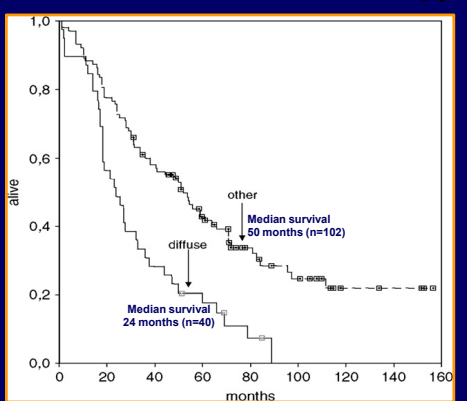


MRI Pattern and ISS



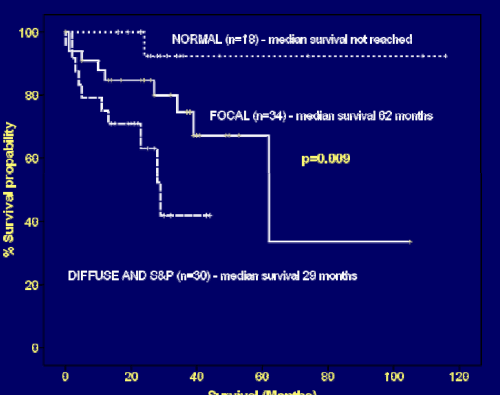
Moulopoulos et al. Leukemia 2010;24:1206-12

MRI Pattern & Overall Survival in Patients Treated Upfront with Conventional Chemotherapy



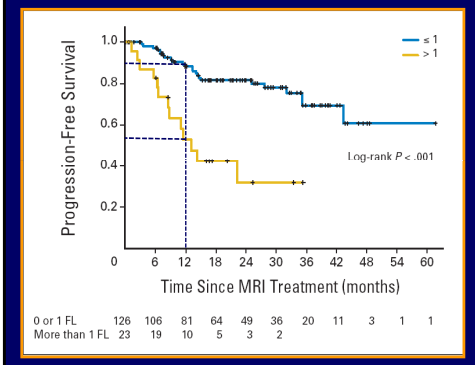
Moulopoulos et al. Ann Oncol 2005;16:1824-28

MRI Pattern & Overall Survival in Patients Treated with Novel-Agent Based Therapies



Moulopoulos et al. Leukemia 2010;24:1206-12

MRI and Asymptomatic MM



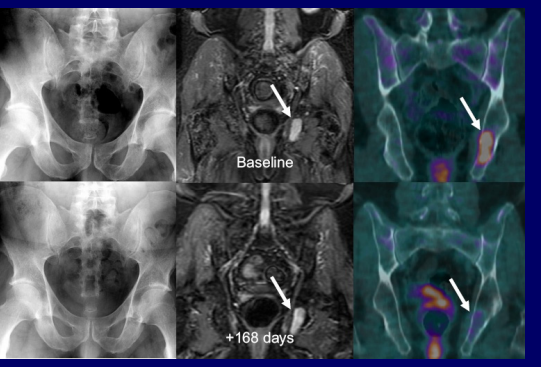
149 patients

Focal lesions: 28%

The presence of focal lesions was the strongest adverse prognostic factor for progression into symptomatic disease (p<0.001)

Hillengass et al. J Clin Oncol 2010;28:1606-10

PET/CT: Promising Results in Myeloma



The sensitivity of FDG PET in detecting myelomatous involvement is approximately 85% and its specificity is approximately 90%

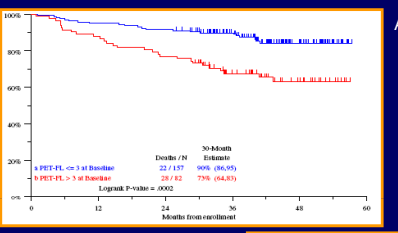
Bartel et al. Blood 2009;114:2068-76

MRI *vs.* PET/CT *vs.* Conventional Radiography

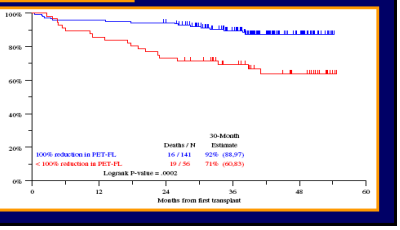
	No of patients (%) with negative findings	No of patients (%) with positive findings	No of lesions Median (range)
Whole Body X-rays	18/46 (39%)	28/46 (61%)	2 (0-10)
MRI of the spine and pelvis	4/46 (8%)	42/46 (92%)	3 (0-10)
PET/CT of the spine and pelvis	19/46 (41%)	27/46 (59%)	2 (0-10)
PET/CT whole Body	13/46 (28%)	33/46 (72%)	10 (0-10)

Zamagni et al. Haematologica 2007;92:50-5

PET/CT & Overall Survival



At diagnosis



At transplant

Bartel et al. Blood 2009;114:2068-76

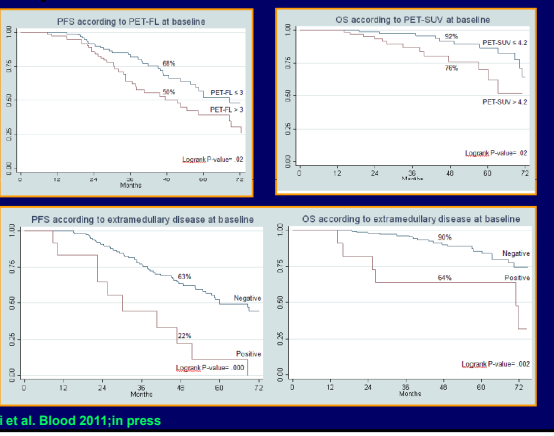
PET/CT In 192 Patients who Received TD and One or Tandem double ASCT

PET/CT	Negative	Positive
At diagnosis	24%	76%
Post-induction	37%	63%
3 months post-Auto-SCT	65%	35%

95% of PET/CT (-) had achieved ≥ vgPR post-ASCT

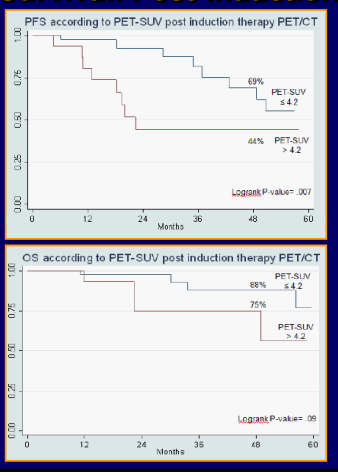
Zamagni et al. Blood 2011;in press

PET/CT & Survival: TD and double ASCT (n=192) – Before Treatment



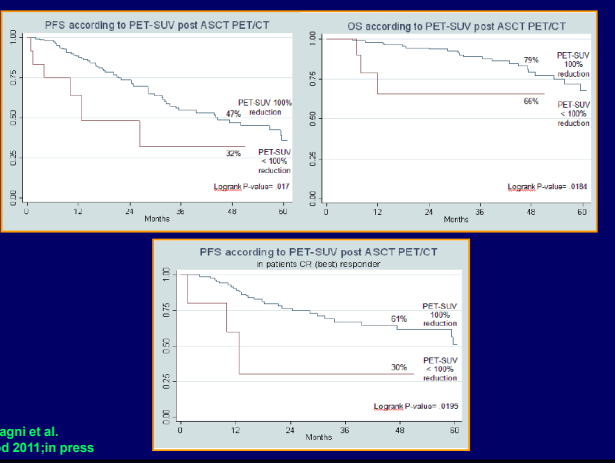
Zamagni et al. Blood 2011;in press

PET/CT & Survival: Post-induction



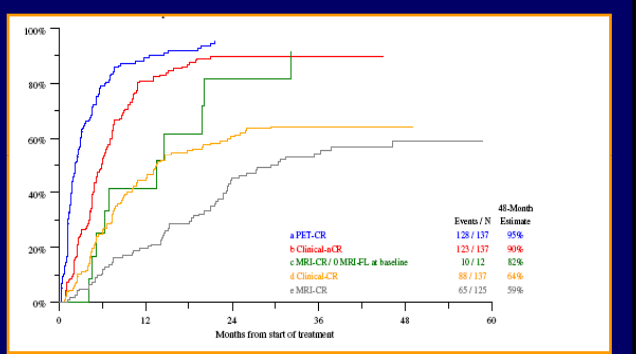
Zamagni et al.
Blood 2011;in press

PET/CT & Survival: Post-ASCT



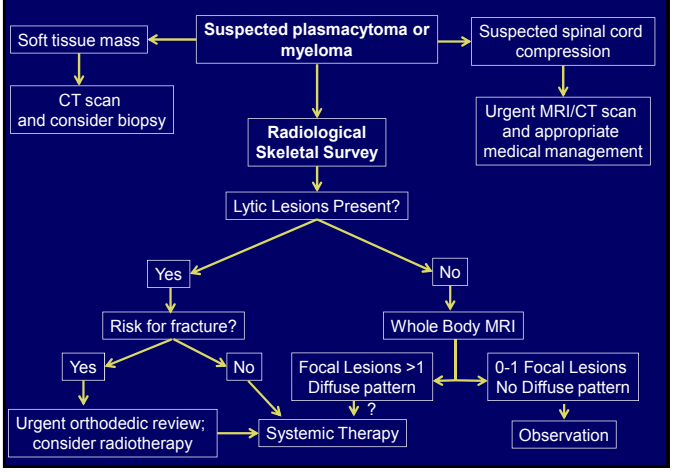
Zamagni et al.
Blood 2011;in press

PET/CT: Useful for Better Definition of CR?



Bartel et al. Blood 2009;114:2068-76

Algorithm for the Use of Imaging in Myeloma



Conclusions (1)

- Conventional radiography remains the gold standard for the evaluation of bone disease in patients with multiple myeloma.
- Whole body MRI can give complementary information to skeletal survey and is recommended in patients with normal conventional radiography.
- MRI of the whole spine should be performed in addition to the skeletal survey as part of staging in all patients with a solitary plasmacytoma of bone.
- Urgent MRI is also the diagnostic procedure of choice to assess suspected cord compression in myeloma patients even in the absence of vertebral collapse.

Conclusions (2)

- CT of the spine or other areas of the skeleton may be considered to clarify cases of clinical concern in the absence of MRI and to guide tissue biopsy.
- PET/CT can give complementary information to MRI but its use in MM has to be clarified by further studies.
- Diffuse MRI pattern and PET/CT positivity correlates with inferior survival even in the era of novel anti-myeloma agents.
- The incorporation of abnormal MRI and/or PET/CT to the definition of symptomatic myeloma and the definition of CR also needs to be clarified.

Future Issues

- Do we have to treat patients with asymptomatic myeloma with lytic lesions or with diffuse pattern in MRI or with lesions in PET/CT?
- Do we have to include in the CRAB criteria the presence of focal lesions on MRI?
- Is there any relationship between MRI or PET/CT lesions with cytogenetic abnormalities?
- Can we use MRI or PET/CT for a better definition of CR or to further improve ISS?

Acknowledgments

Department of Clinical Therapeutics

Plasma Cell Dyscrasias Unit

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- E Eleutherakis-Papaiakovou
- D Mparmparoussi
- C Matsouka
- C Liakou
- T Bagratuni

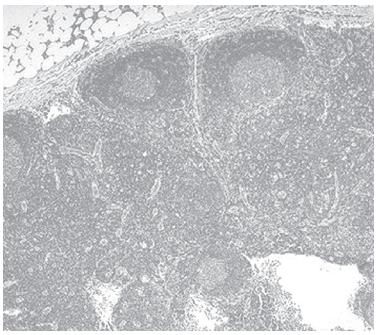
Department of Radiology

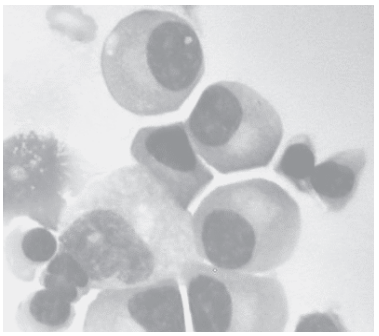
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- A Koureas

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- A Zomas (Athens)
- Z Kartasis (Halkida)
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- I Kotsianidis, E Spanoudakis,
- K Tsatalas (Alexandroupolis)
- A Symeonidis (Patras)
- E Hatzimichail (Ioannina)
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- E Stefanoudaki (Athens)
- P Panayiotidis (Athens)
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Lymphoma & Myeloma 2011
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"High-risk" myeloma: Definition and treatment

Rafael Fonseca, MD

MAYO CLINIC

Rafael Fonseca MD, Mayo Clinic

High Risk Myeloma; Diagnosis and Treatment



Scottsdale, Arizona



Rochester, Minnesota



Jacksonville, Florida

Mayo Clinic College of Medicine
Mayo Clinic Comprehensive Cancer Center

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Disclosures

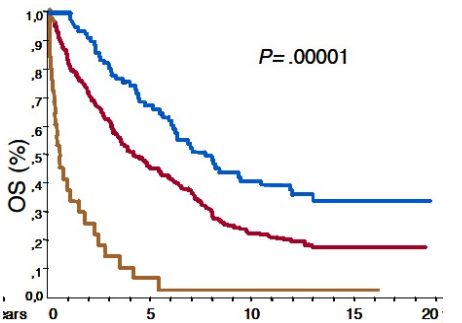
- Consulting: AMGEN, Genzyme, BMS, Otsuka, Celgene, Medtronic, Lilly, Millennium
- Speakers Bureaus: None
- Research: Cylene, Proteolix
- Patent for FISH based prognostication in MM
  - About $1500 per year

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Myeloma is a curable disease

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Spanish Long Term



Blood-2011-01-332320

4

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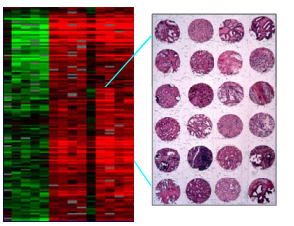
Key questions

- How to integrate this information for treatment selection
- Can we tell all patients "myeloma is becoming a chronic disease"?
- What about "novel" agents?

MAYO CLINIC

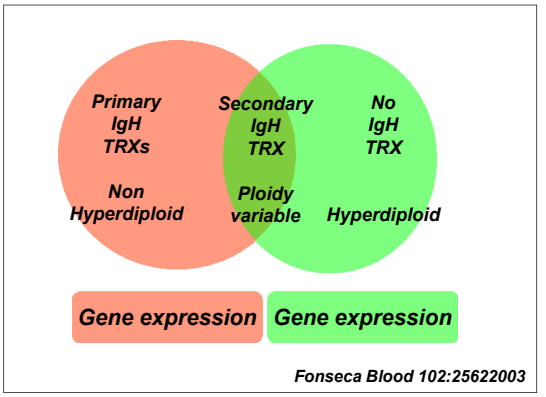
Genetics and Oncology





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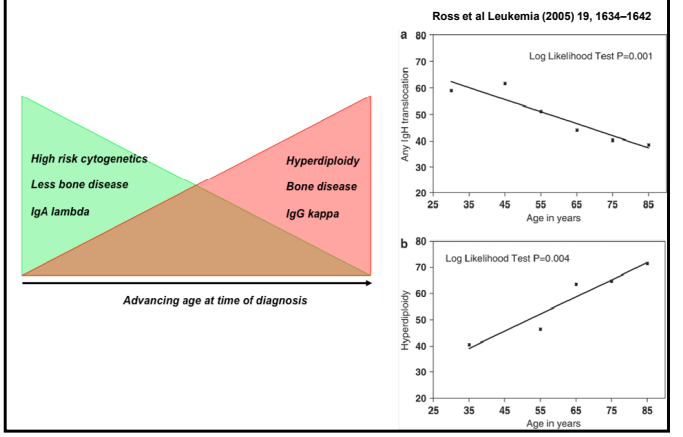
Genetic Classification of MM



Fonseca Blood 102:25622003

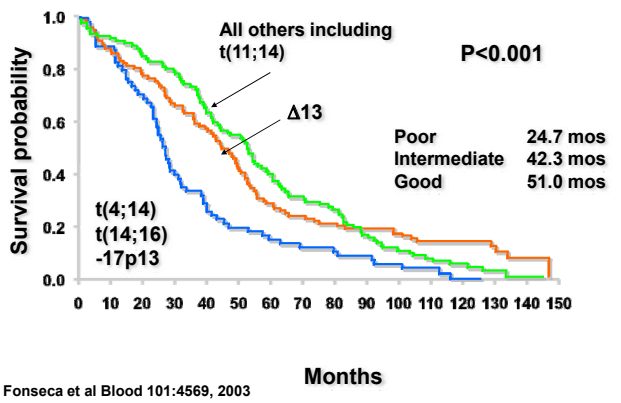
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Ploidy and Age



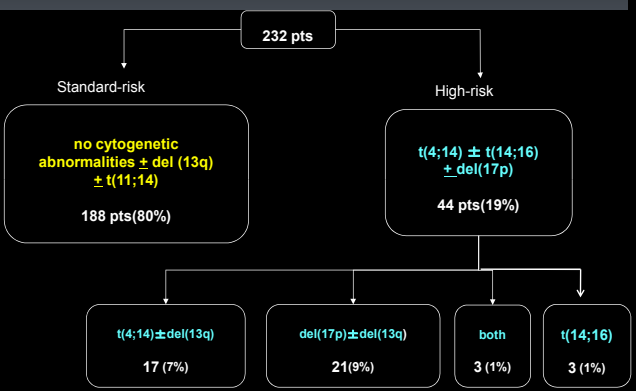
MAYO CLINIC

Molecular Prognostic Model

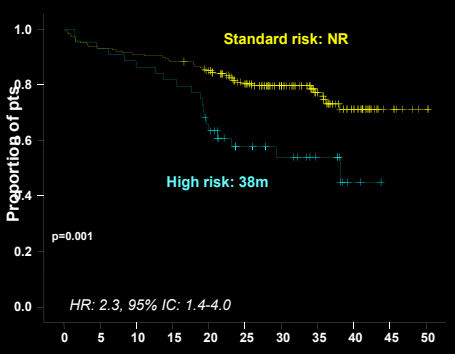


Fonseca et al Blood 101:4569, 2003

Study population stratified according to cytogenetic abnormalities

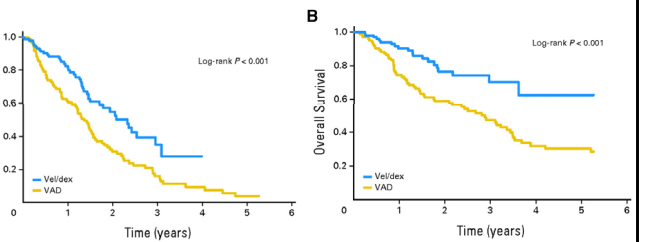


Overall survival according to cytogenetic abnormalities



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EFS and OS; t(4;14) VD (n = 106) vs VAD (n = 98)

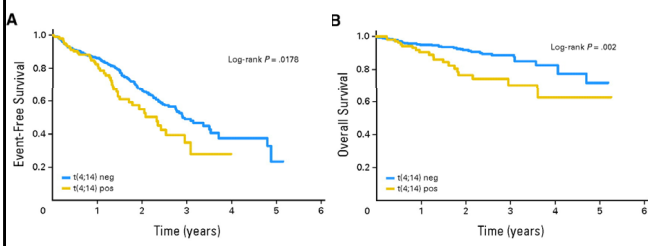


Avet-Loiseau H et al. JCO 2010;28:4630-4634

JOURNAL OF CLINICAL ONCOLOGY

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EFS and OS; VD Treated t(4;14) (n = 106) vs not (n = 401)

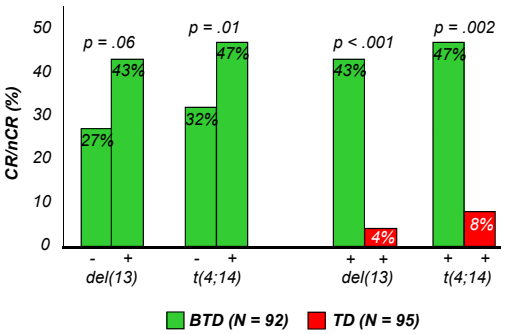


Avet-Loiseau H et al. JCO 2010;28:4630-4634

JOURNAL OF CLINICAL ONCOLOGY

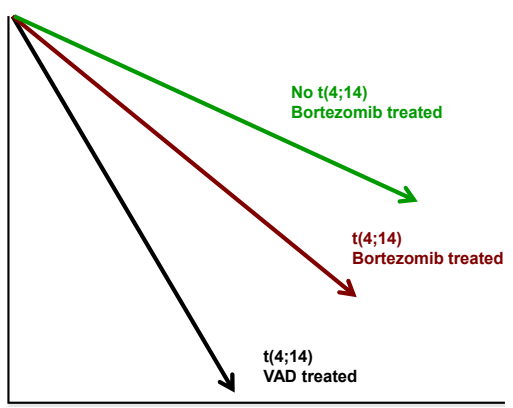
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VTD Vs. TD: Efficacy in High Risk Groups



nCR = near CR. Cavo et al, 2007.

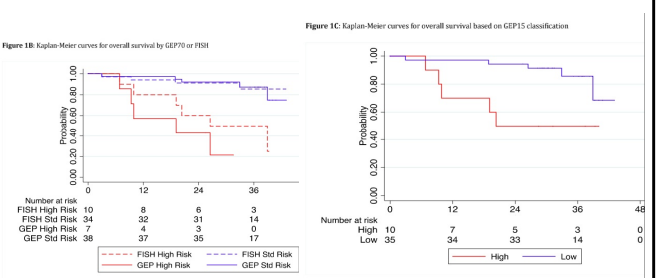
MAYO CLINIC



Avet-Loiseau H et al. JCO 2010;28:4630-4634

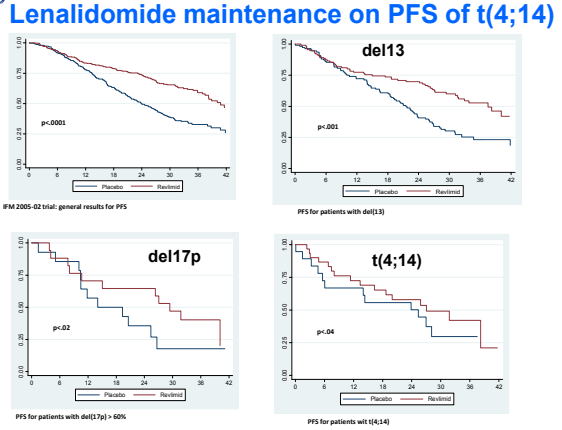
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High Risk in Len Treated Patients



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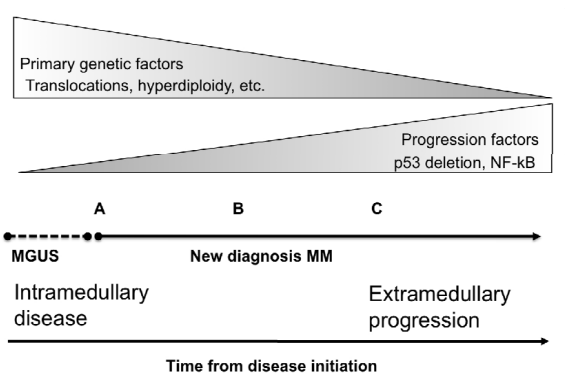
Lenalidomide maintenance on PFS of t(4;14)



Avet-Loiseau ASH 2010

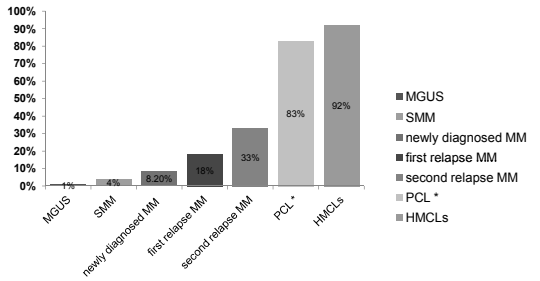
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New Diagnosis MM



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P53 deletion/mutation



Studied 8 patients with 17p deletions at RR 7 did not have deletion at diagnosis

FISH (MGUS n=184, SMM n=116, relapsed MM n=62 and PCL n=26)
aCGH (newly diagnosed MM n=224, relapsed MM n=158 and HMCLs n=48)
p 53 mutational status was evaluated in relapsed MM (n=84) and HMCLs (n=48)

**Tiedemann et al. Leukemia. 2008; 22, 1044-1052*
Fonseca. Manuscript in preparation

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Staging of MM

Clinical staging

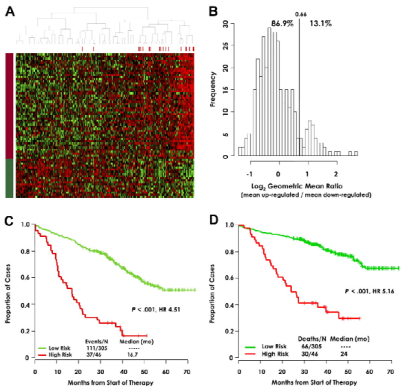
Benign disease MGUS SMM → New diagnosis MM → First relapse → Second relapse

Molecular staging

Dormant clone → Malignant p53 normal → Malignant p53 abnormal → Malignant p53 abnormal plus

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GEP signatures

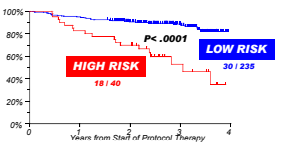


Shaughnessy et al, Blood2007, 109(6), 2276-2284

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UAMS: Total Therapy 4 and 5

OVERALL SURVIVAL

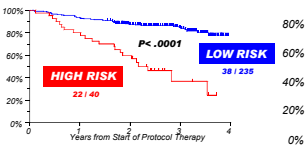


NEW PROTOCOLS:

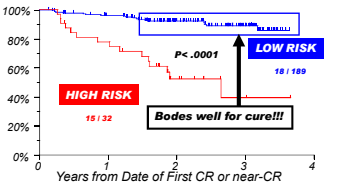
Low risk: TT4 (reduce toxicities)
Randomize TT3 v TT3-lite

High risk: TT5 (sustain CR)
MEL80-VTD- PACE
R-VD / M-VD maintenance

EVENT-FREE SURVIVAL



CR DURATION

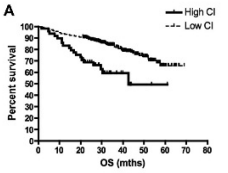


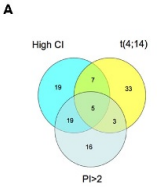
Courtesy of Dr Barlogie

22

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Centrosome Index





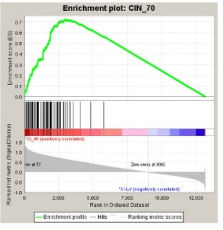
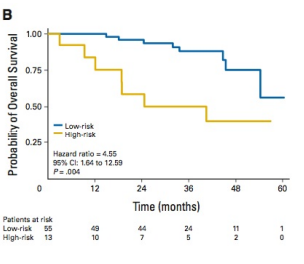


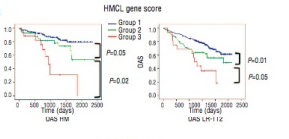
Figure 2. Association of a high CI with other high-risk factors and genomic instability. (A) A Venn diagram showing overlap between tumors with high CI, high PI, and t(4;14). The overlap is less than 50% for 2 of these features, and only 5 (4%) patients have all 3 features. (B) An enrichment plot showing clustering of genes constituting a chromosome instability signature among the top-ranking genes overexpressed in tumors with high CI.

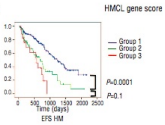
Chng et al BLOOD, 2008;111 1603

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Several Other Signatures







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Genomic complexity and outcomes

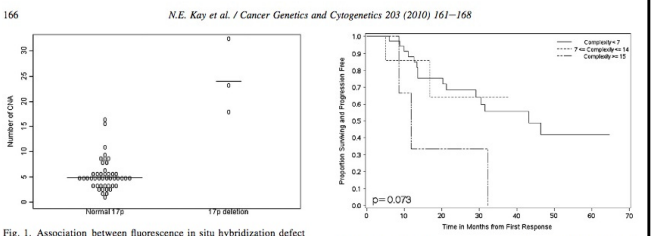


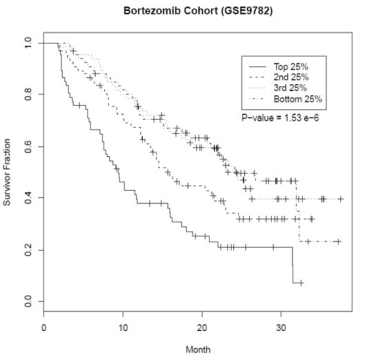
Fig. 1. Association between fluorescence in situ hybridization defect 17p13.1– and total number of copy number abnormalities (CNA); $P = 0.0057$ from Wilcoxon rank sum statistic.

Fig. 3. Association between genomic complexity, defined as the total number of copy number abnormalities and duration of response. Duration of response is defined as the time from first response until progression.

N.E. Kay et al. / Cancer Genetics and Cytogenetics 203 (2010) 161e168

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Genomic complexity and outcomes



Courtesy Wee Joo Chng

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ARTICLE

doi:10.1038/nature09837

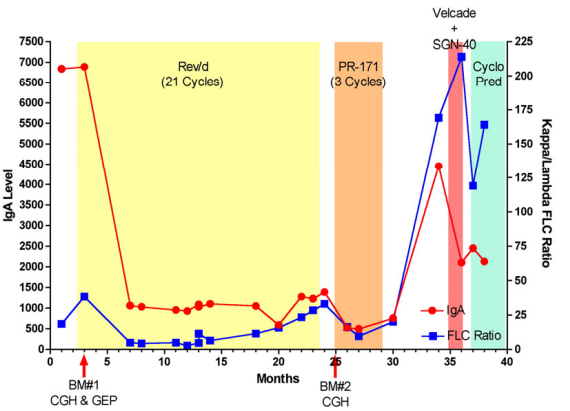
Initial genome sequencing and analysis of multiple myeloma

Michael A. Chapman[1†], Michael S. Lawrence[1], Jonathan J. Keats[2,3], Kristian Cibulskis[1], Carrie Sougnez[1], Anna C. Schinzel[4], Christina L. Harview[4], Jean-Philippe Brunet[4], Gregory J. Ahmann[2,5], Mazhar Adli[1,5], Kenneth C. Anderson[6,7], Kristin G. Ardlie[1], Daniel Auclair[3,6], Angela Baker[7], P. Leif Bergsagel[2,3], Bradley E. Bernstein[1,5,8,9], Yotam Drier[1,10], Rafael Fonseca[2,3], Stacey B. Gabriel[1], Craig C. Hofmeister[3,11], Sundar Jagannath[3,12], Andrzej J. Jakubowiak[3,13], Amrita Krishnan[3,14], Joan Levy[3,6], Ted Liefeld[1], Sagar Lonial[2,15], Scott Mahan[1], Bunmi Mfuko[2,6], Stefano Monti[1], Louise M. Perkins[3,6], Robb Onofrio[1], Trevor J. Pugh[1], S. Vincent Rajkumar[3,16], Alex H. Ramos[1], David S. Siegel[3,17], Andrey Sivachenko[1], A. Keith Stewart[2,3], Suzanne Trudel[3,18], Ravi Vij[2,19], Douglas Voet[1], Wendy Winckler[1], Todd Zimmerman[3,20], John Carpten[7], Jeff Trent[7], William C. Hahn[1,4,8], Levi A. Garraway[1,4], Matthew Meyerson[1,4,8], Eric S. Lander[1,8,21], Gad Getz[1] & Todd R. Golub[1,4,8,9]

Multiple myeloma is an incurable malignancy of plasma cells, and its pathogenesis is poorly understood. Here we report the massively parallel sequencing of 38 tumour genomes and their comparison to matched normal DNAs. Several new and unexpected oncogenic mechanisms were suggested by the pattern of somatic mutation across the data set. These include the mutation of genes involved in protein translation (seen in nearly half of the patients), genes involved in histone methylation, and genes involved in blood coagulation. In addition, a broader than anticipated role of NF-κB signalling was indicated by mutations in 11 members of the NF-κB pathway. Of potential immediate clinical relevance, activating mutations of the kinase BRAF were observed in 4% of patients, suggesting the evaluation of BRAF inhibitors in multiple myeloma clinical trials. These results indicate that cancer genome sequencing of large collections of samples will yield new insights into cancer not anticipated by existing knowledge.

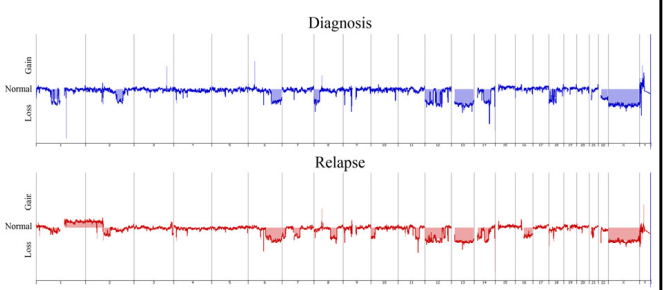
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Clinical Course - Case Report



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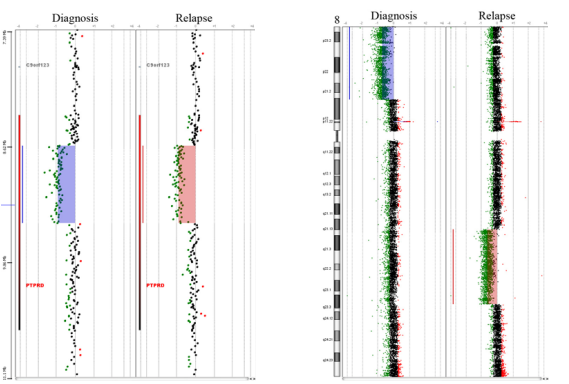
WGS Diagnostic and Relapse



A significant number of differences were detected (The most of any pair studied to date). However, it is possible to sort out the driver events, diagnostic passenger events, and events unique to the relapse sample that may mediate Rev/d resistance

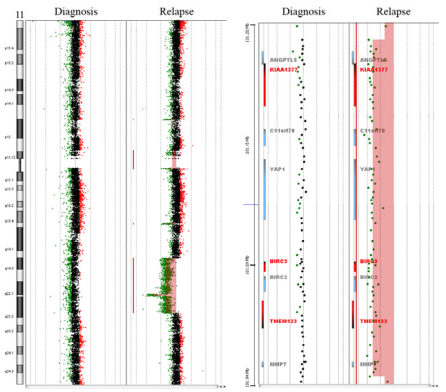
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Common and Unique CNA are Present in the Two Samples

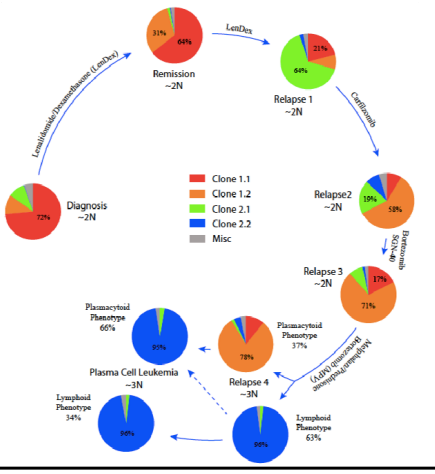


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Acquisition of BIRC2/3 Deletion



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Adding up all factors

- So how do we estimate prognosis?

$$I_x = \frac{4\cos^2\theta\,(\sin^2\theta - n^2)}{(1 - n^2)\,[(1 + n^2)\sin^2\theta - n^2]}$$

$$I_y = \frac{4\cos^2\theta}{1 - n^2}$$

$$I_z = \frac{4\cos^2\theta\sin^2\theta}{(1 - n^2)\,[(1 + n^2)\sin^2\theta - n^2]}$$

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The future

- More and more genetic testing will occur
- Results will come more as an interpretation
- Prices will come down
- Better treatments
- Better outcomes
- Cures!

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In AZ everything is possible!



Acknowledgements

Mayo Clinic
Keith Stewart
Leif Bergsagel
Marta Chesi
Phil Greipp
Robert Kyle
SV Rajkumar
Dysproteinemia Group
Joe Mikhael
Craig Reeder
Gordon Dewald
Syed Jalal
Rhett Ketterling

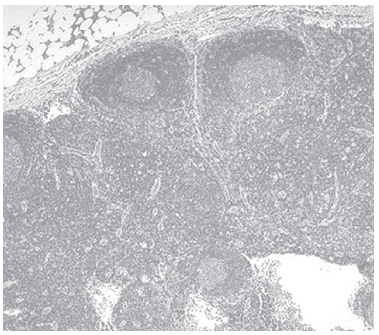
Mayo Clinic
Esteban Braggio
Travis Henry
Samar Issa
Angela Mayo
Jacy Spong

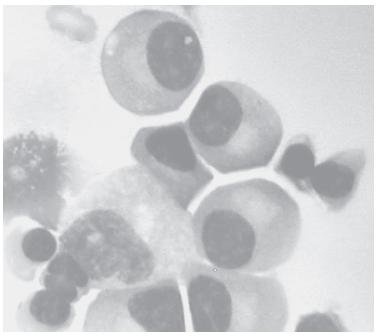
NUS
Wee Joo Chng

TGEN
Jeff Trent
John Carpten
Mike Barrett

Laboratory
Greg Ahmann
Scott Van Wier
Tammy Price-Troska
Rachel Hagerty
Kim Henderson
Laboratory

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Plasma cell leukemia: Should it be treated differently?

Joan Bladé, MD

Plasma Cell Leukemia:
Should it be treated differently?

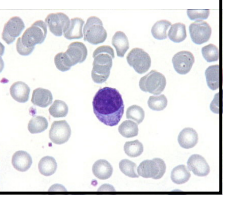
Joan Bladé
Carlos Fernández de Larrea

Department of Hematology
Hospital Clínic de Barcelona
New York, October 20th 2011

Plasma Cell Leukemia: Diagnostic Criteria

Diagnostic criteria

– More than 20% plasma cells in peripheral blood
and
– Absolute plasma cell count more than $2x10^9$/L



Kyle *et al.* Arch Intern Med 1974

Frequency of PCL

– 0.5 to 4%

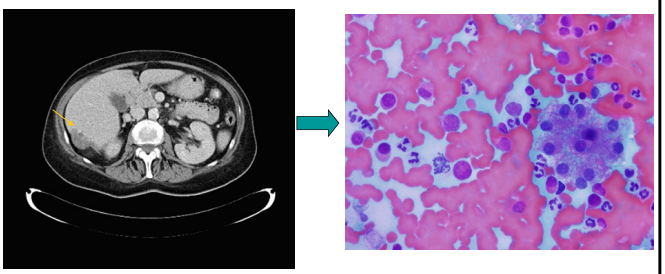
- Primary: 60%
- Secondary: 40%

Bladé & Kyle. Hematol Oncol Clin North Am 1999.
Ramsingh *et al.* Cancer 2009

Presenting Clinical Features (I)

	Noel and Kyle (1987)	Dimopoulos *et al* (1994)	Garcia-Sanz *et al* (1999)	Tiedemann *et al* (2008)	Colovic *et al* (2008)	Peijing *et al* (2009)	Pagano *et al* (2011)
Number of patients	25	27	26	41	30	22	73
Median age (years)	53	57	65	54.5	60	49.5	NA
Sex, M/F	15/10	NA	12/14	24/17	22/8	14/8	43/30
Lytic bone lesions (%)	44	NA	48	35	60	44.4	64
Extramedullary involvement (%)							
Liver	52	32	0	32	56	44.4	23
Spleen	44	18	0	18	53	33.3	18
Lymph nodes	12	6	11	6	3	NA	4
Other	NA	NA	NA	NA	NA	NA	14

Extramedullary involvement



Presenting Clinical features (II)

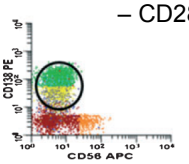
	Noel and Kyle (1987)	Dimopoulos *et al* (1994)	Garcia-Sanz *et al* (1999)	Tiedemann *et al* (2008)	Colovic *et al* (2008)	Peijing *et al* (2009)	Pagano *et al* (2011)
M-protein type (%)							
IgG	12.5	52	54	28	53	54.5	30
IgA	25	15	4	13	23	9.1	8
IgD	6	0	8	2	3	0	3
Light chain	44	28	31	41	20	27.3	30
Nonsecretory	12.5	7	4	8	0	9.1	18

Presenting Clinical features (III)

	Noel and Kyle (1987)	Dimopoulos et al (1994)	Garcia-Sanz et al (1999)	Tiedemann et al (2008)	Colovic et al (2008)	Peijing et al (2009)	Pagano et al (2011)
Hemoglobin <10 g/dL (%)	>50	82	54	>50	100	>50	48
Platetelet count < 100 x 109/L (%)	>50	67	48	>50	100	>50	NA
High β2-microglobulin (%)	NA	91	65	50	64	50	100
High LDH (%)	NA	63	48	50	37	NA	52
Response to treatment (%)	47	37	38	NA	NA	45.5	55
Median survival (months)	6.8	12	8	11.1	4.5	14	12.6

Plasma cell characteristics in PCL (I)
Immunophenotype

- Higher CD20, CD27
- Lower CD9, CD117, CD56, HLA-DR
- CD28: primary versus secondary PCL



García-Sanz *et al*. Blood 1999.
Pellat-Deceunynck *et al*. Cancer 1998
Guikema *et al*. Br J Haematol 2004

Plasma cell characteristics in PCL (II)
Cytogenetics

	Garcia-Sanz et al (1999)	Dimopoulos et al (1994)	Tiedemann et al (2008)	Pagano et al (2011)	Avet-Loiseau et al (2001)	Chiecchio et al (2009)
Hypodiploidy		41	60	12,2	47	41.6
Hyperdiplody			0	4.9	8.8	33.3
Complex karyotype		92	54.5	34.2	58.8	66.7
del(13q14) or monosomy	84	50	85	19	68	58
del(17p13)			50	7.3	11.8	25
t(11;14)			71	19.5	33	42
t(4;14)			0	0	12	8.3
t(14;16)			0	0	16	25

Plasma cell characteristics in PCL (III)
Molecular biology

	%
TP53 mutation	25
c-Myc Amplification	8
3'/myc breakapart	33
5'/myc breakapart	8
PTEN deletion	8
RAS mutation	27

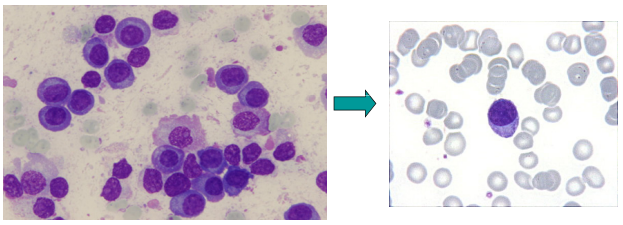
Tiedemann *et al*. Leukemia 2008

Plasma cell characteristics in PCL (IV)
Epigenetics

- p16 inactivation
- Global DNA hypomethylation
- Gene-specific DNA hypermethylation

Mateos *et al*. Haematol J 2001
Walker *et al*. Blood (ASH) 2010.

From Bone Marrow to Peripheral Blood

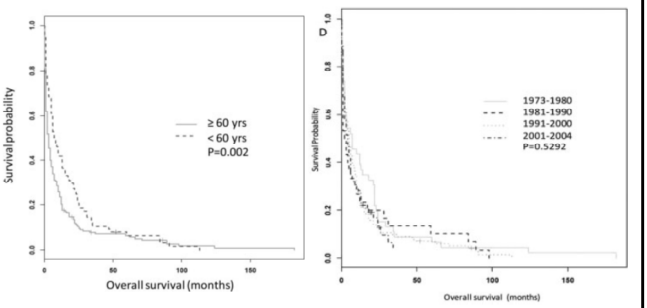


Potential Mechanisms of Extramedullary Spread

Mechanism	
Adhesion molecules	CD56, CD106, CD29, HLA-1, CD40, CD54, CD11a, CD18, CD11b, VLA-4
Chemokine receptors	CCR1, CCR2, CXCR4
Cytokines	IL-6, IL-3, IFN-α

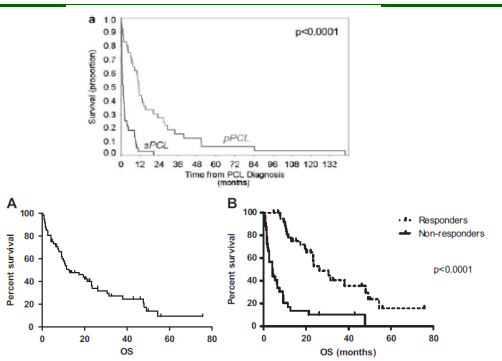
Pellat-Deceunynck *et al*. Leukemia 1998
Pérez-Andrés *et al*. Leukemia 2005
Zhan *et al*. Cancer 1992

Survival (I)



Ramsingh *et al*. Cancer 2009

Survival (II)



Tiedemann *et al*. Leukemia 2008
Pagano *et al*. Ann Oncol 2011

Response to Treatment (I)

Conventional drugs ⇨ Poor results

- Alkylating agent +/- glucocorticoids
  - Overall response rate: 23 to 67%
  - Median OS < 1 yr
- Polychemotherapy (VAD, VCMP, VBAP)
  - Slight improvement of response rate and OS
  - Quicker tumor mass reduction: ↓ early mortality

Bladé & Kyle. Hematol Oncol Clin North Am 1999.

Response to Treatment (II)
Novel drugs

- Thalidomide
  - Limited data with controversial results
- Lenalidomide
  - Better efficacy, but short duration
  - Potentially induces graft-versus-myeloma (SCT)
  - More useful in combination (MPR?)

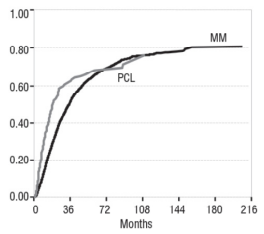
Johnston & Abdalla, Leuk Lymphoma 2002; Bauduer, Br J Haematol 2002; Petrucci MT *et al*, Leuk Lymphoma 2007; Ballanti *et al*, Nat Clin Pract Oncol 2007; Pretz & Medeiros, Am J Hematol 2009; Benson & Smith, Leuk Lymphoma 2007; Musto *et al*, Leuk Res 2008; Olivieri *et al*, Leuk Res 2009; Guglielmelli *et al*, J Oncol 2009

Response to Treatment (III)
Novel drugs

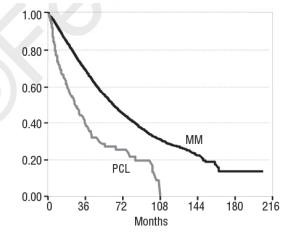
- Bortezomib
  - Promising results
  - 12 patients: response rate 92% (2 CR)
  - Median PFS and OS 8 and 12 months
  - Potential combinations (VTD, PAD or MPV)

Esparis-Ogando A *et al*. Int J Cancer 2005; Musto P *et al*. Cancer 2007; Libby E et al. Am J Hematol 2010; Al-Nawakil C et al. Leuk Lymphoma 2008; Katodritou E et al. Leuk Res 2008.

Response to Treatment (IV)
Autologous stem-cell transplantation



PFS



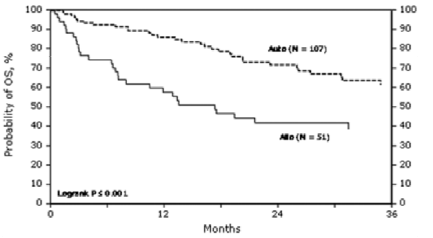
OS

Drake *et al* (EBMT registry). Haematologica 2010.

CLÍNIC Hospital Universitari

Response to Treatment (V)
Autologous vs. Allogeneic stem-cell transplantation

Survival after SCT in PCL



Mahindra *et al* (CIBMTR). Blood (ASH) 2009

CLÍNIC Hospital Universitari

Treatment Algorithm for Primary Plasma Cell Leukemia

Transplant candidate

Bortezomib-based induction (VTD, PAD)

Age ≤ 55 yrs and suitable donor

Yes → **Myeloablative Allo-SCT** (Cy/TBI)

>55 yrs → **ASCT** (Melphalan 200)

Suitable donor

Yes → **Allo-RIC** (Fludarabine/melphalan)

No → **Consolidation/maintenance**

Non-transplant candidate

Bortezomib-based induction (MPV)

Response ≥PR

Yes → **Maintenance** (VRD)

No → **Clinical trials Palliation**

CLÍNIC Hospital Universitari

Treatment Algorithm for Secondary Plasma Cell Leukemia

Fit patients

Bortezomib-based treatment (VTD, PAD)

Transplant candidate

Yes → **SCT**

No → **Maintenance**

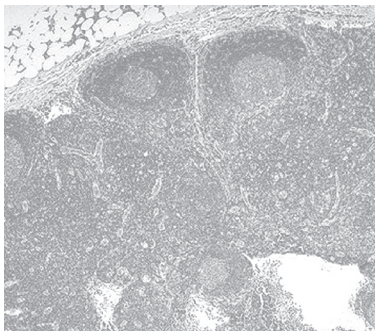
Unfit patients

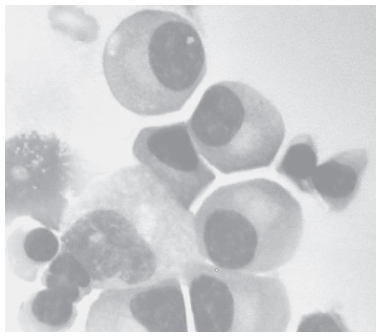
Palliation

CLÍNIC Hospital Universitari



Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





If and when should an allogeneic transplant be done?

Sergio A. Giralt, MD




Allogeneic Stem Cell Transplantation for Myeloma: Who? What? When? Whether?

Sergio A. Giralt, MD
Professor of Medicine
Weill Cornell College of Medicine
Chief, Adult Bone Marrow Transplant Service
Division of Hematologic Oncology
Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, New York

Tales of Two Cases

Case 1

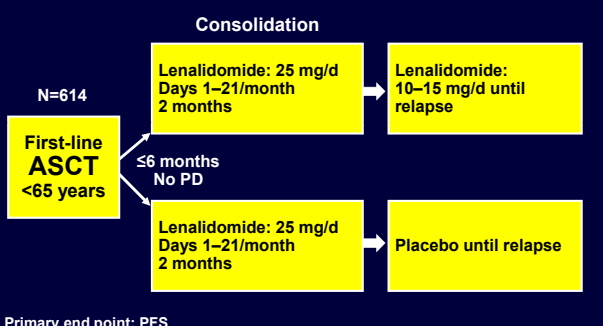
- 55-year-old female presents with asymptomatic anemia of 10 gm/dL and total serum protein 10 gm/L
- Workup reveals
  - 30% plasma cells
  - Cytogenetic diploid
  - IgA kappa peak of 3.2
  - β2M of 3.0
- Receives 4 cycles of Bz/Thal/Dex
- Followed by Auto SCT on day 60 documented stringent CR

Case 2

- 55-year-old female presents with asymptomatic anemia of 10 gm/dL and total serum protein 10 gm/L
- Workup reveals
  - 30% plasma cells
  - Cytogenetic t(4;14)
  - IgA kappa peak of 3.2
  - β2M of 3.0
- Receives 4 cycles of Bz/Thal/Dex
- Followed by Auto SCT on day 60 documented paraprotein peak of 0.4 g/dL

Where does the bar stand today?

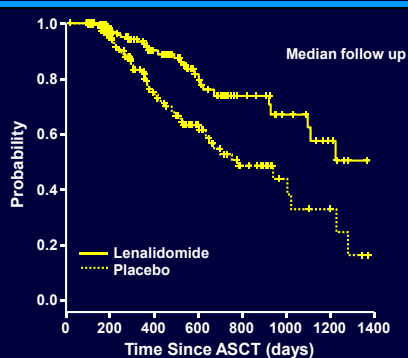
Phase 3 IFM 2005-02: Lenalidomide as Consolidation/Maintenance Post-ASCT



Primary end point: PFS

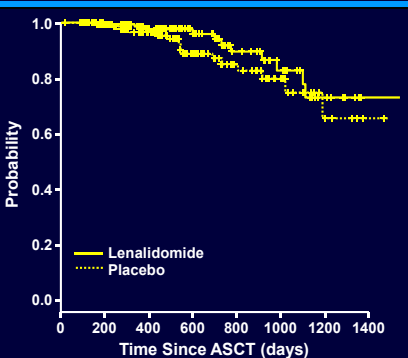
Attal M et al. *Blood*. 2009;114:Abstract 529.
Attal M et al. *J Clin Oncol*. 2010;28: Abstract 8018.

CALGB 100104: Time to Progression



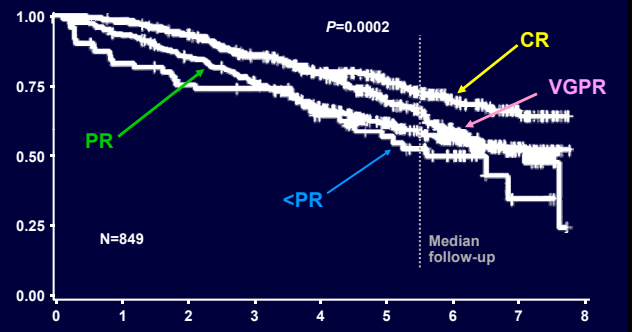
McCarthy PL et al. *J Clin Oncol*. 2010;28: Abstract 8017.

CALGB 100104: Overall Survival



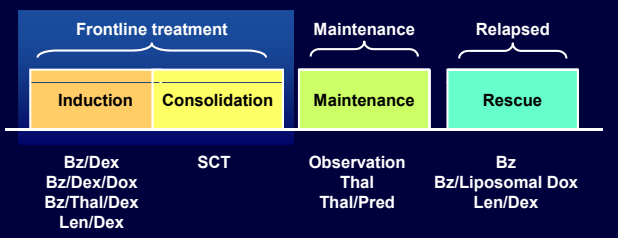
McCarthy PL et al. *J Clin Oncol*. 2010;28: Abstract 8017.

Impact of Response on Outcome: OS After 1 or 2 Transplants



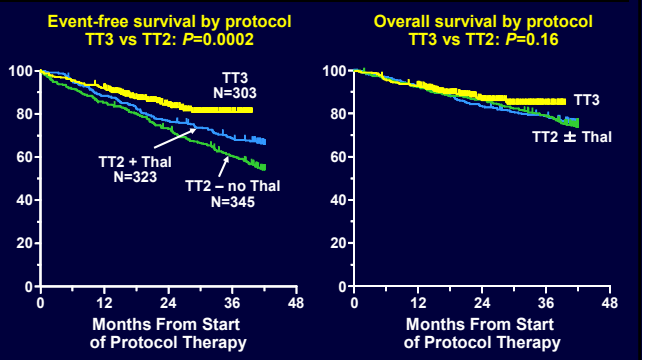
IFM 99 trials courtesy of JL Harousseau.
Harousseau JL et al. *Blood*. (ASH Annual Meeting Abstracts) 2006;108:3077.

Multiple Myeloma Treatment Lines in Transplant-Eligible Patients



National Comprehensive Cancer Network. The NCCN Clinical Practice Guidelines in Oncology Multiple Myeloma (Version 1.2011). http://www.nccn.org/. Accessed October 13, 2010.

Third Tandem Transplant Study (N=303): Projected Median Survival 10+ Years



Pineda-Roman M et al. *Br J Haematol*. 2008;140:625.

Newest Data Available for Allogeneic SCT

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

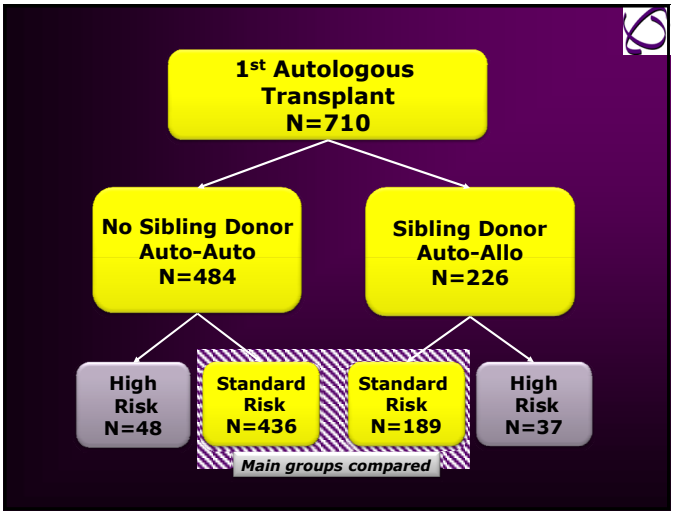
Tandem AutHCT with or without Maintenance Therapy (auto-auto) versus Single AuHCT Followed by HLA Matched Sibling Non-Myeloablative Allogeneic HCT (auto-allo) for Patients with Standard Risk Multiple Myeloma: Results from the BMT-CTN 0102 Trial

Amrita Krishnan, Marcelo Pasquini, Marian Ewell, Edward A. Stadtmauer, Edwin Alyea III, Joseph Antin, Raymond Comenzo, Stacey Goodman, Parameswaran Hari, Robert Negrin, Muzaffar Qazilbash, Scott Rowley, Firoozeh Sahebi, George Somlo, David Vesole, Dan Vogl, Daniel Weisdorf, Nancy Geller, Mary M. Horowitz, Sergio Giralt, David Maloney

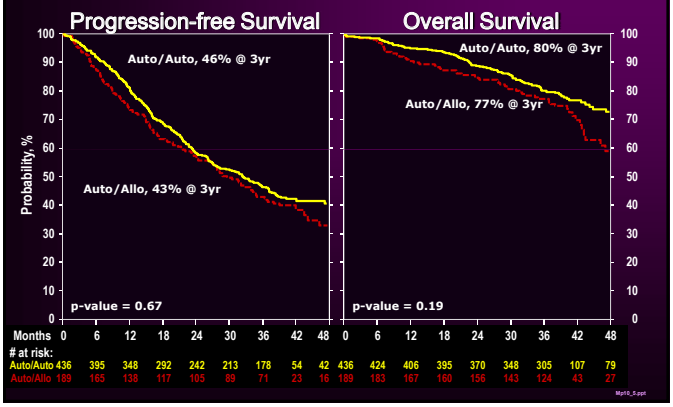
On behalf of the Blood and Marrow Transplant Clinical Trials Network

National Heart Lung and Blood Institute
People Science Health

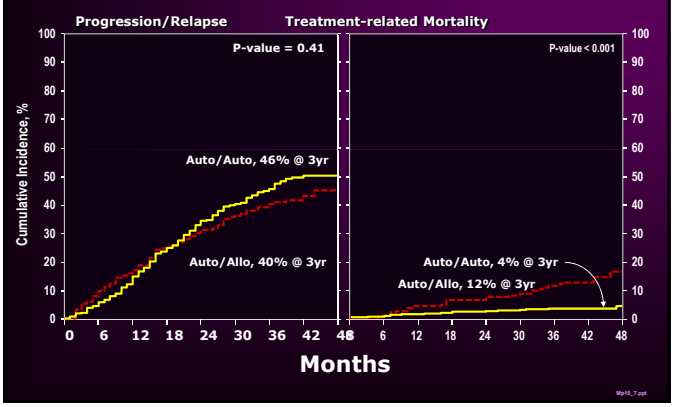
National Cancer Institute



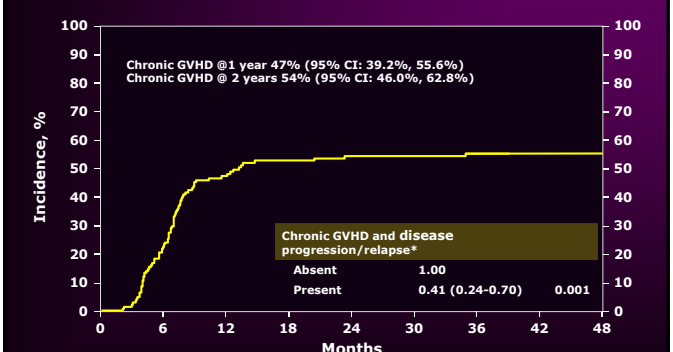
Survival Outcomes after the First Transplant: Auto-Auto vs. Auto-Allo: Intent-to-treat analysis



Cumulative Incidence of Disease Progression/Relapse and Treatment-Related Mortality after First Transplant

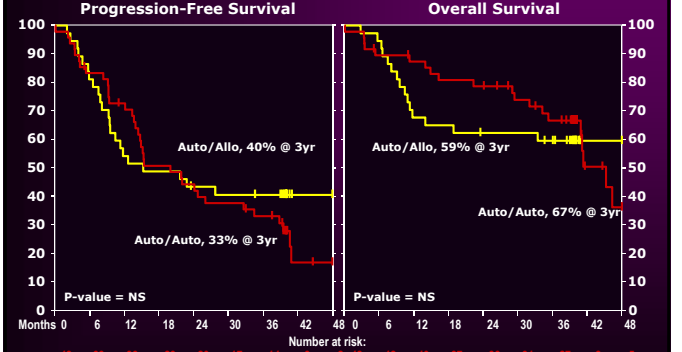


Cumulative Incidence of Chronic GVHD after Allogeneic Transplant

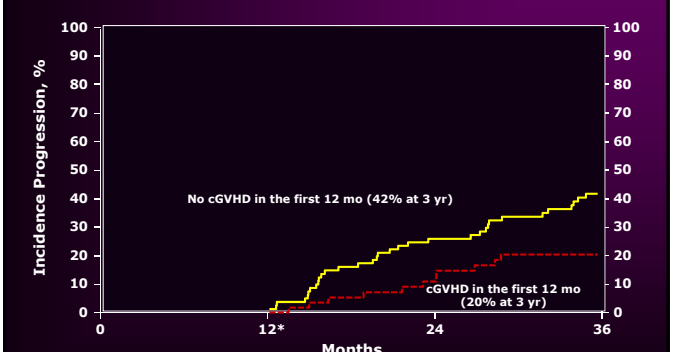


* Chronic GVHD treated as time-dependent covariate and adjusted for disease status at transplant.

Survival Outcomes after the First Transplant: Auto-Auto vs. Auto-Allo: Intention-to-treat analysis

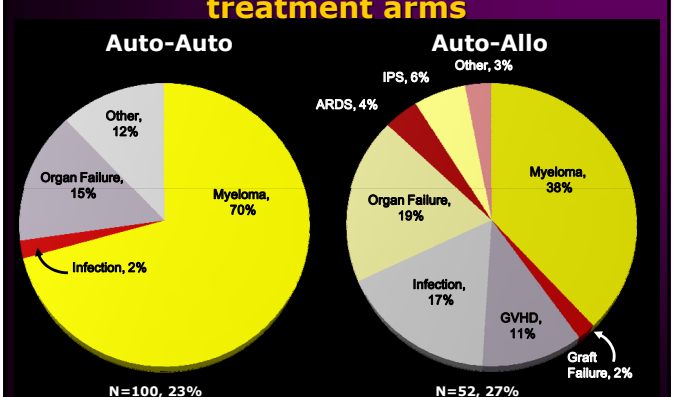


Impact of Chronic GVHD on Disease Progression/Relapse: Patients with Standard Risk Disease

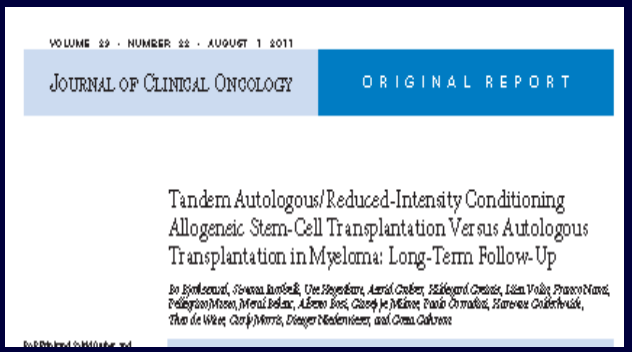


*Landmark analysis at 12 months after the allogeneic transplant.

Causes of death according to treatment arms



The Positive View



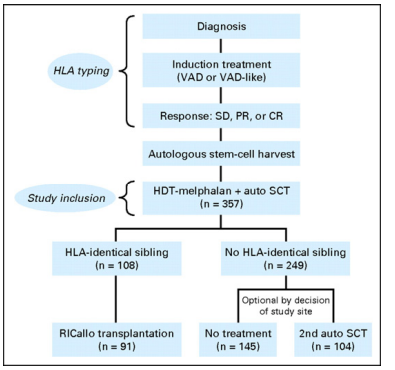
VOLUME 29 · NUMBER 22 · AUGUST 1 2011

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Tandem Autologous/Reduced-Intensity Conditioning Allogeneic Stem-Cell Transplantation Versus Autologous Transplantation in Myeloma: Long-Term Follow-Up

Bo Björkstrand, Sverra Ljungman, Ute Hegenbart, Astrid Gahrton, Hildegard Greinix, Lilian Volin, Franco Narni, Pellegrino Musto, Meral Beksac, Alberto Bosi, Claes Ljungman, Paolo Corradini, Harewen Gahrton, Theo de Witte, Carlo Morris, Dieuwer Niederwieser, and Gema Cabrera

Design of the trial.

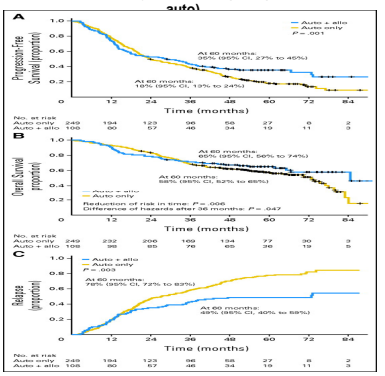


Björkstrand B et al. JCO 2011;29:3016-3022

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JOURNAL OF CLINICAL ONCOLOGY

Intention-to-treat comparison of the two study arms (auto [autologous stem-cell transplantation] + allo [reduced-intensity conditioning allogeneic stem-cell transplantation] v auto)

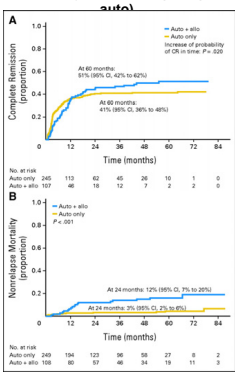


Björkstrand B et al. JCO 2011;29:3016-3022

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JOURNAL OF CLINICAL ONCOLOGY

Intention-to-treat comparison of the two study arms (auto [autologous stem-cell transplantation] + allo [reduced-intensity conditioning allogeneic stem-cell transplantation] v auto)

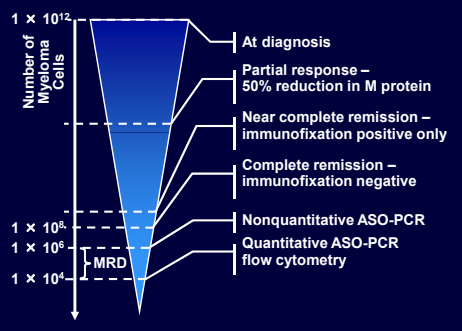


Björkstrand B et al. JCO 2011;29:3016-3022

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JOURNAL OF CLINICAL ONCOLOGY

CR Definition Does Matter With Regards to Depth of Remission



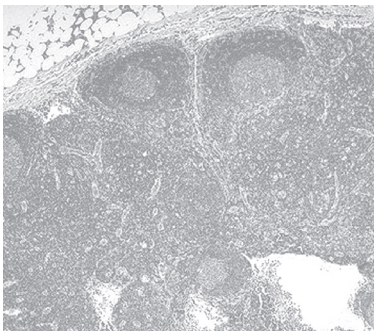
Rate of molecular CR with HDT is 5%

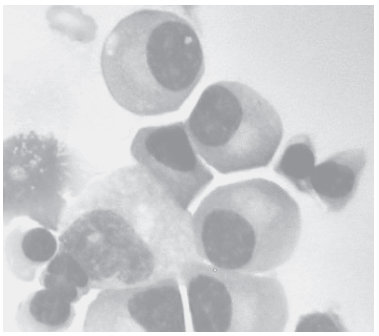
Source TBD.

Summary

- **Current results with both autologous and allogeneic stem cell transplantation justify the following patterns of care:**
  - **In standard practice allogeneic stem cell transplantation can be offered to patients with high risk disease, or younger patients with standard risk disease highly motivated and well informed.**
  - **Allogeneic stem cell transplantation as consolidation of a 1st remission should preferentially be performed under the auspices of a clinical trial.**
  - **Autologous stem cell transplantation remains the most reasonable consolidative therapy for myeloma patients today.**

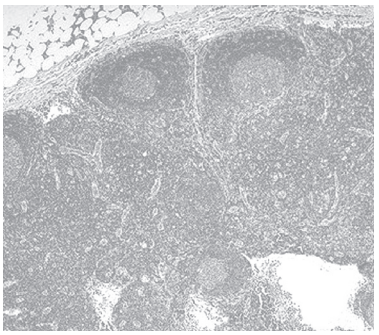
Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies

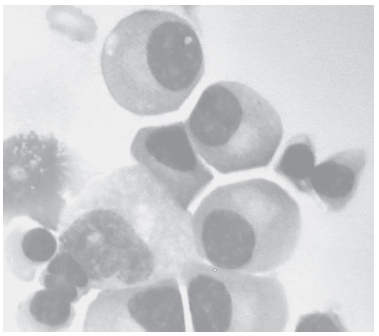




"Consensus" on the standards of treatment in the 21st century: How should we treat transplant-eligible, transplant-ineligible, and relapsed patients

Brian G. M. Durie, MD





Debate: Is maintenance therapy necessary?

Yes: Antonio Palambo, MD

Is maintenance therapy necessary?

YES …

Antonio Palumbo, MD

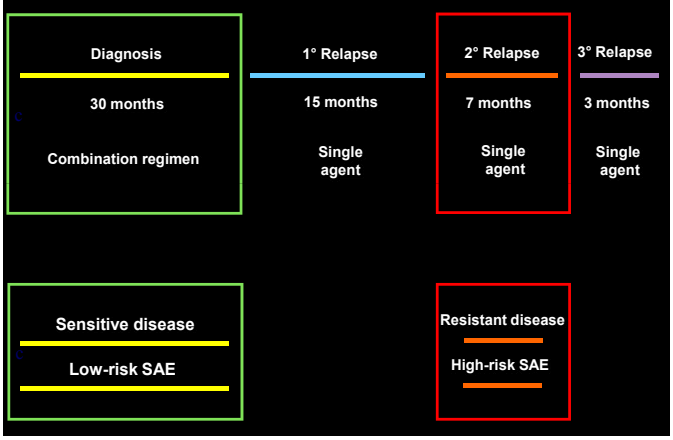
University of Torino, Torino, I, EU

EMN Trialist Group

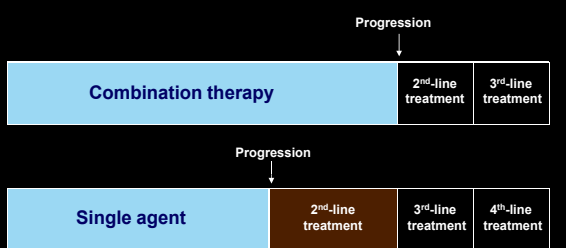
11.30am25m

Treatment strategies

Sensitive vs Resistant Disease

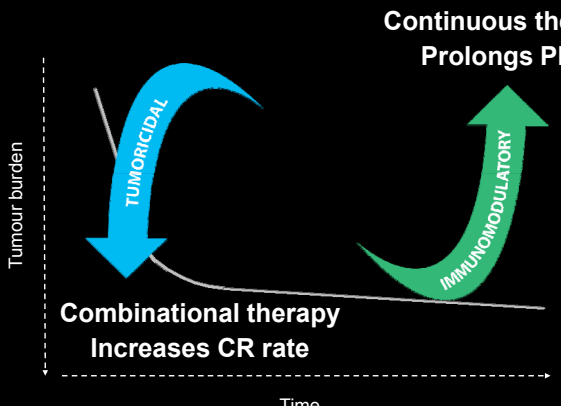


Combination Therapy vs Single Agent



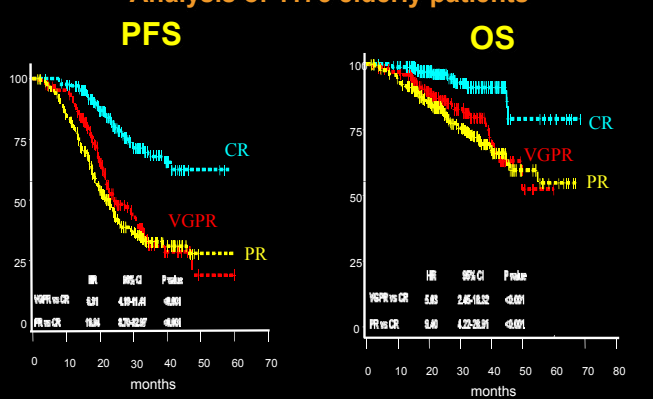
- Combination could improve PFS only
  - quality of life
- Combination could improve OS
  - evidence needed

Treatment strategy



CR predicts long term outcome

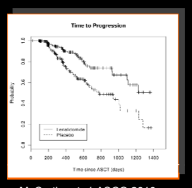
Analysis of 1175 elderly patients



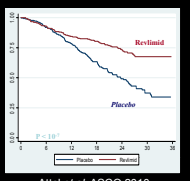
Gay F et al. Blood. 2011

Outcome and continuous treatment

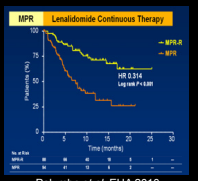
Lenalidomide maintenance



McCarthy *et al.* ASCO 2010

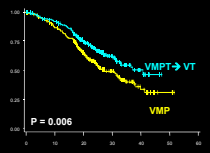


Attal *et al.* ASCO 2010

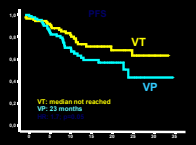


Palumbo *et al.* EHA 2010

Bortezomib maintenance



Palumbo *et al.* J Clin Oncol 2010

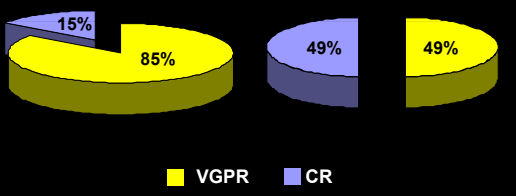


Mateos *et al.* Lancet Oncol 2010

Clinical Impact of VTD Consolidation in VGPR Patients After ASCT

Responses after ASCT
VGPR 85%
CR 15%

Responses after VTD
VGPR 49%
CR 49%



Ladetto M, et al. J Clin Oncol. 2010;28:2077-2084.

Complete Response are all the same?

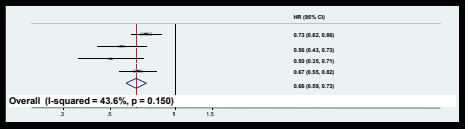
Response Criteria	Tumor gene copy number
Diagnosis	25,000 - 500,000
PR	5,000 – 100,000
VGPR	1,500 – 20,000
Immunofixation-negative CR	1,000 – 10,000
Immunophenotypic CR*	10 – 100
Molecular CR^	5 – 20

**Paiva et al Blood 2009: 114;4369-72; ^Ladetto et al. J Clin Oncol . 2010;28(12):2077-84*

Thalidomide Maintenance

Thalidomide maintenance
Discontinuation and treatment duration

Progression free survival



Overall survival



Discontinuation rate[1-4]	33-47%
Median duration of treatment[1,3,5]	7-14 months

PFS, progression free survival; OS, overall survival

1 Attal et al *Blood* 2006; 2 Spencer et al *J Clin Oncol* 2009; 3 Stewart et al *Clin Cancer Res* 2004; 4 Lokhorst et al *Blood* 2010; 5 Morgan et al. ASH 2010.6 Barlogie et al *N Eng J Med* 2006

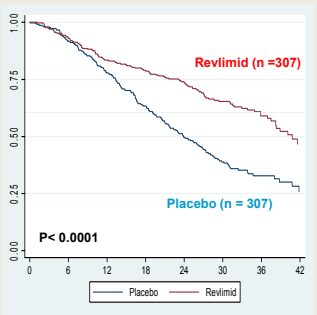
Lenalidomide maintenance

IFM experience

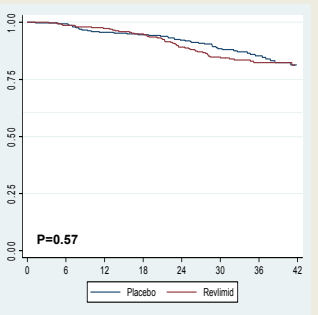
IFM: lenalidomide maintenance

Median follow up: 34 months post randomization, 44 months post diagnosis

PFS from randomization



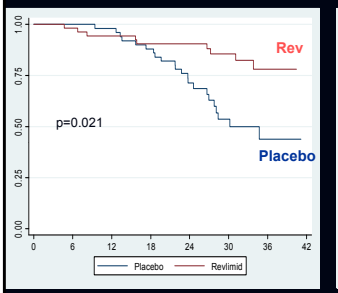
OS from randomization



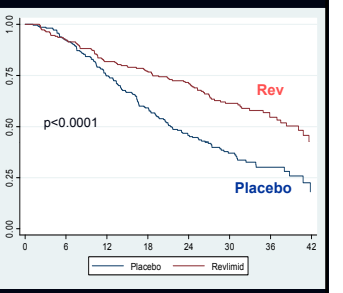
Attal et al. ASH 2010

PFS according to Response Post-Consolidation

CR



Not in CR



HR= 0.31 - CI 95% [0.14-0.68]

HR= 0.50- CI 95% [0.38-0.65]

Attal et al. ASH 2010

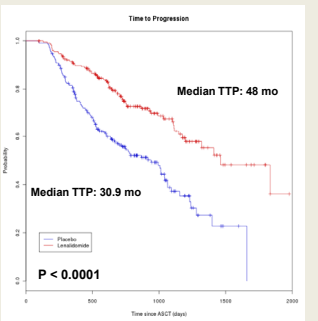
Lenalidomide maintenance

CALGB experience

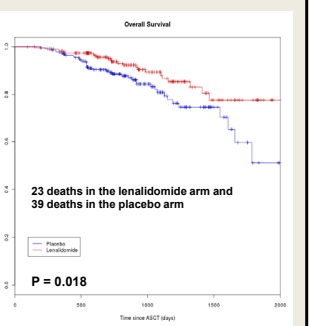
CALGB: lenalidomide maintenance

ITT analysis with median follow-up of 28 months

Time to Progression



Overall Survival



McCarthy et al. IMW 2011

ITT, intention to treat

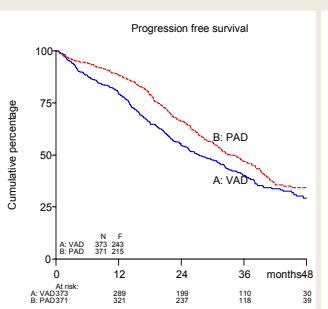
Bortezomib maintenance

HOVON experience

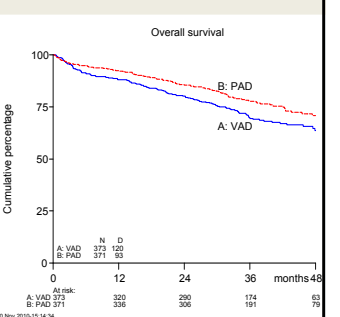
PAD-Vel vs VAD-Thal

HOVON: PAD-Vel vs VAD-Thal

Progression-free survival



Overall survival



HR = 0.79 (0.66-0.95), P=0.01

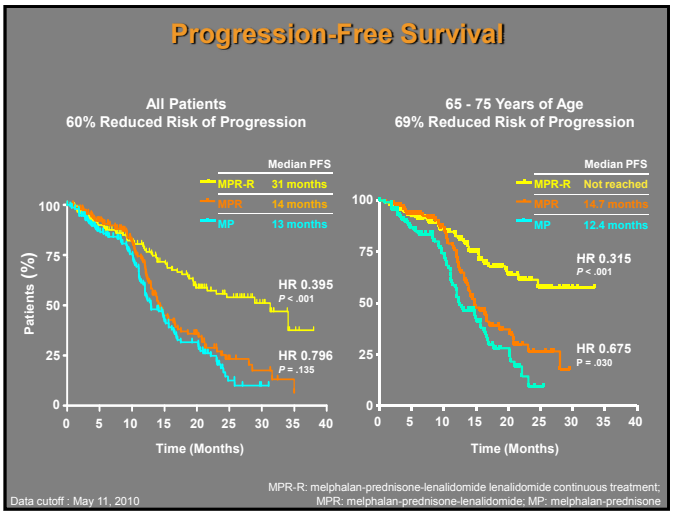
HR = 0.73 (0.56-0.96), P=0.02

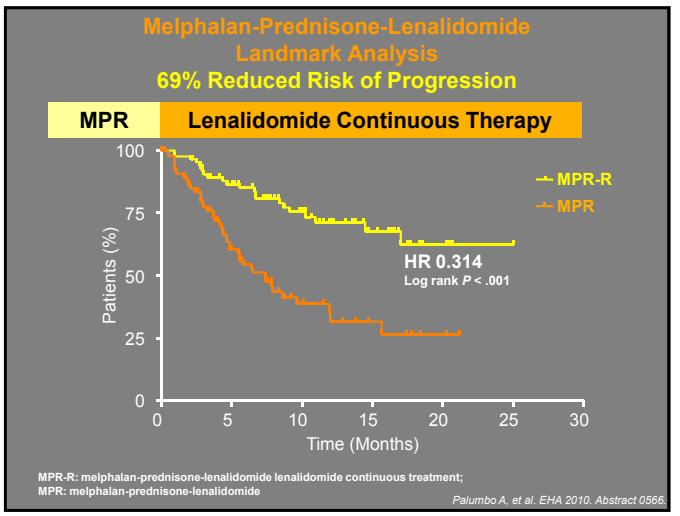
Sonneveld et al. ASH 2010 (Abstract 344)

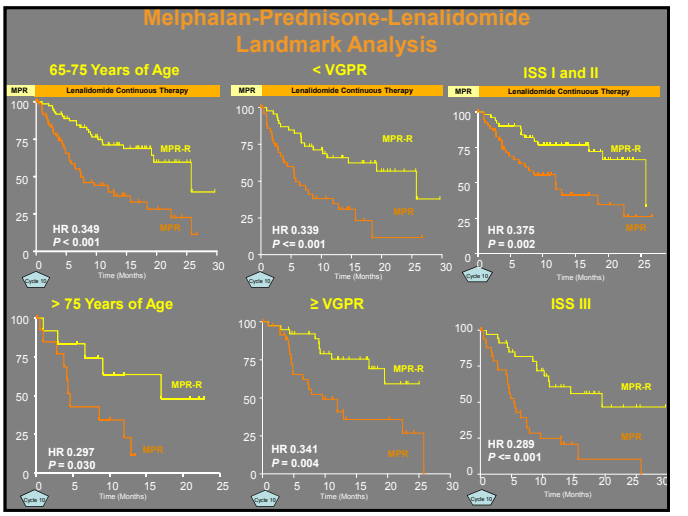
Lenalidomide maintenance

MM015

MPR-R vs MPR vs MP



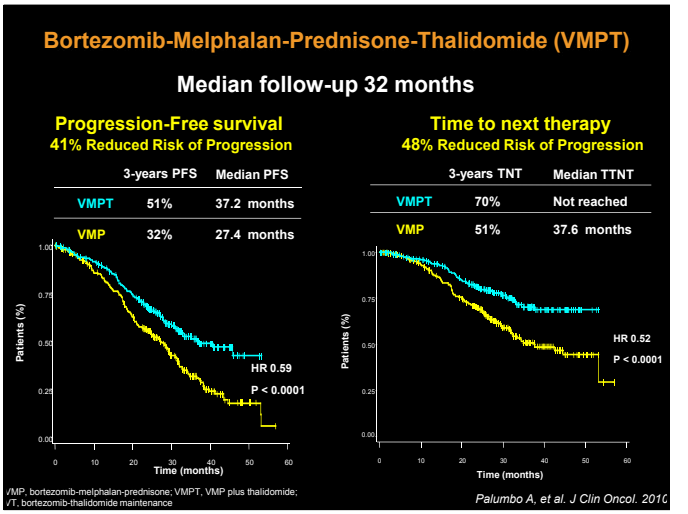




Bortezomib maintenance

GIMEMA experience

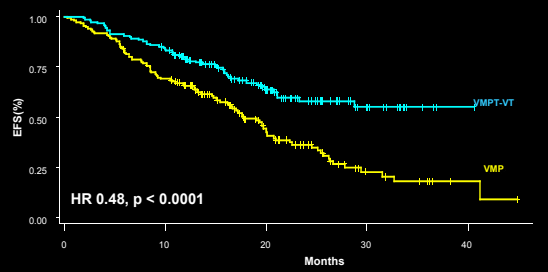
VMPT-VT vs VMP



Landmark Analysis
52% Reduced Risk of Progression

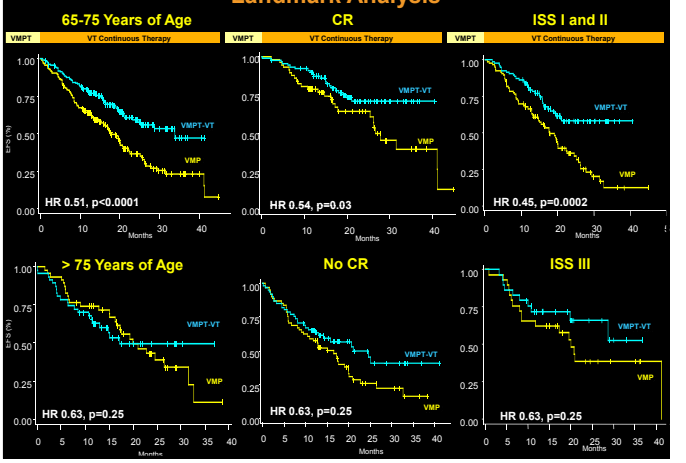
Median maintenance duration: 18 months

VMPT	VT Continuous Therapy



VMPT; bortezomib-melphalan-prednisone-thalidomide; VT, bortezomib-thalidomide maintenance; EFS, event free survival; HR, hazard ration

VMPT-VT
Landmark Analysis



Safety

Thalidomide maintenance
Discontinuation and treatment duration

Discontinuation rate[1-4]	33-47%
Median duration of treatment[1,3]	7-14 months

PFS, progression free survival; OS, overall survival

1 Attal et al *Blood* 2006; 2 Spencer et al *J Clin Oncol* 2009; 3 Stewart et al *Clin Cancer Res* 2004; 4 Lohhorst et al *Blood* 2010,

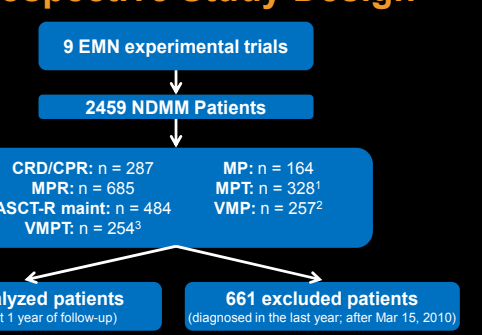
Lenalidomide and bortezomib maintenance
Toxicities

Grade 3-4	LENALIDOMIDE MAINTENANCE			BORTEZOMIB MAINTENANCE
	IFM[1] (%)	CALGB[2] (%)	MM015[3] (%)	VMPT-VT[4] (%)
Neutropenia	43	43	5*	38
Thrombocitopenia	12	13	3*	22
Infections	10	16	3	13
DVT	2	1	2	5
PN	0.7	NA	0	8
Fatigue	1	5	2	6
Rash	6	4	1	4

DVT, deep vein thrombosis; PN, peripheral neuropathy; NA, not available; VT, bortezomib plus thalidomide; *Grade 3 only

1 Attal et al. ASH 2010; 2 McCarthy et al. IMW 2011; 3 Palumbo et al. ASH 2010; 4 Palumbo et al. J Clin Oncol 2010

Retrospective Study Design

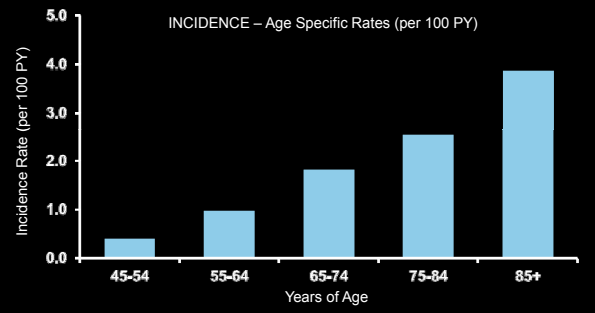


• Times of observation were censored on Mar 15, 2011

ASCT-R, autologous stem cell transplantation followed by lenalidomide maintenance; CRD, cyclophosphamide, lenalidomide, dexamethasone; CPR, cyclophosphamide, prednisone, lenalidomide; EMN, European Myeloma Network; MP, melphalan, prednisone; MPR, melphalan, prednisone, lenalidomide; MPT, melphalan, prednisone, thalidomide; NDMM, newly diagnosed multiple myeloma; SPM, second primary malignancy; VMP, bortezomib, melphalan prednisone; VMPT, bortezomib, melphalan, prednisone, thalidomide.

1. Palumbo A, et al. *Blood.* 2008;112:3107-3114.
2. Palumbo A, et al. *J Clin Oncol.* 2010;28:5101-5109.
Gay F, et al. *Eur J Haematol.* 2010;85:200-208.
www.clinicaltrials.gov.

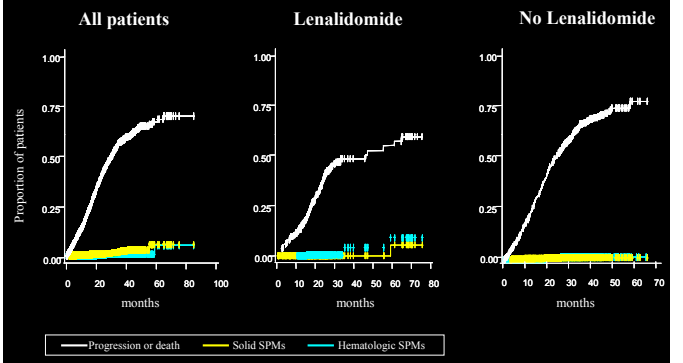
Incidence of Second Primary Malignancies in Normal Population



PY, person-year.

Piedmont Cancer Registry, Italy, City of Turin, 2005-2007.

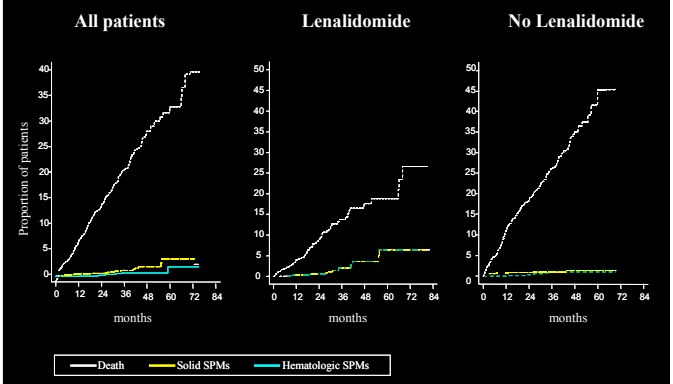
Second Primary Malignancies and MM Progression Risk



MM, multiple myeloma; SPM, second primary malignancy.

Palumbo et al, IMW 2011

Second Primary Malignancies and MM Death Risk



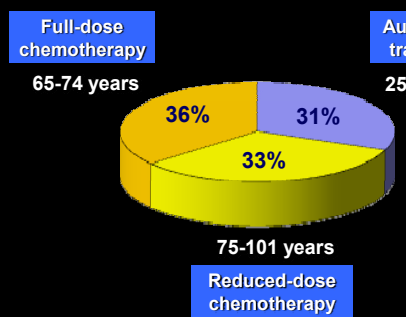
MM, multiple myeloma; SPM, second primary malignancy.

Palumbo et al, IMW 2011

Frail patients

Age-Adjusted Therapy

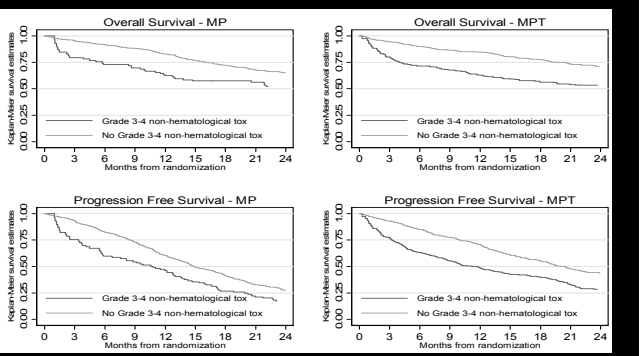
INCIDENCE: 2002 8.9/100.000



Regione Piemonte, Assessorato Sanità 2006

Impact of AEs on outcome

Safety meta-analysis of 6 MPT trials[1]



MPT, melphalan-prednisone-thalidomide; AE, adverse event

1 Fayers P et al Blood 2011, in press

Frail patients: treatment algorithm

RISK FACTORS
- Age over 75 years
- Mild, moderate or severe frailty: help needed for housholds and personal care
- Comorbidities and organ dysfunction Cardiac Pulmonary Hepatic Renal

Go-go ***moderate-go*** ***slow-go***

DOSE LEVEL 0	DOSE LEVEL – 1	DOSE LEVEL – 2
No risk factors	At least one risk factor	At least one risk factor + any G 3-4 non hematologic AE

Palumbo personal communication

Frail patients: treatment algorithm

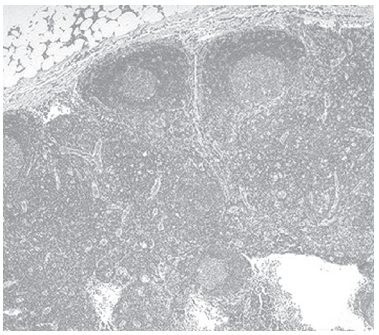
Dose reductions

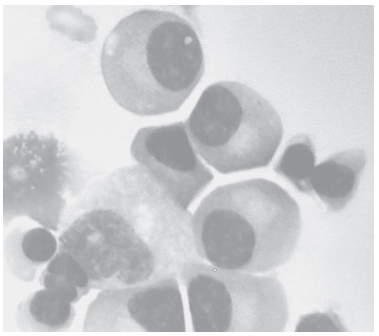
Agent	Dose level 0	Dose level – 1	Dose level – 2
Bortezomib	1.3 mg/m^2 twice / wk d 1,4,8,11 / 3 wks	1.3 mg/m^2 once / wk d 1,8,15,22 / 5 wks	1.0 mg/m^2 once / wk d 1,8,15,22 / 5 wks
Thalidomide	100 mg/d	50 mg/d	50 mg qod
Lenalidomide	25 mg/d d 1-21 / 4 wks	15 mg/d d 1-21 / 4 wks	10 mg/d d 1-21 / 4 wks
Dexamethasone	40 mg/d d 1,8,15,22 / 4 wk	20 mg/d d 1,8,15,22 / 4 wk	10 mg/d d 1,8,15,22 / 4 wk
Melphalan	0.25 mg/kg d 1-4 / 4-6 wks	0.18 mg/kg d 1-4 / 4-6 wks	0.13 mg/kg d 1-4 / 4-6 wks
Prednisone	50 mg qod	25 mg qod	12.5 mg qod
Cyclophosphamide	100 mg/d d 1-21 / 4 wks	50 mg/d d 1-21 / 4 wks	50 mg qod d 1-21 / 4 wks

Wk, week; d, day; qod, every other day

Palumbo & Anderson, New Engl J Med 2011

Conclusions





Debate: Is maintenance therapy necessary?

No: David Vesole, MD

Is Maintenance Therapy Necessary?

NO!!!

David H. Vesole, MD, PhD
Co-Director, Myeloma Division
Director, Myeloma Research
John Theurer Cancer Center
Hackensack University Medical Center

John Theurer Cancer Center at Hackensack University Medical Center
Providing Extraordinary Care



Disclosures

- Advisory Boards: Celgene, Onyx
- Speakers Bureaus: Celgene, Millennium

Why Maintenance Therapy?

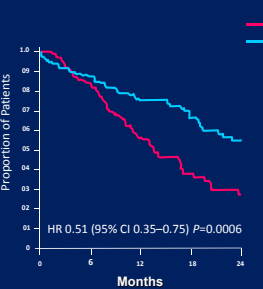
Can maintenance therapy:

- prevent or delay disease progression?
- convert partial responses to complete responses?
- improve overall survival?

Induction Therapy: Non-Transplant Candidates Melphalan, Prednisone, Thalidomide (MPT)*

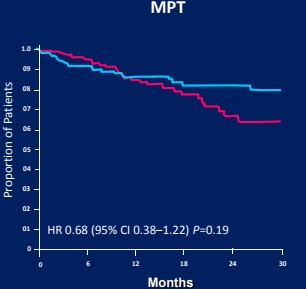
EFS

49% ↓ in risk of event for MPT



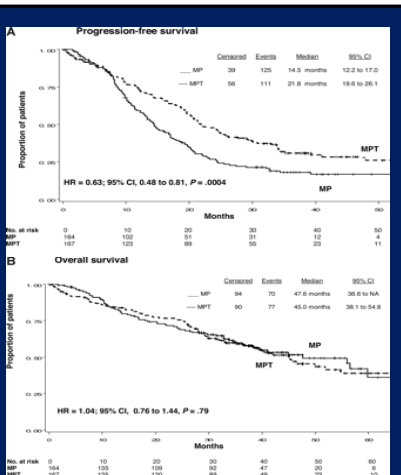
OS

65% ↓ in risk of death at >9 mo for MPT



*Thalidomide continued until relapse

Palumbo et al. *Lancet* 2006;367:825



Palumbo, A. et al. Blood 2008;112:3107-3114

MPT vs MP: The Meta-Analysis Controversy

Kapoor et al Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant ineligible patients with multiple myeloma: a meta-analysis. Leukemia 2011;25:689-96.

- The pooled odds ratio of responding to therapy with MPT vs MP was 3.39 (P<0.001). The pooled hazard ratios for PFS and OS were and 0.68 (P<0.001) and 0.80 (P=0.07), respectively, in favor of MPT.
- "Our meta-analysis demonstrates that in previously untreated, transplant ineligible, elderly myeloma patients, the addition of T to MP results in significantly improved RR and PFS with a trend towards improvement in OS compared with MP alone, but at a cost of significantly greater toxicity."

Favors et al Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. Blood 2011;118:1239-47

- The thalidomide regimen was associated with superior PFS (HR= 0.68, P < .0001). There was a highly significant benefit to OS from adding thalidomide to MP (HR = 0.83; P = .004), representing increased median OS time of 6.6 months, from 32.7 months (MP) to 39.3 months (MPT).
- "We conclude that thalidomide added to MP improves OS and PFS in previously untreated elderly patients with multiple myeloma, extending the median survival time by on average 20%."

MM-015: Study Design

N = 459, 82 centers in Europe, Australia, and Israel

Double-Blind Treatment Phase | Open-Label Extension Phase

Cycles (28-day) 1-9 | Cycles 10+

RANDOMIZATION

- MPR-R: M: 0.18 mg/kg, days 1-4; P: 2 mg/kg, days 1-4; R: 10 mg/day po, days 1-21 → Maintenance: Lenalidomide 10 mg/day days 1-21
- MPR: M: 0.18 mg/kg, days 1-4; P: 2 mg/kg, days 1-4; R: 10 mg/day po, days 1-21 → Placebo
- MP: M: 0.18 mg/kg, days 1-4; P: 2 mg/kg, days 1-4; PBO: days 1-21 → Placebo

Disease Progression → Lenalidomide (25 mg/day) +/- Dexamethasone

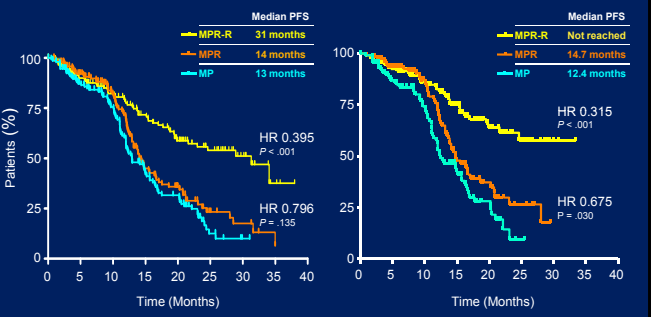
- Stratified by age (≤ 75 vs > 75 years) and stage (ISS I/II vs III)
- Primary comparison: MPR-R vs MP

ISS, International Staging System; MP, melphalan, prednisone; MPR, melphalan, prednisone, lenalidomide; MPR-R, melphalan, prednisone, lenalidomide with lenalidomide maintenance; PBO, placebo.

MM015: Progression-Free Survival

All Patients
60% Reduced Risk of Progression

65 - 75 Years of Age
69% Reduced Risk of Progression



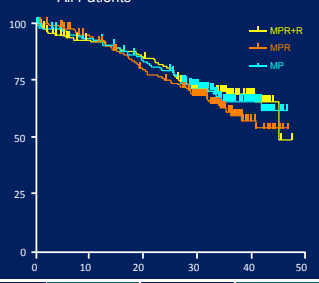
Data cutoff : May 11, 2010

8

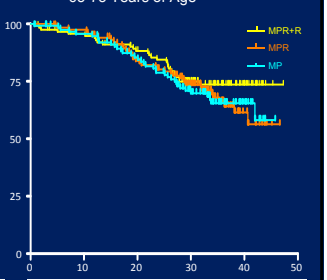
MM-015: Overall Survival

(ITT Population)

All Patients



65-75 Years of Age



	MPR-R (N = 152)	MPR (N = 153)	MP (N = 154)
Comparison	MPR-R vs. MPR	MPR vs. MP	MPR-R vs. MP
P value	0.254	0.378	0.806
HR [95% CI]	0.791 [0.528 – 1.185]	1.195 [0.804 – 1.778]	0.949 [0.626 – 1.439]

	MPR-R (N = 116)	MPR (N = 116)	MP (N = 116)
	MPR-R vs. MPR	MPR vs. MP	MPR-R vs. MP
	0.267	0.952	0.254
	0.758 [0.464 – 1.239]	0.986 [0.623 – 1.560]	0.751 [0.458 – 1.231]

Data cutoff : February 28, 2011

Lenalidomide + Low- or High-Dose Dex
ECOG E4A03

Newly Diagnosed Multiple Myeloma N = 445

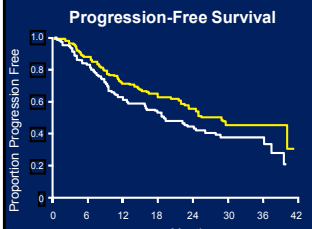
- Lenalidomide High-Dose Dexamethasone (LD) → SCT or Continue Off Study
- Lenalidomide Low-Dose Dexamethasone (Ld) → Continue On Study

Primary Endpoint Response at 4 months

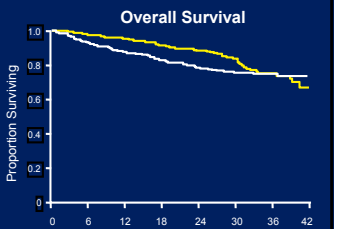
Lenalidomide: 25 mg daily, days 1-21 in a 28-day cycle
High-dose Dex: 40 mg, d1-4, 9-12, 17-20 (total 480 mg)
Low-dose Dex: 40 mg, d1, 8, 15, 22 (total 160 mg)
Aspirin:

ECOG E4A03, Phase III

Progression-Free Survival



Overall Survival



High dose
Low dose

Median follow-up: 35.8 months
Median PFS: 19.1 months RD; 25.3 months Rd; *P* = 0.026
Median OS: Not reached

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(11):29-37.

IFM 2005-02 trial

Lenalidomide Maintenance after Autologous Transplantation for Myeloma: Final analysis of a prospective randomized study of the Intergroupe Francophone du Myélome

CALGB 100104

Phase III Randomized, Double-Blind Study of Maintenance Therapy With Lenalidomide (CC 5013) or Placebo Following Autologous Stem Cell Transplantation for Multiple Myeloma

IFM 2005-02: Study design

Phase III randomized, placebo-controlled trial
N= 614 patients, from 78 centers, enrolled between 7/2006 and 8/2008

Patients < 65 years, with non-progressive disease, ≤ 6 months after ASCT in first line

Randomization: stratified according to Beta-2m, del13, VGPR

Consolidation:
Lenalidomide alone 25 mg/day p.o.
days 1-21 of every 28 days for 2 months

Arm A=	Arm B=
Placebo	Lenalidomide
(N=307)	(N=307)
until relapse	10-15 mg/d until relapse

Primary end-point: PFS.
Secondary end-points: CR rate, TTP, OS, feasibility of long-term lenalidomide….

ASCT = autologous stem cell transplant. IFM = Intergroupe Francophone du Myelome.

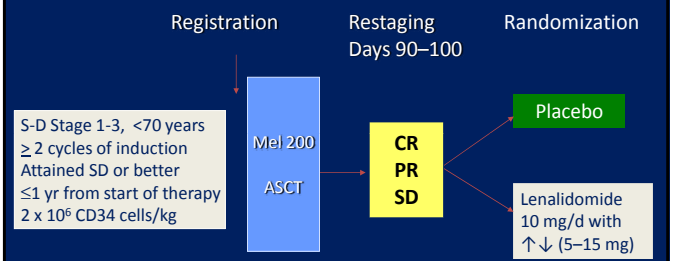
IFM 2005-02 : PFS (April 2011)

	Arm A N = 307	Arm B N = 307	P
Progression or Death	192	120	
Median PFS post rando (m)	24	41	
4-year post diag PFS (or 3-year post rando)	34%	61%	
Hazard Ratio	1	0.5	$< 10^{-9}$

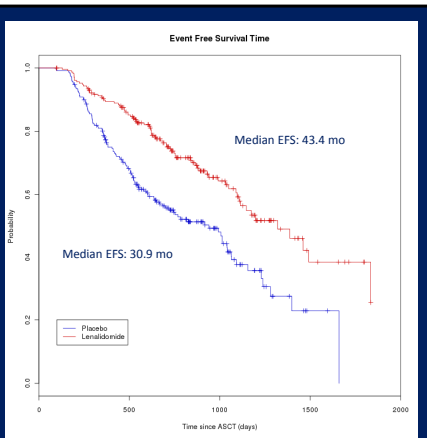
IFM 2005-02 : OS (April 2011)

	Placebo N=307	Len N=307	p
Death	53	57	
5-year post diag OS (or 4-year post Rando)	73%	79%	
Hazard Ratio	1	1.05 (0.7-1.5)	0.8

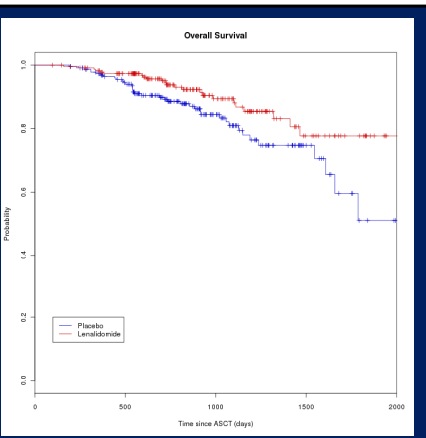
CALGB 100104 Schema



Stratification based on diagnostic β-2M and thalidomide and lenalidomide use during Induction



CALGB 100104, follow up to 04/17/2011



CALGB 100104, follow up to 04/17/2011

Overall Survival Results

- OS was a secondary endpoint of this study
- OS was calculated from day 0 of ASCT
- As of 12/17/2009, when the study was un-blinded, of 231 lenalidomide patients, there were 13 deaths and of 229 placebo patients, there were 24 deaths (p = 0.05)
- The HR is 0.51 (95% CI = 0.26 to 1.014)
- As of 04/17/2011, there were 23 deaths in the lenalidomide arm and 39 deaths in the placebo arm (p = 0.018)

Second Primary Cancers*

IFM			
	Len	17/299	5.5%
	Placebo	3/292	1.0%
CALGB			
	Len	15/231	6.5%
	Placebo	6/229	2.6%
MM015			
	MPR	11/355	3.1%
	Placebo	2/154	1.3%

*Numbers and % as of 2/6/11

Basal cell cancers excluded



Should maintenance post-transplant be standard?

Response:

- Not enough evidence for clear decision:

Unanimous

(Recognize response may be different depending on the US vs. European perspective)

Lenalidomide post-transplant

Should patients be selected by quality of response to induction therapy?

- No – include all patients with stable disease or better

Should lenalidomide maintenance be standard of care?

- **Not enough evidence for a clear decision at this time**

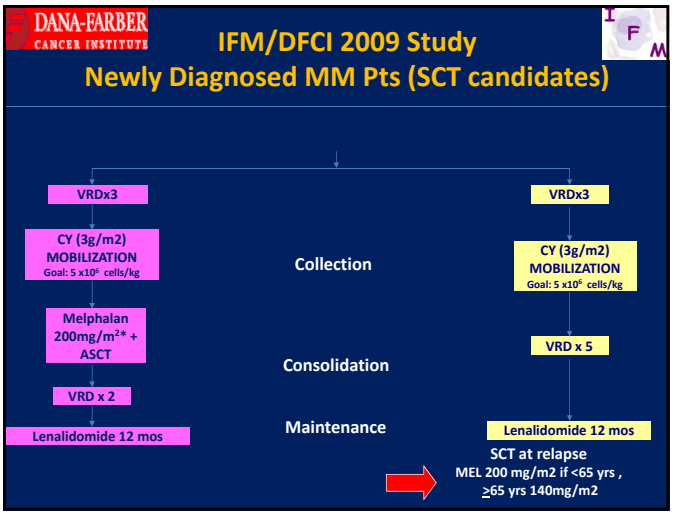
Maintenance: Why Not?

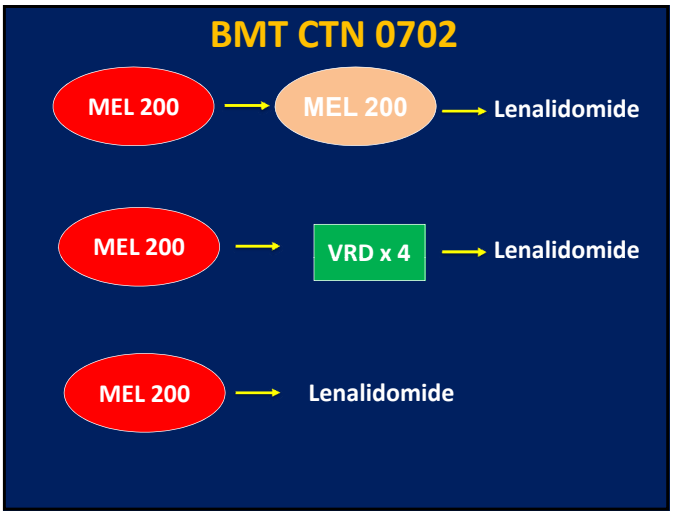
-No survival advantage in IFM or MM-015 trials
  -Longer follow up needed in ALL trials

-Cost $8000/month

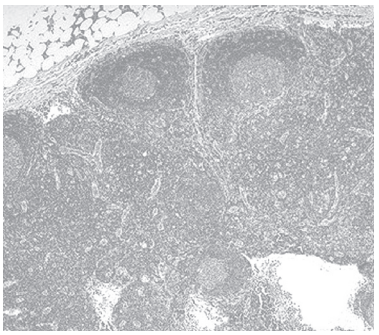
-Toxicities
  -Myelosuppression
  -Second primary malignancies

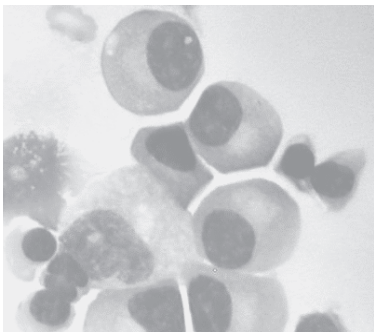
-Unknown response to higher doses of lenalidomide at relapse
  -? Development of resistant clones


DANA-FARBER CANCER INSTITUTE
IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)
I F M
VRDx3
CY (3g/m2) MOBILIZATION
Goal: 5 x10⁶ cells/kg
Melphalan 200mg/m²* + ASCT
VRD x 2
Lenalidomide 12 mos
Collection
Consolidation
Maintenance
VRDx3
CY (3g/m2) MOBILIZATION
Goal: 5 x10⁶ cells/kg
VRD x 5
Lenalidomide 12 mos
SCT at relapse
MEL 200 mg/m2 if <65 yrs ,
≥65 yrs 140mg/m2


BMT CTN 0702
MEL 200
MEL 200
Lenalidomide
MEL 200
VRD x 4
Lenalidomide
MEL 200
Lenalidomide

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Debate: Are transplants necessary as frontline therapy?

Yes: Bart Barlogie, MD, PhD

CLASH OF PHILOSOPHIES

CURE vs CONTROL

Bart Barlogie

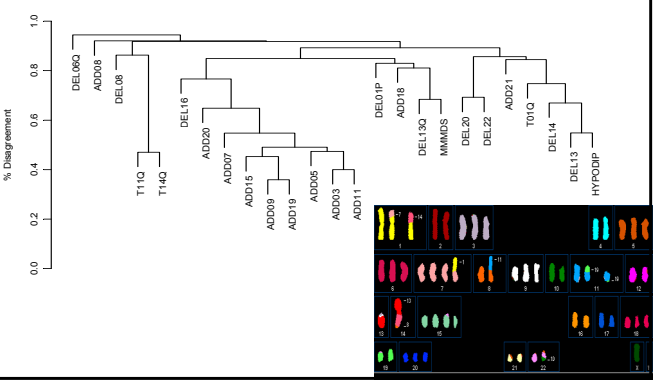
Outline of talk

- TT trial results
  - Impact of addition of thalidomide in TT2 and bortezomib in TT3
  - Importance of GEP70/80
  - Importance of imaging with MRI and PET
- Cure modeling
- Personalized medicine for low- vs high-risk MM
- How to safely abandon transplants

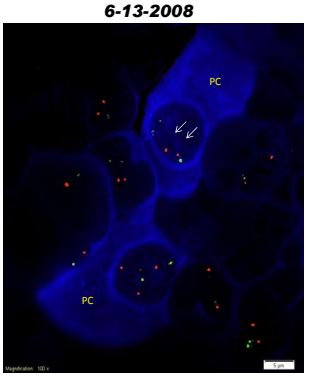
THE CLASH OF PHILOSOPHIES

- ***CURE***
  - ***Long-term relapse-free survival***
    - ***>10, 15, 20yr?***
    - ***Supported by data***
  - ***Scientific rationale***
    - ***Tumor heterogeneity well documented***
      - ***Non-secretory focal lesions in >80% of MM***
    - ***Inevitable escape of high-risk subclone with ongoing 1q21 amplification***
    - ***Only chance of "durable control" (cure) is combination therapy as in Total Therapy up-front, avoiding lingering and facilitation of further mutations***
    - ***Identify prior to therapy "cure" signature***

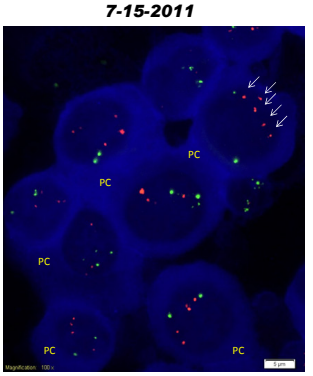
GENOMIC CHAOS IN MYELOMA: CLUSTER TREE OF CHROMOSOMAL ABNORMALITIES



6-13-2008



7-15-2011



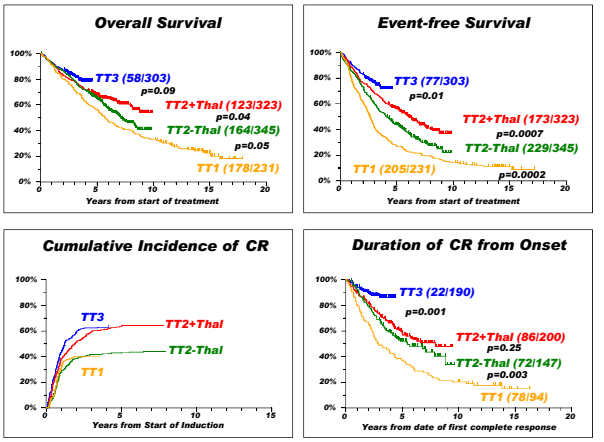
Lambda clg
1q21 Red
1p13 Green

1q21 amplification from 1-2 to 5 copy number

MYELOMA THERAPY AT MIRT

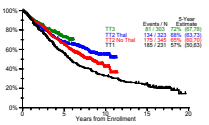
- ***Raise CR rate as sine-qua-non toward cure***
  - ***TT1 with tandem MEL transplants***
  - ***Thalidomide effective as >4th line salvage therapy***
  - ***TT2 phase III -/+ thalidomide***
  - ***TT3 phase II with thal + bortezomib***
- ***Durable non-CR state***
  - ***MGUS-like, compatible with cure of MM***
- ***Cytogenetics and GEP dominantly affecting outcomes***
  - ***Higher grade sub-clones persist in responders***
  - ***Progression to higher grade with each relapse***
- ***Imaging with MRI + PET recognizing focal lesions (FL) persisting in CR***
  - ***Non-secretory disease***

ADVANCING OUTCOMES WITH TOTAL THERAPY



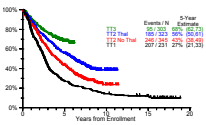
STEADY PROGRESS IN CLINICAL OUTCOMES WITH TRANSITION FROM TT1 TO TT2- TO TT2+ TO TT3

Overall Survival



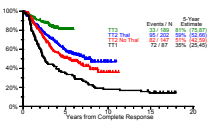
Comparison	P Value
TT1 vs. TT2 No Thal	0.0401
TT1 vs. TT2 Thal	<.0001
TT1 vs. TT3	<.0001
TT2 Thal vs. TT2 No Thal	0.0450
TT2 No Thal vs. TT3	0.0319
TT2 Thal vs. TT3	0.9116

Event-free Survival

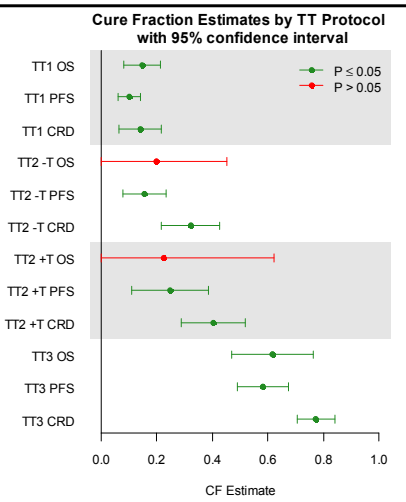


Comparison	P Value
TT1 vs. TT2 No Thal	0.0148
TT1 vs. TT2 Thal	<.0001
TT1 vs. TT3	<.0001
TT2 Thal vs. TT2 No Thal	0.0002
TT2 no Thal vs. TT3	<.0001
TT2 Thal vs. TT3	0.0750

CR Duration



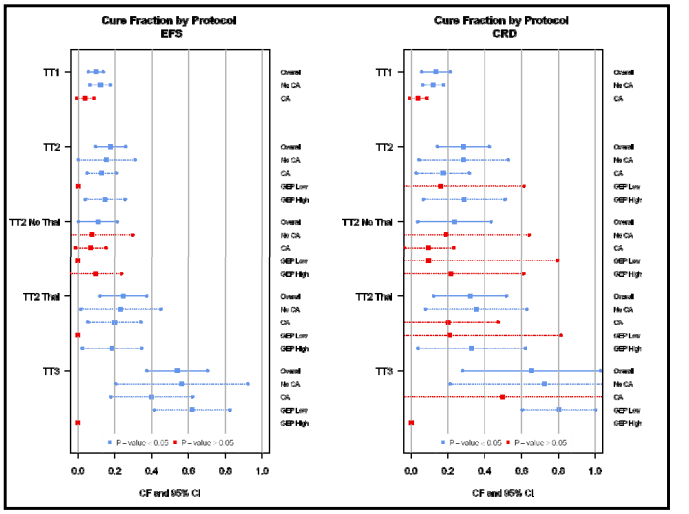
Comparison	P Value
TT1 vs. TT2 No Thal	0.0339
TT1 vs. TT2 Thal	0.0002
TT1 vs. TT3	<.0001
TT2 Thal vs. TT2 No Thal	0.1191
TT2 No Thal vs. TT3	<.0001
TT2 Thal vs. TT3	0.0053



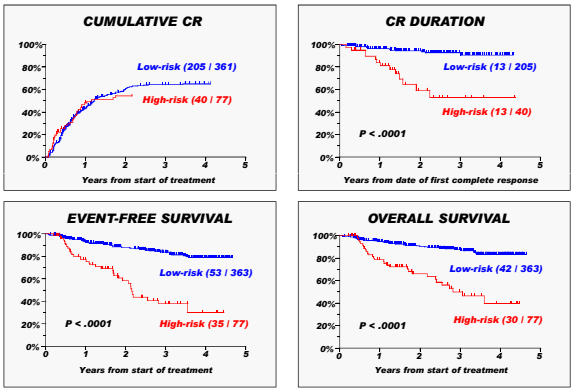
CURING MYELOMA WITH TOTAL THERAPIES

APPLYING OS, PFS AND CR DURATION ALGORITHMS

BASED ON EXPONENTIAL / PLATEAU MODELING OF KAPLAN-MEIER PLOTS

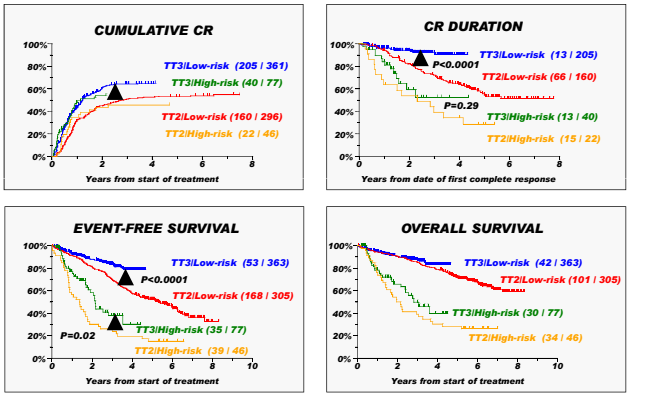


TREATMENT OUTCOMES BY GEP-DEFINED RISK all TT3 patients



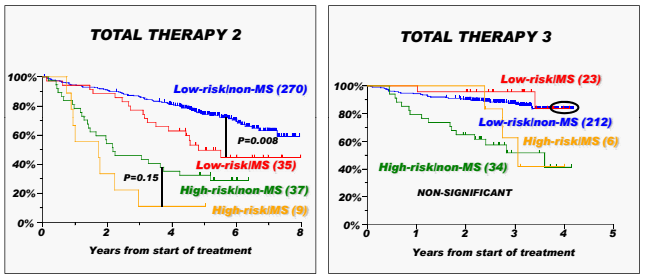
PROGNOSTIC POWER OF GEP-DEFINED RISK VALIDATED

TREATMENT OUTCOMES BY GEP RISK both TT3A & TT3B versus TT2



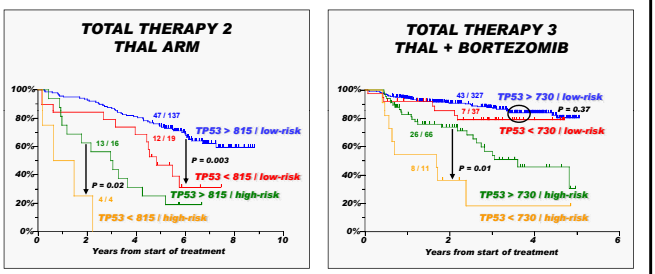
STRIKING BENEFIT OF TT3 v TT2 IN LOW-RISK MYELOMA

TT3 / TT2: SURVIVAL IN T(4;14)-TYPE MYELOMA ACCORDING TO GEP-DEFINED RISK



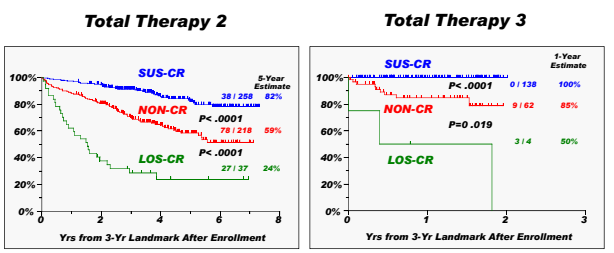
TRANSLOCATION (4;14) NO LONGER ADVERSE FEATURE IN TT3

TT3 / TT2 SURVIVAL ACCORDING TO GEP-DEFINED TP53 STATUS AND RISK

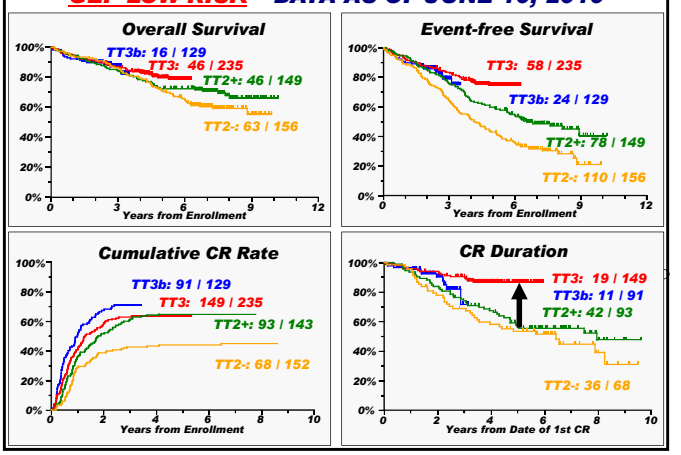


BORTEZOMIB IN TT3 OVERCOMES ADVERSE IMPLICATIONS OF DEL-TP53 IN LOW-RISK DISEASE

IMPACT OF CR STATUS (SUS/NON/LOS) ON OVERALL SURVIVAL IN TT2 & TT3



TOTAL THERAPIES 2, 3 FOR UNTREATED MM GEP LOW-RISK – DATA AS OF JUNE 10, 2010

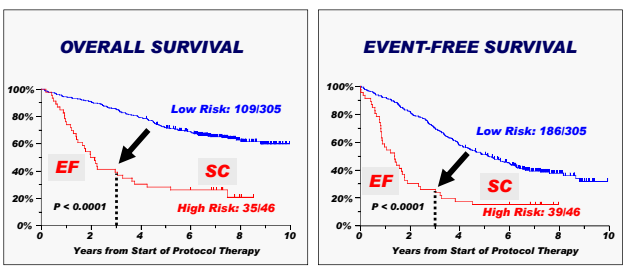


TT3 v TT2 BENEFIT

- *GEP70-defined low risk MM (85% of patients)*
- *FGFR3 [t(4;14)] regardless of risk*
- *delTP53 in low-risk subset*

- *3-yr sustained CR beneficial in both trials*
  - *Better than not achieving CR*
  - *Better than achieving and losing CR in 3yr*

TT2 (BOTH ARMS): CLINICAL OUTCOMES ACCORDING TO GEP-DEFINED RISK



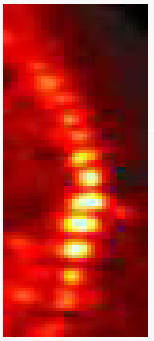
2 distinct components in high-risk disease: early failure (EF) and sustained control (SC): breakpoint at 3 years

MRI & FDG-PET REVEAL ENORMOUS DISEASE BURDEN/ACTIVITY OFTEN WITH NORMAL X-RAYS

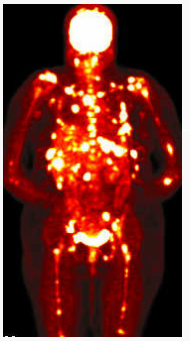
FOCAL LESIONS TYPICALLY PERSIST IN CLINICAL CR, RESOLVE WITH LONG LAG TIME AND ARE SITES OF MYELOMA RELAPSE



Sagittal STIR MRI

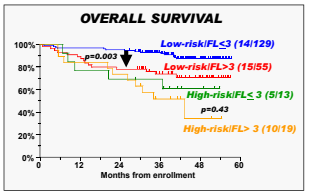


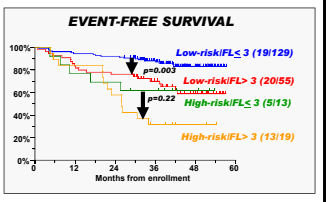
Sagittal FDG PET



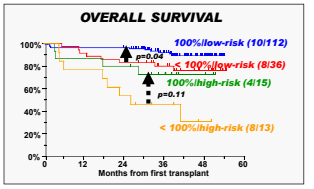
AP FDG PET

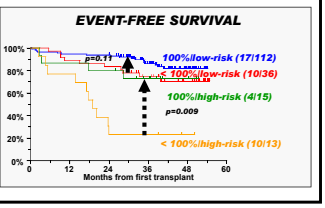
TT3 SURVIVAL BY GEP RISK & FDG-FL AT BASELINE



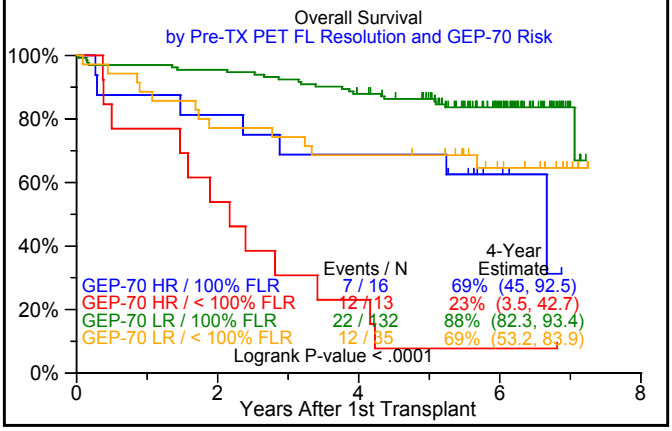


TT3 SURVIVAL BY 100% FDG SUPPRESSION PRE-Tx





PET-FL Suppression at 1st Transplant & GEP70 Risk

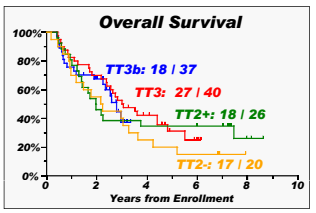


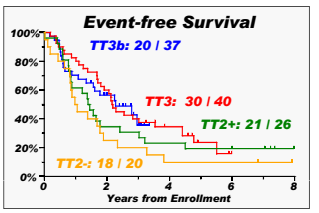
MV ANALYSIS OF BASELINE VARIABLES & 100% FDG SUPPRESSION ON TT3 SURVIVAL

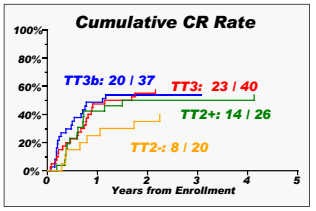
Multivariate Analysis		*Overall Survival from 1st transplant*			*Event-free Survival from 1st transplant*		
without gene array data (n = 196)	%	HR	P	R^2	HR	P	R^2
100% FDG-FL reduction	*71*	*0.33*	*0.001*	*37%*	*0.47*	*0.013*	*48%*
FDG-FL > 3	35	NS	NS	NS	2.01	0.028	37%
LDH >= 190 U/L	23	2.27	0.024	43%	2.61	0.002	25%
B2M > 5.5 mg/L	19	2.45	0.015	49%	2.00	0.033	43%
with gene array data (n = 175)	%	HR	P	R^2	HR	P	R^2
100% FDG-FL reduction	*72*	*0.41*	*0.017*	*37%*	*0.51*	*0.038*	*56%*
GEP high-risk	*16*	*2.64*	*0.015*	*52%*	*2.12*	*0.032*	*48%*
Cytogenetic abnormalities	35	2.59	0.018	58%	NS	NS	NS
CRP >= 8 mg/L	33	2.43	0.018	57%	NS	NS	NS

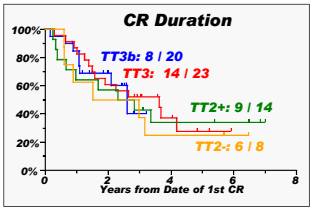
Clinical CR did not enter the model!

TOTAL THERAPIES 2, 3 FOR UNTREATED MM
GEP HIGH-RISK – DATA AS OF JUNE 10, 2010

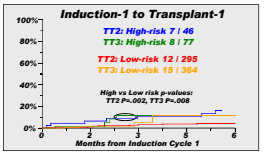


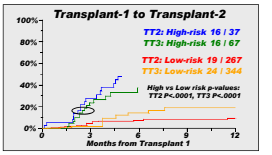


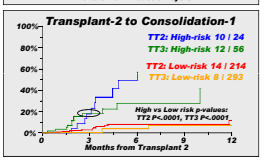


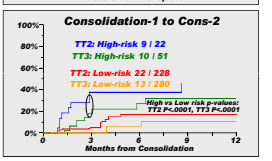


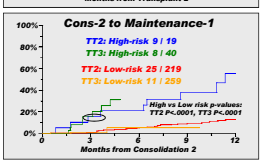
TREATMENT FAILURE BY PROTOCOL PHASE AND GEP RISK

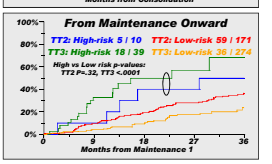




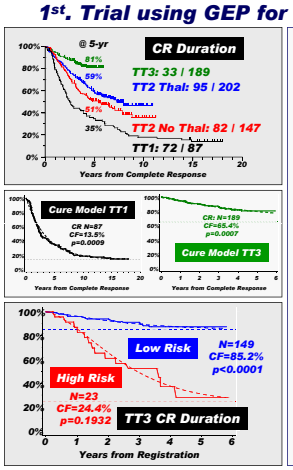






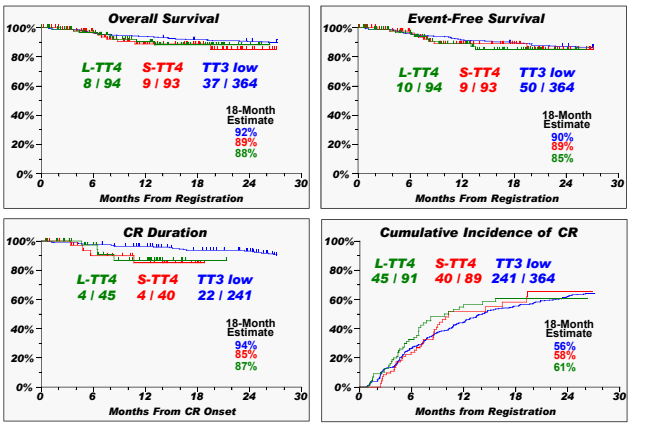


Background Behind TT4 and TT5 Trials
1st. Trial using GEP for MM Treatment Assignment

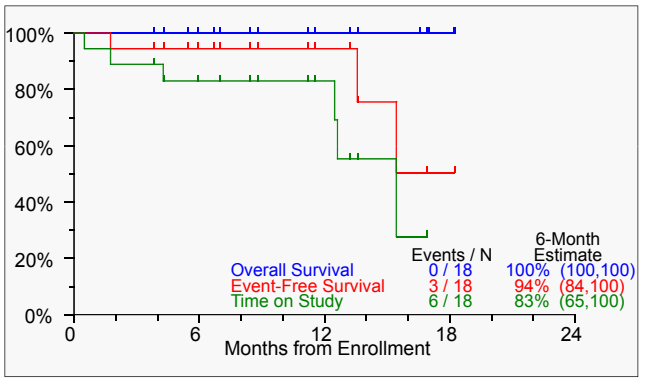


- ***CR Duration markedly extended***
  - *TT1 → TT2-THAL - → TT2-THAL + → TT3*
    - *TT3 with upfront THAL + bortezomib*
- ***Curability of myeloma with TT1, TT2, TT3 protocols (ASH 2009)***
  - *>80% estimate with TT3 in GEP-defined low-risk myeloma (LOW) patients who achieved CR*
- ***Limited progress in high-risk MM (HIGH) justifies separate trials for LOW & HIGH MM***
  - *Phase II TT5 for HIGH MM (15%) emphasizes dose-density by reducing dose-intensity*
  - *Phase III TT4 for LOW MM (85%) randomizes pts between standard & light TT3*
    - *toxicity and length of therapy while retaining efficacy.*
    - *Results of first 180 pts*

Outcomes Similar in TT4 and TT3 Low-Risk

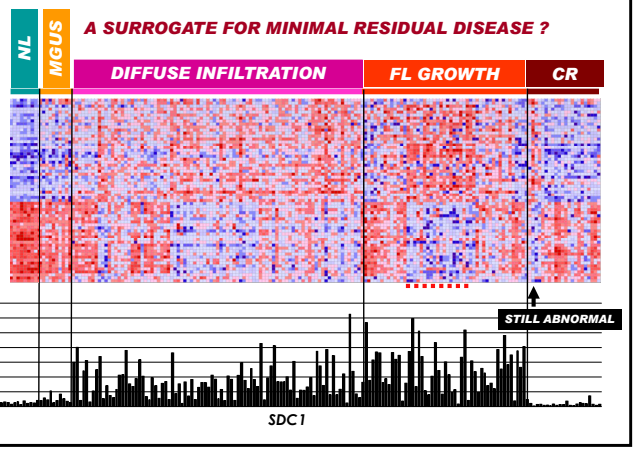


TT5: SURVIVAL OUTCOMES



NORMALIZATION OF MICRO-ENVIRONMENT-ASSOCIATED GENES IN COMPLETE REMISSION:

A SURROGATE FOR MINIMAL RESIDUAL DISEASE ?



"SHORTCUT TO CURABILITY"

- ***Take advantage of vast serial GEP & imaging data***
  - *Define by GEP PC baseline signature that is compatible with >10yr PFS*
  - *Define GEP stroma signature normalization v normal donors*
- ***Toward abandoning transplants***
  - *High-risk MM with PFS <2yr*
  - *Frail patients ineligible for intensive therapy*
  - *Phase III trials in progress*
    - *>10yr F/U needed*

LET'S NOT CLASH!

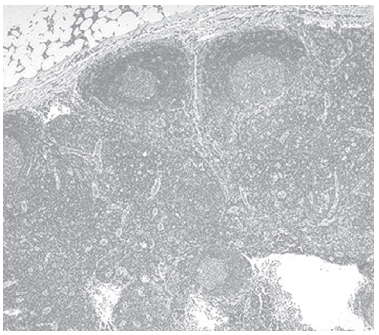
- ***Pursuit of cure strategies for >20yr should not now be abandoned because of cure data***
  - *Important as framework for "control" strategies*
- ***Continue tight monitoring of all trial patients and check for 2nd malignancies***
- ***Collective effort toward improving high-risk MM will ultimately benefit also low-risk MM as high grade transformation inevitable***
- ***Segregate low-risk subset with high-risk transformation potential***

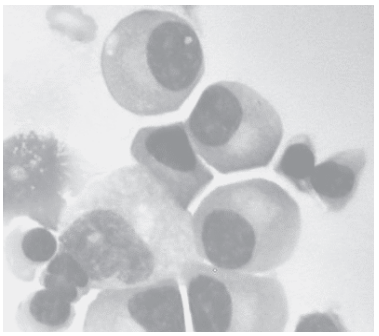
If we focus on young patients, it would be relevant to learn from previously incurable and now curable diseases such as Hodgkin's disease and acute lymphoblastic leukemia, in which the primary goal was to achieve a cure and only then to focus on reducing toxicity. **In MM, for example, when considering whether ASCT is still needed upfront, one of the arguments against it is that other treatments offer similar efficacy with lower toxicity. Our position is that the philosophy for a cure should be based on the knowledge of those treatments that have demonstrated efficacy, and the investigation of optimal combinations, sequences, and of novel agents, instead of looking for soft replacements of equivalent efficacy that do not improve survival. Examples of this strategy are the results reported by Cavo *et al*., and the total therapy programs developed by the Arkansas group that integrate all treatment tolls through induction, consolidation and maintenance. This approach has resulted in a 4-year CR duration estimated at 89% in patients defined as low-risk by GEP, equivalent to an estimated cure rate of 50%. If the long-term follow up confirms this figure, for the first time we would be in the position to say that MM has become a potentially curable disease.** Nevertheless, it should be noted that, as occurs in ALL, effective treatment is not always a matter of dose intensity but of dose density; in other words, the successful combination of sequential treatments. Regarding risk-adapted treatment, to offer intensive therapies to high-risk patients while using softer approaches for those at low risk could be a mistaken philosophical approach. **Thus, the benefit of treatment intensification in low-risk patients was recently demonstrated in a cohort who, although they were already in more than VGPR after ASCT, received intensification with VTD, and none of those who achieved a molecular remission has so far relapsed. Accordingly, the risk of under-treating low-risk patients by concluding that they are already in conventional CR could be a serious error if cure is the goal. Clinical investigation based on large phase III randomized trials that integrate comprehensive genetic studies upfront and sensitive tools for monitoring treatment efficacy will be the best way to find appropriate answers to these questions.** In summary, although we have made great progress in both the understanding of MM biology and the discovery of novel drugs, we are still not in a position to be able to offer a cure for a substantial proportion of patients in the immediate future. In order to achieve this aim, we probably first need to accept that MM should no longer be considered as a single entity, and hence adapt our strategies as appropriate to the MM subtype, as occurs in other hematologic malignancies. ***SAN MIGUEL ET AL, HAEMATOLOGICA 2011***

THANKS

- ***Patients***
- ***Referring MD's***
- ***Arkansas team***
- ***Funding***
  - ***NCI: PO1***
  - ***MMRF***
  - ***IMF***
  - ***Philanthropy***
    - ***Grand, LeBow, Lambert***

- ***Pleading***
  - ***Consensus to move forward with national & eventually international effort toward high-risk MM***
- ***Unprecedented opportunity***

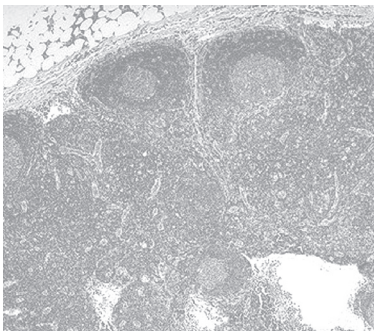


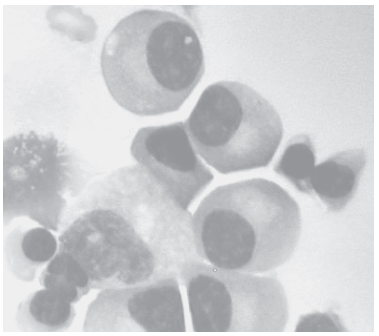


Debate: Are transplants necessary as frontline therapy?

No: Sundar Jagannath, MD

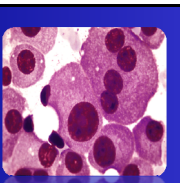
Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





New treatments and how best to use them in lymphoma and myeloma: Carfilzomib

Ruben Niesvizky, MD

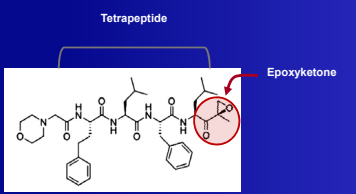


Carfilzomib in Myeloma: Present and Future

Rubén Niesvizky
Director, Myeloma Service, New York Presbyterian Hospital/Weill-Cornell Medical College

Carfilzomib:
Selective and Irreversible Proteasome Inhibitor

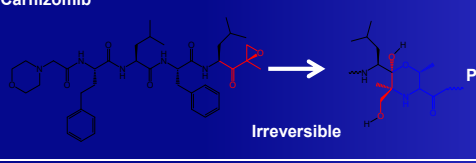
Carfilzomib is the first in a new class of selective and irreversible proteasome inhibitors that are associated with prolonged target suppression, improved antitumor activity and low neurotoxicity



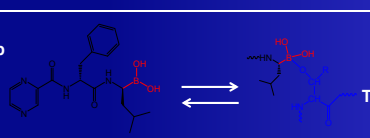
Mechanism of Binding to Active Site

Unique chemistry drives selectivity and prolonged inhibition

Carfilzomib



Bortezomib



Carfilzomib and Bortezomib in Chronic Toxicology Studies

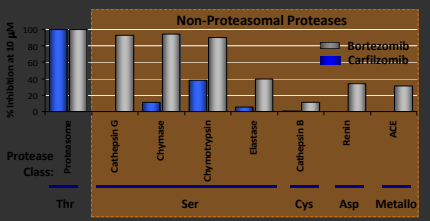
Chronic Toxicity Studies in Rats (6 months) and Monkeys (9 months)

Toxicity	Bortezomib (D1/D4)	Carfilzomib (D1/D2)
Neurotoxicity	Tremors; reduced motor activity Nerve degeneration ↓ Conduction velocity	*No neurobehavioral deficits* *No histologic changes*
Hematological	Decreased RBCs Decreased platelets Decreased WBCs	Decreased platelets *No Neutropenia*
GI	Mucosal hyperplasia and inflammation	
Cardiovascular	Sporadic cardiac inflammation	
Renal	Chronic progressive nephropathy	

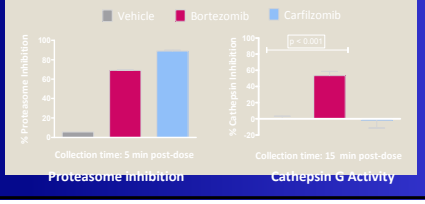
Cavaletti G, et al. *Exp Neurology*. 2007;204:317-325.

Carfilzomib Is Not Associated With Significant Off-Target Activities

In vitro
Carfilzomib has minimal off target activity



In vivo
Bortezomib inhibits Cathepsin G:
an off-target serine protease



Kapur et al. (2008) Blood, 112: 2657

Clinical Studies with Carfilzomib

Trial	N	Design/Population	Enrollment Status
001	29	Phase 1, Single Agent; Relapsed/refractory MM	Completed
002	47	Phase 1, Single Agent; Relapsed/refractory NHL	Completed
003-A0	46	Phase 2, Single Agent; Relapsed /refractory MM	Completed
003-A1	269	Phase 2b, Single Agent; Relapsed /refractory MM	Completed
004	155	Phase 2, Single Agent; Relapsed MM	Completed
005	50	Phase 2, Single Agent Relapsed MM with renal insufficiency/failure	Completed
006	85	Phase 1b, Comb. with Revlimid/dexamethasone; Relapsed MM	Completed
007	235	Phase 1b/2, Single Agent; Relapsed Solid Tumors and MM	Ongoing
009	700	Phase 3, Comb with Rev/Dex vs.. Rex/Dex; Relapsed MM	Ongoing
011	70	Phase 3, Single Agent vs. BSC; Relapsed MM	Ongoing
010	40	Roll-over protocol	Ongoing

Carfilzomib Safety and Efficacy is Being Evaluated in a Broad Clinical Development Program (total n* = 820)

Trial	N	Design/Population	Status
001	29	Ph 1 Single Agent Hematological Malignancies (2 wk cycles)	Completed
002	48	Ph 1 Single Agent Hematological Malignancies (4 wk cycles)	Completed
003-A0	46	Ph 2 Single Agent Relapsed & Refractory MM	Completed
003-A1	270	Ph 2b Single Agent Relapsed & Refractory MM	Enrolled
004	165	Ph 2 Single Agent Relapsed MM	Enrolled
005	50	Ph 1 Single Agent Relapsed & Refractory MM with Renal Impairment	Enrolled
007	113	Ph 1b/2 Single Agent Dose-Escalation Relapsed Solid Tumors and MM	Ongoing
008	15	Ph 2 Drug-Drug Interaction (Midazolam)	Ongoing
010	35	Ph 2 Maintenance Therapy for Subjects Previously Enrolled in CFZ Treatment Trials	Ongoing
006	84	Ph1b Combination Lenalidomide + Dexamethasone Relapsed MM	Enrolled
009	700	Ph 3 Combination CRd vs. Rd Relapsed MM (SPA granted)	Ongoing
011	84	Ph 3 Single Agent vs. Best Supportive Care Relapsed & Refractory MM	Planned 2010Q2

*N is based on enrollment numbers as of 2010 April 30

Phase 2 Trial of Carfilzomib in Relapsed and Refractory Multiple Myeloma

PX-171-003: Study Design

Study expanded to pivotal trial

Study Population
- Relapsed from ≥2 prior therapies (must include BTZ and THAL or LEN)
- Refractory to last treatment
  - ≤25% response on therapy
  - Progression on therapy or within 60 days of therapy discontinuation

003-A0 *(N=46)*: Carfilzomib 20 mg/m² IV QD x 2 for 3 weeks (28-day cycle)

003-A1 *(N=250)*: Dose escalation to 27 mg/m² after 1st cycle

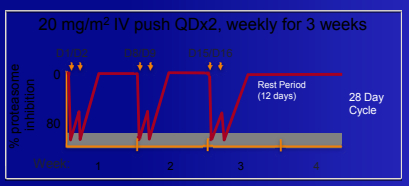
- Overall survival added as endpoint
- Tumor lysis syndrome prophylaxis guidelines implemented
- Safety Oversight Group instituted
- Efficacy assessed by Independent Review Committee

Primary endpoint: Overall response rate (CR+PR) (IMWG criteria), OS

Secondary endpoints: Clinical benefit rate (CR+PR+MR), duration of response, PFS, TTP, safety

Adapted from Jagannath S, et al. ASH 2009. ASH/ASCO joint session oral presentation. PX-171-003

PX-171-003-A0: Phase 2 Trial of Carfilzomib in Relapsed/Refractory Multiple Myeloma



- Relapsed from ≥ 2 prior therapies
  - Must include bortezomib and thalidomide or lenalidomide
- Refractory to last treatment
  - ≤ 25% response to therapy, or progression during or ≤60 days of ceasing therapy
- Primary endpoint: Overall response rate (CR + PR) IMWG
- Secondary endpoints
  - Clinical benefit response (CR + PR + MR), DOR, PFS, TTP, OS, safety

Jagannath et al. J Clin Oncol.ppt; 27 15s 2009 (suppl abstr 8504)

Study Comprised of Highly Refractory Patients with a Median of 5 Prior Therapies

Patient characteristics (N=46)	
Median number of prior therapies (range)	5 (2-15)
≥4 prior therapies	80%
Bortezomib	100%
As last therapy	57%
Immunomodulatory agent	100%
Lenalidomide	89%
Thalidomide	91%
Corticosteroid	100%
Alkylator (melphalan, cyclophosphamide, carmustine)	94%
Stem cell transplant	83%
Anthracycline	80%

Jagannath S, et al. ASH 2009. ASH/ASCO joint session oral presentation. PX-171-003-A0

Majority of Patients Achieved Durable Responses to Carfilzomib

	003-A0 (20 mg/m²)	003-A1 (27 mg/m²) *preliminary data*
N	39*	266
Response rate		
≥PR	18%	24%
MR	8%	12%
SD	41%	*n/a*
PD	28%	*n/a*
Median time to progression	5.1 months	*not reached*
Median duration of response (≥PR) (range)	7.4 months (2.3+-13.8)	7.4 months
Mean treatment duration (range)	4.5 months (1-11.6)	*n/a*

*7 subjects excluded from response analysis (4 serum free light chain only, 2 <1 cycle of therapy (PD), 1 no baseline value)

Jagannath S, et al. ASH 2009. ASH/ASCO joint session oral presentation.
Data on file. Onyx Pharmaceuticals (as of July 26, 2010). PX-171-003

Carfilzomib Was Well Tolerated With a Low Incidence of Grade 3/4 AEs

Treatment-Emergent Adverse Events*	003-A0 (N=46) (20 mg/m²) All Grades (%)	003-A0 (N=46) (20 mg/m²) Grade 3/4 (%)	003-A1 (N=141)* (27 mg/m²) All Grades (%)	003-A1 (N=141)* (27 mg/m²) Grade 3/4 (%)
Hematologic (≥15%)				
Anemia	73.9	37.0	31.2	13.5
Thrombocytopenia	50.0	26.1	24.8	16.3
Neutropenia	21.7	4.3	12.1	3.5
Non-hematologic (≥25%)				
Fatigue	69.6	8.7	28.4	4.3
Upper respiratory tract infection	37.0	2.2	16.3	3.5
Creatinine increased	34.8	4.3	17.7	0
Nausea	34.8	0	26.2	0.7
Diarrhea	32.6	0	19.9	0
Dyspnea	28.3	8.7	19.9	2.1
Other				
Peripheral neuropathy	21.7	2.2	9.9	0.7
Renal failure (acute)	15.2	13.0	7.8	2.8
Tumor lysis syndrome	4.3	4.3	0	0

*Related and unrelated AEs (data through August 2009)

Jagannath S, et al. ASH 2009. ASH/ASCO joint session oral presentation. PX-171-003

Baseline Patient Characteristics

	Cohort 1 20 mg/m²		Cohort 2 20/27 mg/m²
	BTZ-treated (N=36)	BTZ-naïve (N=59)	BTZ-naïve (N=60)
Median age, years (range)	63 (40–77)	64 (38–82)	65 (45–85)
Median yrs from diagnosis (range)	3.6 (1–13)	3.5 (0.7–24)	3.8 (0.7–11)
Median serum β_2 microglobulin (range), mg/L	3.2 (1.6–9.8)	2.9 (1.1–24.5)	3.3 (1.3–8.1)
Immunoglobulin Subtype*, n (%)	24 (67)	33 (56)	47 (78)
IgG	5 (14)	18 (31)	12 (20)
IgA	6 (17)	8 (14)	1 (2)
Light Chain Only			
Baseline evaluation, %			
Peripheral neuropathy	50	42	43
CrCl <50 mL/min	11	14	17

One patient in the BTZ-treated cohort had IgD disease

Stewart AK, et al. EHA 2010. Abstract 1099 (oral presentation). PX-171-004

Single Agent Anti-tumor Activity
BTZ-treated patients

	Cohort 1 20 mg/m² (N=34)*
Response Rate	
CR	0%
VGPR	9%
PR	12%
MR	12%
SD	35%
PD	32%
ORR	21%
CBR	33%
Median DOR, mos (95% CI)	
≥MR	8.5 (7.3-NE)
≥PR	11.5 (7.2-15.2)
Median TTP, mos (95% CI)	8.1 (2.8-11.1)

*Response-evaluable population
NE=not estimable

Stewart AK, et al. EHA 2010. Abstract 1099 (oral presentation). PX-171-004

Single Agent Anti-tumor Activity
BTZ-naive patients

	Cohort 1 20 mg/m² (N=53)*	Cohort 2 20/27 mg/m² (N=53)*
Response Rate		
CR	2%	0%
VGPR	13%	17%
PR	30%	38%
MR	13%	8%
SD	30%	26%
PD	9%	11%
ORR	45%	55%
CBR	58%	62%
Median DOR, mos (95% CI)		
≥MR	8.3 (7.2-NE)	11.5 (11.0-NE)
≥PR	10.2 (6.2-NE)	11.5 (11.0-NE)
Median TTP, mos (95% CI)	8.3 (6.0-12.0)	11.5 (9.9-NE)

*Response-evaluable population
NE=not estimable

Stewart AK, et al. EHA 2010. Abstract 1099 (oral presentation). PX-171-004

Adverse Events Reported in ≥20% or ≥Grade 3 in ≥5% (Safety Population)

Adverse Event* (N=155)	All Grades (%)	≥ Grade 3 (%)
Hematologic		
Anemia	32	9.7
Neutropenia	25	9.7
Thrombocytopenia	25	9.0
Non-hematologic		
Pneumonia	11	11
Fatigue	54	5.2
Dyspnea	34	3.9
Upper respiratory infection	28	1.9
Vomiting	25	1.9
Diarrhea	28	1.3
Headache	28	1.3
Peripheral edema	21	1.3
Nausea	45	0.6
Pyrexia	27	0.6
Increased creatinine	20	0.6
Cough	27	0

*Includes both related and non-related AEs

Adapted from Stewart AK, et al. EHA 2010. Abstract 1099 (oral presentation). PX-171-004

Treatment-Emergent Neuropathy Was Infrequent and Not Treatment Limiting

	All Patients† %, (N=155)
Active Grade 1/2 peripheral neuropathy at baseline*	45
Treatment-emergent neuropathy	
Grade 1	11
Grade 2	4
Grade 3	1
Grade 4	0
Treatment discontinuations due to peripheral neuropathy	*<1*

*Grade based on physical assessment at screening (NCI-CTC scale); † Safety Population

Stewart AK, et al. EHA 2010. Abstract 1099 (oral presentation). PX-171-004

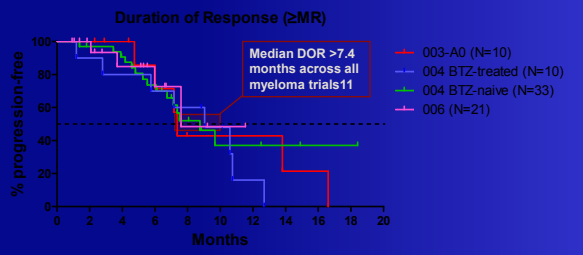
Efficacy Summary
Single Agent Carfilzomib

Study 003	Median # prior tx	ORR	TTP	DOR (≥PR)
Carfilzomib (20 mg/m²) *(n=39)*	5	18%	5.1 mo	7.4 mo
Carfilzomib (20/27 mg/m²) *(n=266)*	5	24%	NR	7.4 mo
Study 004*	**Median # prior tx**	**ORR**	**TTP**	**DOR (≥PR)**
Carfilzomib (20 mg/m²) *BTZ-treated (n=34)*	3	21%	8.1 mo	11.5 mo
Carfilzomib (20 mg/m²) *BTZ-naïve (n=53)*	3	45%	8.3 mo	10.2 mo
Carfilzomib (20/27 mg/m²) *BTZ-naïve (n=53)*	2	55%	11.5 mo	11.5 mo

Many patients continue to receive reduced frequency CFZ in extension study

ORR = ≥PR; NR = not reached, *based on interim analysis
Stewart AK, et al. EHA 2010. Abstract 1099 (oral presentation). Jagannath S, et al. ASH 2009. ASH/ASCO joint session oral presentation. Data on file. Onyx Pharmaceuticals (as of July 26, 2010).

Responses with Carfilzomib are Durable Across Phase 2



Study	003-A0	004 BTX-treated	004 BTX-naïve	006
Population	Rel & Ref	Rel or Ref	Rel or Ref	Rel or Ref
# prior Tx	6	1–3	1–3	1–3
Dosing	20 mg/m² single agent	20 mg/m² single agent	20 mg/m² single agent	15 – 20 mg/m² + Len/Dex

PX-171-006

Dose Schedule

Study Design: Phase 1b, multi-center, escalation trial
Population: Relapsed multiple myeloma: 1 to 3 prior treatments
Study Treatment (28 day cycles – cohorts 1-6):

Cycles 1-4:	Cycles 5-8:	Cycles 9-16:
CFZ Days 1, 2, 8, 9, 15, 16 Len Days 1-21 Dex Days 1, 8,15, 22	CFZ Days 1, 2, 8, 9, 15, 16 Len Days 1-21 Dex Days 1	CFZ Days 1, 2, 15, 16 Len Days 1-21 Dex Days 1

PX-171-006

Eligibility

- Relapsed or progressive disease after 1- 3 prior therapies
- M protein >1 g/dL SPEP or monoclonal light chain >200 mg by 24-hour UPEP within the past 4 wks
- If previously treated with lenalidomide or bortezomib, the subject must not have progressed during the first 6 months of treatment
- Neuropathy (G 1/2 without pain) allowed at baseline
- Hemoglobin > 8 g/dL; platelets > 50,000/mm³; ANC > 1,000/mm³
- Bilirubin < 2 mg/dL, ALT and AST < 3 times ULN
- Creatinine < 2 mg/dL or CrCl ≥ 50 mL/min

PX-171-006

Adverse Events and Toxicity

N = 27	n (%)	
Adverse Events ≥20%	All Grades	Grade 3/4
Fatigue	12 (44)	
Diarrhea	9 (33.3)	
Neutropenia	9 (33.3)	6 (22.2)
Anemia	7 (25.9)	4 (14.8)
Back Pain	7 (25.9)	
Cough	7 (25.9)	
Dyspnea	7 (25.9)	
Thrombocytopenia	6 (22.2)	6 (22.2)
Arthralgia	6 (22.2)	
Rash	6 (22.2)	
Upper Respiratory Tract Infection	6 (22.2)	

No DLTs, drug-related SAEs, or deaths through Cohort 6

No fatigue ≥ G3 or thrombotic events

No peripheral neuropathy adverse events reported*

* Peripheral Neuropathy is defined as: Neuropathic Pain, Neuropathy, Neuropathy Peripheral, Peripheral Motor Neuropathy, Peripheral Sensory Neuropathy

PX-171-006

Activity in Evaluable Patients (N = 29)

	CRd (%) N=29	VRD* (%)	
		Prior BTZ N=35	Prior IMID N=51
CR/nCR	17	20	18
≥VGPR	35	20	22
≥PR	55	60	59
≥MR	76	77	78

- All responses observed at sub-MTD CFZ doses
- Responses improve with continuing therapy (≥3 months)

* Richardson, ASCO 2009 # 8536

Carfilzomib, Lenalidomide, and Dexamethasone (CRd) in Newly Diagnosed Myeloma: Updated Results of Phase I/II MMRC Trial

AJ. Jakubowiak[1], D. Dytfeld[1,2], K. Griffith[1], S. Jagannath[3], DH. Vesole[4], T. Anderson[1], B. Nordgren[1], A. Al-Zoubi[1], D. Lebovic[1], K. Stockerl-Goldstein[5], M. Mietzel[1], R. Ott[6], S. Kelley[6], J. Barrickman[7], M. Kauffman[8], JA. Leveque[8], R. Vij[5]

[1]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, [2]Poznan University of Medical Sciences, Poznan, Poland; [3]Mount Sinai Medical Center, New York, NY, [4]John Theurer Cancer Center, Hackensack, NJ; [5]Washington University School of Medicine, St. Louis, MO, [6]Multiple Myeloma Research Consortium, Norwalk, CT, [7]Celgene, Inc, Summit, NJ; [8]Onyx Pharmaceuticals, South San Francisco, CA

Treatment Schema

Eligibility: Newly diagnosed MM requiring first-line therapy
(transplant eligible and ineligible)



CRd x 4 cycles → ≥ PR → CRd x 4 cycles → CRd maintenance

Stem Cell Collection
ASCT deferred

Same regimen except no Cfz on days 8, 9

Cfz: dose escalation
LEN: 25 mg (days 1-21)
Dex: 40 mg (days 1, 8, 15, 22) and 20 mg (cycles 5–8 and maintenance)
ASCT = autologous stem cell transplant

Jakubowiak A, et al. IMW 2011. Abstract 318 (poster presentation).

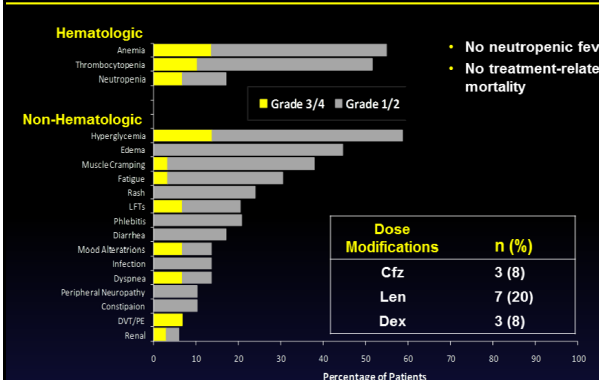
Best Response to Date

Response, %	(N=33*)
sCR / CR / nCR	60
sCR	27
CR/nCR	33
≥VGPR	82
≥PR	97

*As of data cutoff date: 28 February 2011
Phase 1 patients only

Jakubowiak A, et al. IMW 2011. Abstract 318 (poster presentation).

Toxicities



- No neutropenic fevers
- No treatment-related mortality

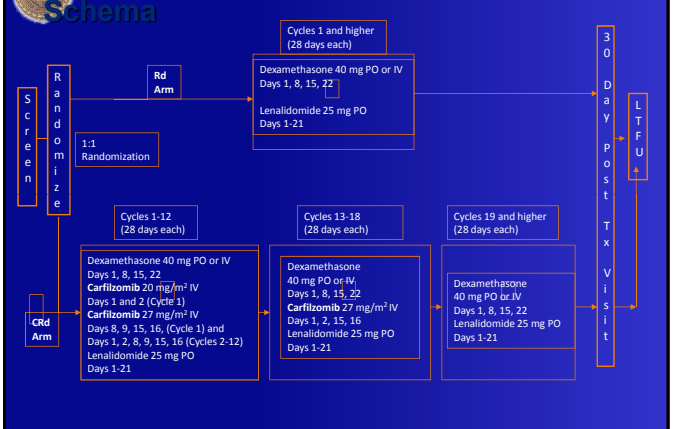
Dose Modifications	n (%)
Cfz	3 (8)
Len	7 (20)
Dex	3 (8)

Jakubowiak A, et al. IMW 2011. Abstract 318 (poster presentation).

Carfilzomib Phase 3 Studies Commencing in 2010

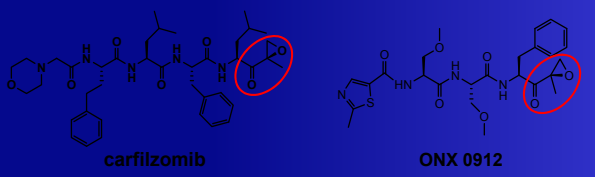
- **ASPIRE**
  - CRd vs. Rd in Relapsed MM (1-3 priors)
  - Required for full approval in US, Canada and EU
- **FOCUS**
  - Single agent carfilzomib vs. 'best supportive care'
  - Required for EMA approval

PX-171-009 Study Design – Treatment Schema



ONX 0912 – Oral Proteasome Inhibitor

ONX 0912 is similar to Carfilzomib

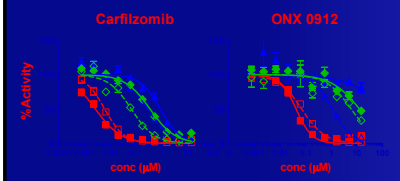


carfilzomib ONX 0912

- **Result of carfilzomib analog medicinal chemistry program**
  - >500 analogs tested in rodent models
    - *J. Med. Chem.* 2009 52:3028 - 3038
  - Multiple comparisons to carfilzomib in preclinical models
    - Pharmacodynamics/biodistribution
    - Toxicity profile (absolute & relative to % target inhibition)
    - Anti-tumor activity in vitro and in vivo

Proteasome Active Site Selectivity of ONX 0912

- Chymotrypsin-like activity is primary target for both ONX 0912 and carfilzomib
- ONX 0912 and carfilzomib differ in their secondary activities
  - Contribution of secondary sites to efficacy and safety are unknown



	Constitutive proteasome	Immuno-proteasome
Chymotrypsin-like	beta5	LMP7
Caspase-like	beta1	LMP2
Trypsin-like	beta2	Mecl1

32

Nonclinical Toxicity Profiles of ONX 0912 and Carfilzomib

	Carfilzomib (IV)	ONX 0912 (PO)
Species	Rats & Monkeys	Rats & Dogs
Min. Dose for 80% PI (Blood)	6 mg/m^2	30 mg/m^2
Single Dose MTD	36 – 42 mg/m^2	300 mg/m^2
QDx5 MTD	12 mg/m^2	120 – 180 mg/m^2
Findings		
Hematology	Thrombocytopenia	Thrombocytopenia
Clinical Chemistry	↑ Creatinine & BUN (pre-renal azotemia)	No pre-renal azotemia
GI	Weight loss, sporadic hemorrhage/necrosis	Weight loss/Diarrhea DLT in Dogs

33

33

MyelomaCenter.org

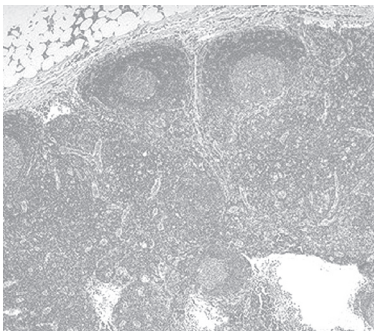
NewYork-Presbyterian Hospital
Weill Cornell Medical Center
Weill Cornell Medical College
The Leukemia & Lymphoma Society
Fighting Blood-Related Cancers

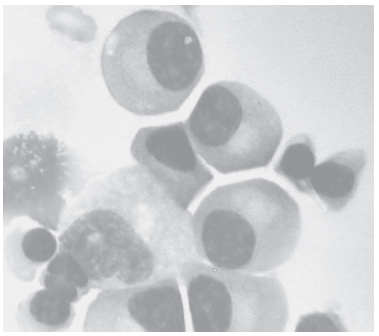
NCI K23 Award: CA109260-01

Morton Coleman
Roger N Pearse
Tomer Mark
Faiza Zafar
Karen Pekle
Tsiporah Shore
Joseph Lane
Alan Weinstein

Selina Chen-Kiang
Scott Ely
David S. Jayabalan
Stanley Goldsmith
Madhu Mazumdar
Paul Christos
Susan Mathew
Patty Garcia

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





New treatments and how best to use them in lymphoma and myeloma: Pomalidomide

Tomer Mark, MD

New Therapies for Myeloma: Pomalidomide

Lymphoma and Myeloma 2011

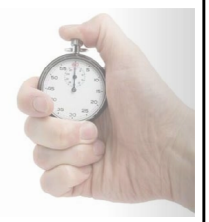
Disclosures:

- Speakers' bureau, research funding, and advisory board: Celgene Inc.
- Speakers' bureau: Millennium Inc.
- Speakers' bureau: Genzyme Inc.

Pomalidomide has not been approved yet for treatment of patients with multiple myeloma

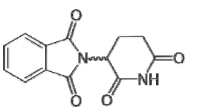
Outline

- Main point: Pomalidomide is great
- What pomalidomide is and how it works
- Demonstrate why pomalidomide is great
- Remind you that pomalidomide is great

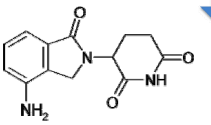


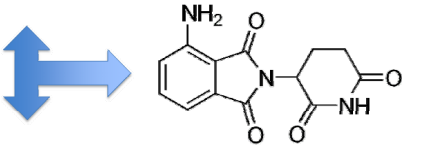
Pomalidomide (CC-4047)

Thalidomide



Lenalidomide





Analog of thalidomide – 2nd generation IMiD

- Equivalent anti-angiogenic activity
- 8x greater stimulation of apoptosis
- 15,000x greater inhibition of TNF-alpha production
- Stimulates ADCC

Pomalidomide Mechanisms of Action:

- Anti-proliferative
  - Demonstrated upregulation of $p23^{WAF1}$, inhibiting CDK pathway, leading to G1/G0 arrest
- Pro-apoptotic
  - Enhanced sensitivity to Fas and TRAIL-induced apoptosis
- Antiangiogenic
  - Decreased VEGF secretion
- Modulates bone resorption
  - Inhibition of differentiation of osteoclasts by down-regulating PU.1

Phase 1 Studies

	Regimen	N	Schedule	Doses	MTD (DLT)	PR and better	PFS/DOR /OS, months
Schey et al. JCO 2004 (MM-001)	Pom	24	28/28	1,2,5, or 10mg	2 mg (neutropenia)	54%	9.7/ - / 22.5
Streetly et al. BJH 2008	Pom	20	28/28	1,2,5, or 10 mg	5mg QOD (neutropenia)	50%	10.5 / - / 33
Richardson et al. 2011 (MM-002)	Pom +/- Dex	38	21/28	2 to 5mg	4 mg (neutropenia)	25%	5.0 /5.0 / 19.9

Lessons from Phase 1 studies

- Dose limiting toxicities are hematologic
- Venous thromboses can occur
- There is promising activity as both a single agent and with dex.
- So far, so good.

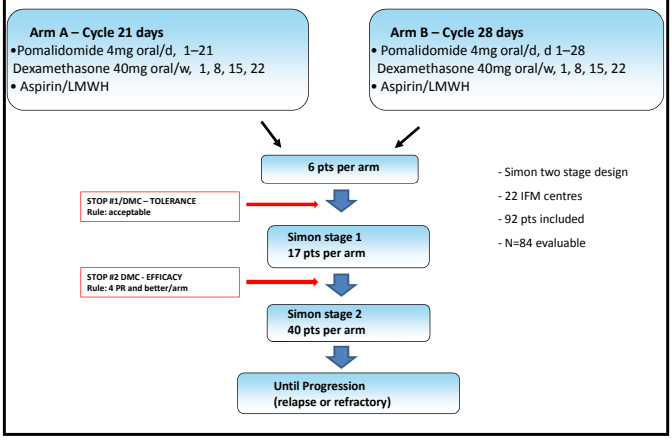


Phase 2 Studies (1)

Study / (# prior regimens)	Regimen	N	Schedule	Doses	OR R	SD	MR	PR	≥ VGPR	PFS/DOR/OS, months
Lacy et. al JCO 2009 (2)	Pom / Dex	60	28/28	2 mg	63%	25%	-	30%	33%	11.6 / 21.3 / 94% at 6 months, 76% at 2 years
Lacy et al. Leuk 2010 * (4)	Pom / Dex	34	28/28	2 mg	32%	35%	15%	23%	9%	4.8 / 9.1 / 13.9
IFM 2009-02 Leleu IMW 2011 ✪ (4)	ARM A	43	21/28	4 mg	42%	46.5%		26.5%	16%	7m / - / 88% alive at 6m
	ARM B	41	28/28	4 mg	39%	51%		27%	12%	9.7 / - / 85% alive at 6m

* Lenalidomide refractory subjects
✪ Lenalidomide and bortezomib refractory subjects

IFM 2009-02



Patient Characteristics at entry into IFM2009-02

Arm	21/28 N = 43	28/28 N = 41
Median age, years (range)	54 (39-78)	53 (36-69)
Gender ratio (M/F)	2	2
Neuropathy (all grades), N (%)	34 (79)	25 (61)
DVT/PE prophylaxis, N(%) LWMH	10 (23)	8 (19.5)
VKA	7 (16)	4 (10)
Median Hb, g/dL (range)	11 (7-14)	13 (6-14)
Median PNn, x10^9/L (range)	2.6 (1.0-10)	2.8 (0.9-8)
Median Plat, x10^9/L (range)	168 (51-366)	142 (63-269)
T(4;14), N(%)	0	3 (7)
Del17p, N(%)	5 (12)	4 (10)
Prior line of therapy, N (range)	**4 (1-8)**	**4 (1-8)**
Thalidomide, N (%)	20 (46.5)	24 (58.5)
Revlimid, N (%)	(100)	(100)
Velcade, N (%)	(100)	(100)

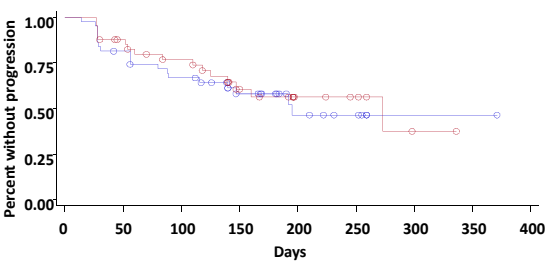
DVT: Deep Veinous Thromboembolism/PE: Pulmonary Embolism; LWMH: Low Weight Molecular Heparin; VKA: Vitamin K antagonist

Response (ITT - Central lab)

Arm	21/28 N=43	28/28 N=41
Number of cycle, median	**5**	**5**
ORR (PR and better), N(%)	**18 (42)**	**16 (39)**
sCR	0	0
CR	1 (2)	0
VGPR	3 (7)	2 (5)
PR	14 (32.5)	14 (34)
Stable disease, N(%)	20 (46.5)	21 (51)
Progression, N(%)	5 (12)	1.7 (10)
Time to best response, months (range)	**2 (1-9)**	**1.7 (1-9)**

Time To Progression (TTP)

Median follow-up is 6.5 months (arm A 21/28) and 7 months (arm B 28/28)



Arm	O/N	Median, months	Range
21/28	19/43	7	(4 -)
28/28	16/41	9.7	(4 -)

O/N: observed number / total number

Phase 2 Studies (2)

	Regimen	N	Schedule	Doses	ORR	SD	MR	PR	≥ VGPR	PFS/DOR/OS, months
Richardson, et. al IMW 2011⊙ (5)	Pom +/- Dex	120	21/28	4 mg	33%	63%		26%	6%	- / - / -
Lacy et. al Blood 2011✪ (6)	Low dose	35	28/28	2 mg	25%	-	23%	11%	14%	6.5 / - / 78% alive at 6m
	High dose	35	28/28	4 mg	29%	-	14%	17%	12%	3.2 / - / 67% alive at 6m
Mark et. al ASH 2011⊙	ClaPD	46	21/28	4 mg	TBD					

✪ Bortezomib and Lenalidomide refractory subjects
⊙ Bortezomib and Lenalidomide relapsed subjects

MM-002: Efficacy and Impact of Cytogenetics

	Assessment of Best Response		
N = 120	Adverse Cytogenetics n = 45 N (%)	Normal Cytogenetics n = 74 N (%)	IMWG - Overall N (%)
≥PR	8 (18)	22 (30)	30 (25)
CR	0	1 (1)	1 (1)
PR	8 (18)	21 (28)	29 (24)
MR	8 (18)	8 (11)	16 (13)
SD	25 (56)	38 (51)	64 (53)
PD	4 (9)	6 (8)	10 (8)

Adverse Cytogenetics: presence of del 13q14, del17p13, t(4;14), t(14;16)

Impact of Prior Therapy

- **POM: clinical efficacy in heavily pretreated pts following lenalidomide (LEN) treatment at a dose of 2 mg given continuously with dex**

Phase 2 IIT study: POM 2 mg + low-dose dexamethasone (dex)[1-3]			
	ORR	PFS	OS
1-3 prior therapies[1]	63%	11.6 mos	94% at 6 mos
Refractory to LEN[2]	32%	4.8 mos	13.9 mos
Refractory to LEN & Bz[3]	26%	8 mos	86% at 6 mos

1. Lacy et al. J Clin Oncol. 2009;27:5008-5014. 2. Lacy et al. Leukemia. 2010;Sept 9:Epub ahead of print. 3. Lacy et al. ASCO 2010 Presentation (Abstract 8002). 4. Richardson P, et al. Blood. 2009;114:126-127[abstract 301].

Toxicities in Phase 2 studies

Toxicity	Lacy 2009 (n=60)	Lacy 2010 (lenalidomide refractory RRMM) (n=34)	Lacy 2011 (double - refractory RRMM)(n=70)		Leleu 2010 (IFM 2009-02) (n=84)	
			2 mg	4 mg	4 mg 21/28 days	4 mg 28/28 days
Hematological (%)					23.5*	26.5*
Neutropenia	32	29	51	65		
Thrombocytopenia	3	9	32	31		
Anemia	5	12	26	26		
Non-hematological (%)			23*	13*	12*	9*
Fatigue	17	9	9	9		
Pneumonia	8	3	31	3		
Hyperglycemia	5	3	9	3		
Peripheral neuropathy	2	0	0	3		
Thromboembolic complications	2	0				

* No breakdown of grade 3 or 4 adverse events reported

Lessons from Phase 2 Studies

- Activity present in lenalidomide-refractory patients
  - ORR 32% in len-refractory
  - ORR 25% in both len and bortez-refractory
- 4 mg daily is NOT better than 2mg
- 4 mg daily is NOT better than 4mg 21/28 days
- ORR correlates with # of prior lines of therapy
- Significant response rate in high-risk cytogenetics



Summary Slide 1

- Pomalidomide is:
  - 2nd generation IMiD
  - Has anti-proliferative, anti-angiogenic, and IMiD properties
  - Primary toxicities are similar to lenalidomide:
    - Myelosuppression
    - Venous thromboses

Summary Slide 2

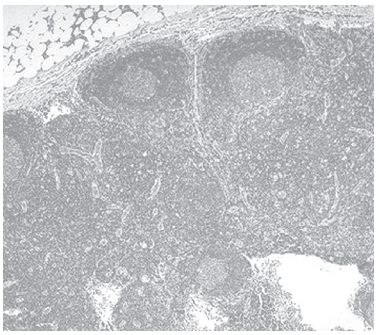
- Pomalidomide is:
  - Active as a single agent
  - Synergizes with dexamethasone
  - Active in MM that is lenalidomide-refractory
  - Active in MM that is double-refractory
  - Less active as number of prior lines of therapy increases

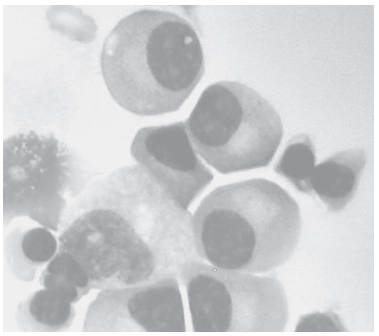
Lingering Questions



- We still don't know the optimal dosing schedule
- We still don't know it's optimal drug partners:
  - Clarithromycin?
  - Bortezomib?
  - Newer agents?
- How will it work in the first-line setting? In patients with renal insufficiency?
- Will it have a survival benefit?

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





New treatments and how best to use them in lymphoma and myeloma: Elotuzumab

Paul G. Richardson, MD

DANA-FARBER CANCER INSTITUTE

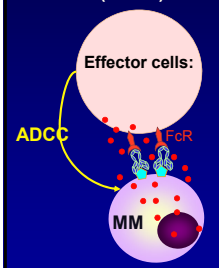
Elotuzumab in the Treatment of Multiple Myeloma

Paul G. Richardson, MD

Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute,
Harvard Medical School
Boston, MA

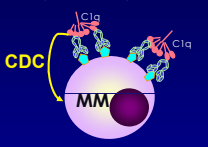
MAb-Based Therapeutic Targeting of Myeloma

Antibody-dependent Cellular cytotoxicity (ADCC)



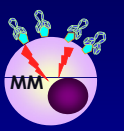
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1)
- Daratumumab (CD38)
- XmAb®5592 (HM1.24)

Complement-dependent Cytotoxicity (CDC)



- Daratumumab (CD38)

Apoptosis/growth arrest via targeting signaling pathways



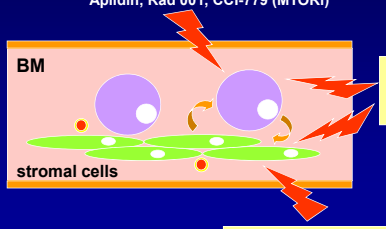
- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- 1339 (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab (CD38)

Tai & Anderson Bone Marrow Research 2011

Novel Therapies Targeting Myeloma Cells in the BM Microenvironment

Targeting MM Cell

IGF-1 inhibitors, CD40 MoAb, CSI MoAb
17-AAG, IPI504, AUI (HSP 90 inhibition),
Aplidin, Rad 001, CCI-779 (MTORi)

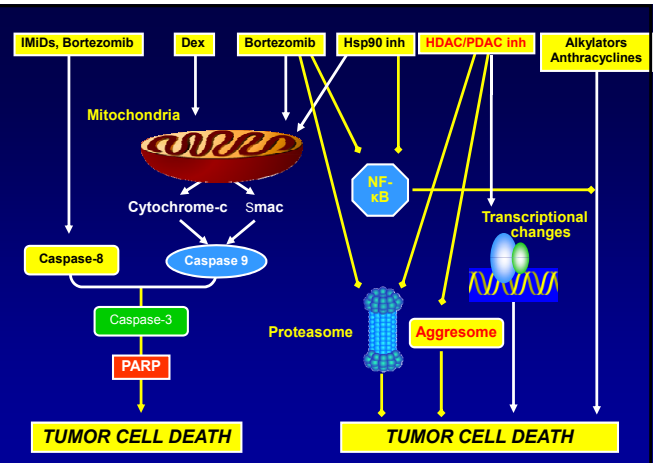


Targeting MM Cell and BM Milieu

Bortezomib, PR171, NPI052
MLN 9078, Thalidomide,
Lenalidomide,
Pomalidomide, SAHA,
LBH, Romidepsin, Perifosine

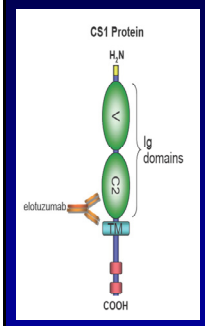
Targeting BM Milieu

IKK inhibitors, defibrotide, AMD 3100
p38MAPK inhibitors, anti - IL6 MoAb



Synergistic anti-MM activity: Bortezomib/IMiD-based Combos with other novel agents, including HDAC inhibitors

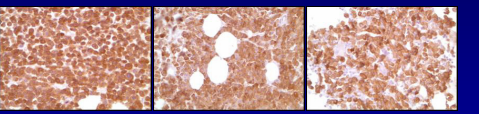
Elotuzumab- a Monoclonal Antibody to CS1



- A humanized monoclonal IgG1 targeting human CS1 protein
  - No cross-reactivity with non-human species, including primates
- CS1 exhibits a restricted expression profile
  - Multiple myeloma and normal plasma cells
  - NK, NKT, subset of CD8 T cells, activated monocytes
  - Not on normal stem cells or most other normal tissues
- The role of CS1 on plasma cells is not known

Elotuzumab: Background

- Elotuzumab (HuLuc63) is a humanized monoclonal IgG1 antibody targeting human CS1, a cell surface glycoprotein[1,2]
- CS1 is highly and uniformly expressed on MM cells[1–3]
  - Restricted expression on NK cells
  - Little to no expression on normal tissues



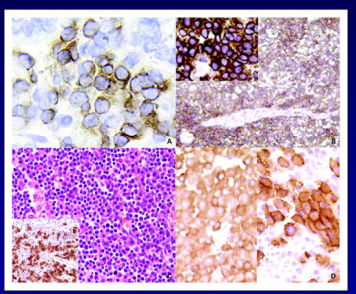
- In a MM xenograft mouse model, the antitumor activity of elotuzumab was enhanced by the addition of lenalidomide[4]

MM, multiple myeloma; NK, natural killer.

1. Hsi ED et al. *Clin Cancer Res*. 2008;14:2775-2784. 2. Tai YT et al. *Blood*. 2008;112:1329-1337
3. van Rhee F et al. *Mol Cancer Ther*. 2009;8:2616-2624. 4. Lonial S et al. *Blood*. 2009;114:432

CS1 has high level of expression on plasma Cells

Normal plasma cells



Plasmacytoma

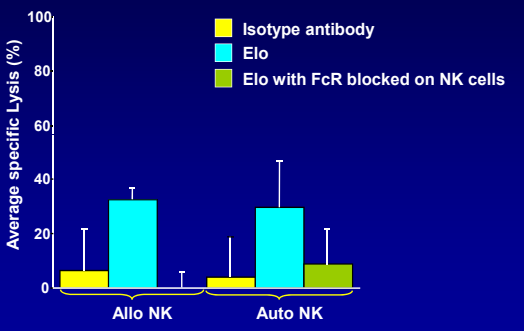
Lymphoplasmacytic lymphoma

Myeloma cells in bone marrow

CS1 is highly and uniformly expressed on multiple myeloma cells but minimally expressed by normal cells

Hsi, E.D. et al. *Clin Cancer Res* 2008;14:2775-2784.

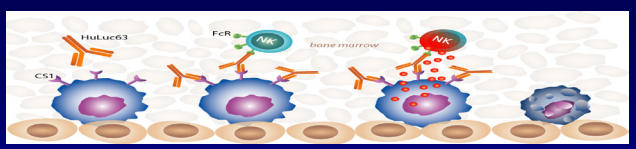
Elotuzumab Mediates ADCC *In Vitro* Against Primary Myeloma



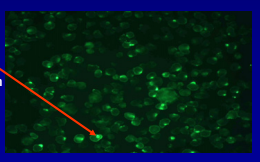
30 : 1 Effector: primary myeloma cell

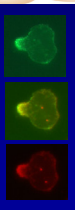
S. Szmania, F. van Rhee (UAMS)

Elotuzumab MoA: Antibody-dependent NK Cell Mediated Cytotoxicity (ADCC)



CS1 expressed on uropods in MM cells





Elotuzumab-AF488

Merged images

CD138-APC

Location of CS1 on polarized cell may make for optimal ADCC target

Nature Mol Cell Bio May 2009 "Bringing up the rear: defining the roles of the uropod"

HuLuc63-1701: Elotuzumab as Monotherapy

- No monotherapy activity seen in relapsed/refractory MM
  - Median prior therapies = 4.5
  - All pts previously progressed on Velcade, Thal and/or Rev
  - Overall best response was SD (26%), at 10/20 mg/kg doses (35%)
  - In SD patients, median TTP was 4.5 months
- Potential reasons for lack of activity
  - Possible impaired/sub-optimal NK function in heavily pretreated, advanced MM
  - Possible sub-optimal dosing

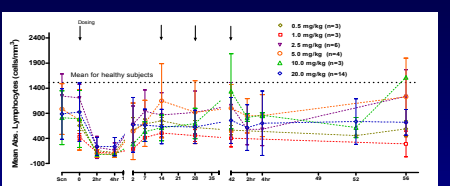
J. Zonder et al. Blood. 2008;112(11): Abstract 2773.

HuLuc63-1701: Well Tolerated

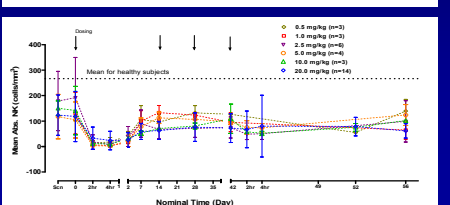
- MTD was not reached up to the highest dose level of 20 mg/kg
- Key SAEs were first dose infusion reactions (IR)
  - Gr 3 allergic reaction, Gr 2 rigors, fever, chest pressure, bradicardia
  - No dose correlation seen for IR
  - No serious infusion reactions following IV corticosteroid premedication
- No neutropenia or thrombocytopenia
- Reduction in lymphocytes seen following first dose

J. Zonder et al. Blood. 2008;112(11): Abstract 2773.

Elotuzumab Induces Cycle 1 Lymphopenia With Partial Recovery– Not Clinically Significant

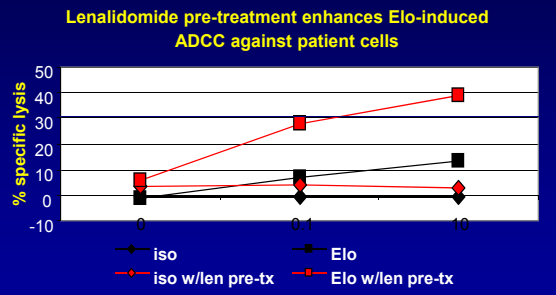


Total Lymphocytes



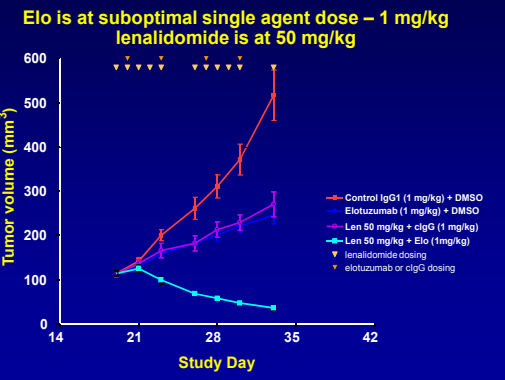
NK Cells

Lenalidomide Pre-treatment Enhances Elo-mediated ADCC Against Patient Cells



Y.-T. Tai, K. Anderson, et al. *Blood*. 112:1329-37,2008.

Elotuzumab Significantly Enhances Anti-tumor Activity of Lenalidomide

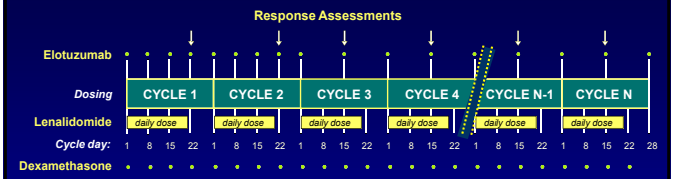


Phase I Trial of Elotuzumab/Lenalidomide/Dexamethasone in Relapsed Multiple Myeloma

- 28 treated pts with a median of 3 prior MM treatments
  - MTD not reached up to 20 mg/kg
  - Two SAEs of infusion reaction
- Overall 23/28 (82%) patients responded: 21/22 (95%) lenalidomide-naïve patients achieved ≥ PR
- Phase 2 expansion study: identify the optimal dose of elotuzumab (10 vs. 20 mg/kg) in combination with lenalidomide and low dose dexamethasone

Lonial S, et al. ASH 2009

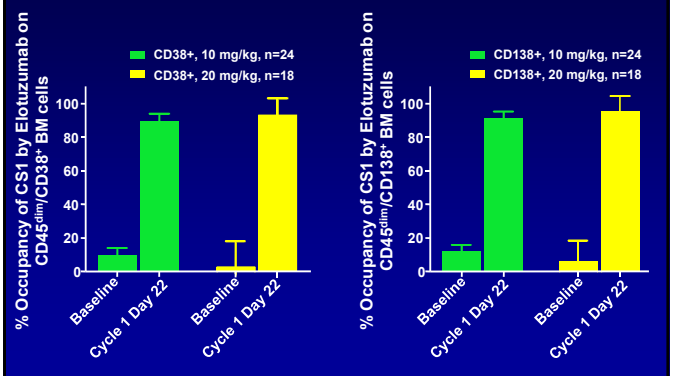
Elo + Rd: Randomized Phase 2 Study Schema



- Pts randomized to receive elotuzumab 10 or 20 mg/kg IV, in combination with lenalidomide 25 mg PO and low-dose dexamethasone 40 mg PO wkly (28-day cycles)
- Treatment continued until PD or unacceptable toxicity
- Premedication regimen (30–60 mins prior to elotuzumab infusion)
  - Methylprednisone 50 mg IV
  - Diphenhydramine 25–50 mg PO or IV (or equivalent)
  - Ranitidine 50 mg IV (or equivalent)
  - Acetaminophen 650–1000 mg PO

Richardson et al, ASH 2010

CS1 Saturation on CD38+ and CD138+ in Patient BM MM Cells



Richardson et al, ASH 2010

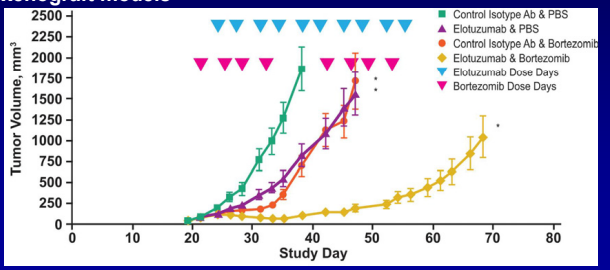
Elo + Rd~ Conclusions

- Elotuzumab + len/dex was generally well tolerated
  - Gr 3/4 AEs >10%: neutropenia (14%), lymphopenia (14%), thrombocytopenia (13%)
  - Premedication regimen appears to mitigate the incidence and severity of infusion reactions
- High ORR in previously-treated MM pts
  - Phase 1: 82%[1,2]
  - Phase 2: 81% ORR, 37% VGPR/CR
- 10 mg/kg elotuzumab is recommended Phase 3 dose
  - High activity (90% ORR, 42% VGPR/CR), similar safety and CS1 saturation to 20 mg/kg
  - High ORR in β2M ≥3.5 mg/L, prior thalidomide and median ≥2 prior therapies
- Phase 3: Randomized, Open Label Trial of Lenalidomide/Dexamethasone With or Without Elotuzumab in Relapsed or Refractory MM anticipated to start early 2011 (NCT 01239797)

1. Lonial S et al. ASCO 2010; Abstract 8020 (Oral). 2. Lonial S et al. ASH 2010; Abstract 1936.

Efficacy of Elotuzumab and Bortezomib in Multiple Myeloma Xenograft

- Elotuzumab in combination with bortezomib exhibited significantly enhanced *in vivo* antimyeloma activity in mouse xenograft models



*Statistically significant compared to control ($p<0.05$)
Ab, antibody; PBS, phosphate buffered saline.

van Rhee F et al. *Mol Cancer Ther.* 2009;8:2616-2624
Rice AG et al. *Blood.* 2007;110(11): Abstract 2517

Study Objectives

Primary objective

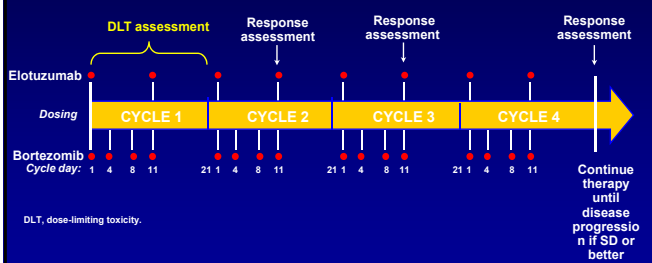
- Establish maximum tolerated dose (MTD)* of elotuzumab in combination with bortezomib

Secondary objectives

- Determine overall safety and tolerability of the combination
- Evaluate clinical efficacy of the combination
- Determine pharmacokinetics, pharmacodynamics, and immunogenicity of elotuzumab

A. J. Jakubowiak et al. J Clin Oncol 28: 15s, 2010.

Study Schema



DLT, dose-limiting toxicity.

A. J. Jakubowiak et al. J Clin Oncol 28: 15s, 2010.

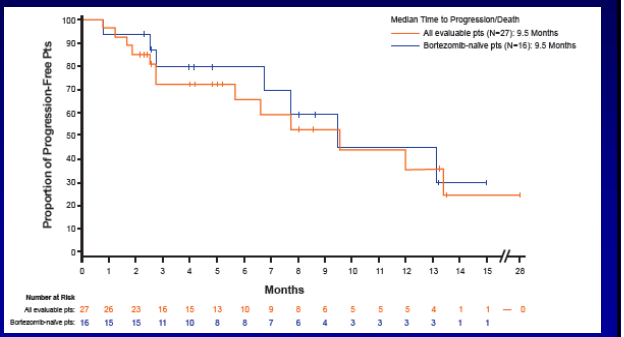
Best Confirmed Response (EBMT)

Parameter	All Patients	By Prior Therapy			
		Bortezomib-naive	Prior Bortezomib	Refractory to Prior Bortezomib	Refractory to Last Line of Therapy
Total evaluable patients,* n	27	16	11	3	11
ORR (≥ PR), n (%)	13 (48)	8 (50)	5 (45)	2 (67)	5 (45)
ORR 95% CI, %	29-68	25-75	17-77	9-99	17-77
Clinical response rate (≥ MR), n (%)	17 (63)	12 (75)	5 (45)	2 (67)	7 (64)
CR, n (%)	2 (7)	2 (13)	0	0	1 (9)
PR, n (%)	11 (41)	6 (38)	5 (45)	2 (67)	4 (36)
MR, n (%)	4 (15)	4 (25)	0	0	2 (18)
SD, n (%)	8 (30)	3 (19)	5 (45)	0	3 (27)
PD, n (%)	2 (7)	1 (6)	1 (9)	1 (33)	1 (9)

*Patients who completed 2 cycles of therapy or progressed earlier.
CI, confidence interval; CR, complete response; EBMT, the European Group for Blood and Marrow Transplantation; MR, minimal response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

A. J. Jakubowiak et al. J Clin Oncol 28: 15s, 2010.

PFS of All Evaluable Patients and Prior Bz-Naïve Patients



A. J. Jakubowiak et al. J Clin Oncol 28: 15s, 2010.

Elotuzumab Clinical Trials

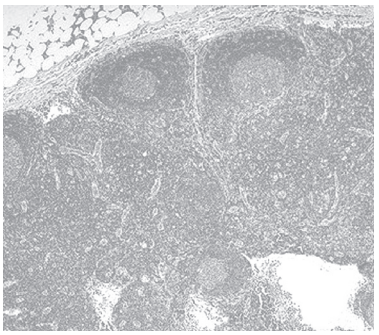
Population	Design	Study
Studies that are open and recruiting		
Newly diagnosed symptomatic MM	Phase 3 open label: lenalidomide +/- elotuzumab	ELOQUENT - 1
Relapsed/refractory MM (1-3 prior therapies)	Phase 3 open label: lenalidomide +/- elotuzumab	ELOQUENT - 2
Studies that are pending recruitment		
Symptomatic MM, newly diagnosed or relapsed/refractory	Phase 1b: elotuzumab + lenalidomide in patients with normal renal function, severe renal impairment, or ESRD requiring dialysis	CA204-007
High risk smoldering MM	Open label biomarker association study in patients treated with elotuzumab monotherapy	CA204-011

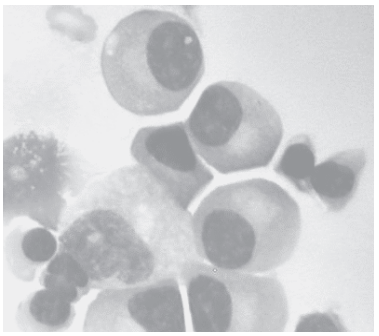
Elotuzumab Anti-CS MoAb in MM

- CS1 is highly and uniformly expressed on MM cells
- Elotuzumab (Elo) is a humanized monoclonal IgG1 antibody targeting CS1
- Clinical trial of Elo in MM achieved SD
- Anti-MM activity of Elo enhanced by lenalidomide (len) in preclinical models
- Phase I/II trials: 80-90% response to len dex elo in relapsed MM
- Phase III trial of len dex elo versus len dex in relapsed MM for new drug approval

Hsi ED et al. Clin Cancer Res. 2008;14:2775-2784; Tai YT et al. Blood. 2008;112:1329-1337
Van Rhee F et al. Mol Cancer Ther. 2009;8:2616-2624; Lonial S et al. Blood. 2009;114:432
Richardson et al Blood 2010:864

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





New treatments and how best to use them in lymphoma and myeloma: HDAC inhibitors

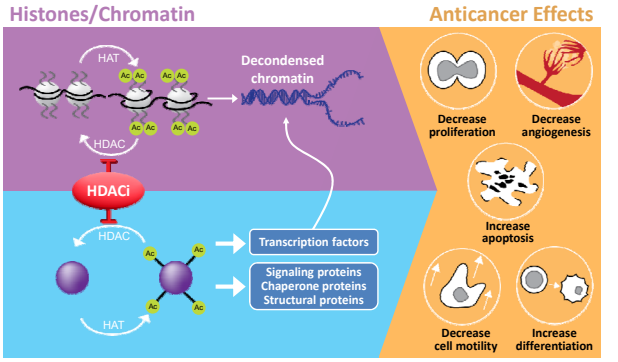
Kenneth C. Anderson MD

Histone Deacetylase Inhibitors in Myeloma

Kenneth C. Anderson, M.D.

Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Harvard Medical School

HDAC Inhibition Affects Histone and Nonhistone Proteins, Leading to Multiple Anticancer Effects



Nonhistone Protein: *p53, Hsp90, Tubulin, HIF-1*

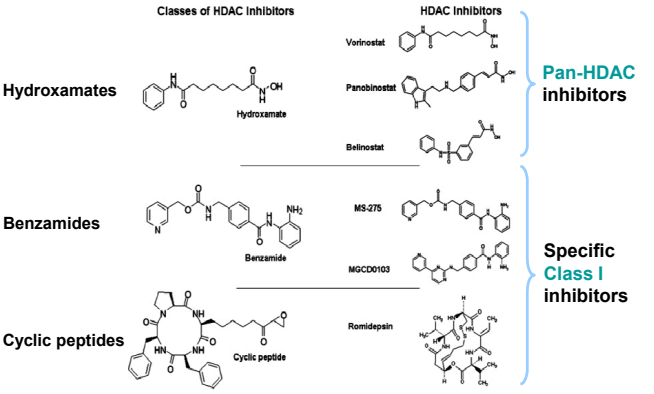
Adapted from Paik PK, Krug LM. J Thorac Oncol. 2010;5(2):275–279

Deacetylase (HDACs) Classification

- Class I…….. HDAC **1**, **2**, **3**, 8
  . Are restricted to the nucleus of the cell
  . P53, MEF2D, Stat 3 and E2F are relevant substrates
- Class II A…….. HDAC 4, 5, 7, 9
  . Are both nuclear & cytoplasmic
- Cass II B…….. HDAC **6**, 10
  . Are Cytoplasmic
  . α–tubulin & HSP90 are relevant substrates
- Class IV…….. HDAC 11

* *Class I, II & IV-are called "classical HDAC"*
* *Class III are called Sirtuins*

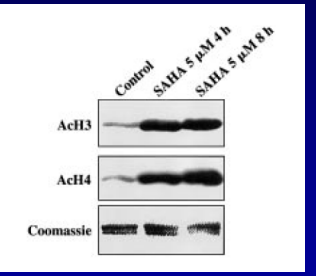
Types of HDACi in the clinic



Atadja P. Cancer Lett. 2009

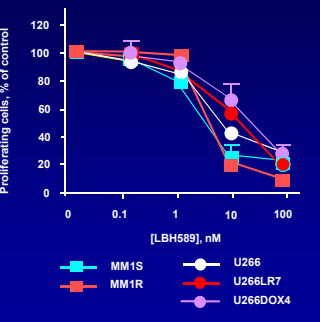
Vorinostat Preclinical Activity in Multiple Myeloma

- Induces accumulation of acetylated histones in MM cell lines



Mitsiades N. *Blood.* 2003;101:4055-4062

Panobinostat Induces Growth Arrest and Apoptosis in Drug-Resistant Myeloma Cell Lines



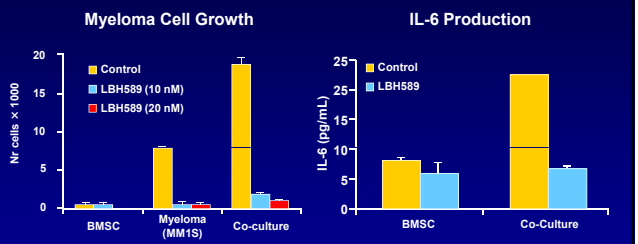
Myeloma cell lines which are resistant to

- Dexamethasone (MM1R)
- Melphalan (U266 and U266LR7)
- Doxorubicin (U266Dox4)

are sensitive to panabinostat

Maiso P, et al. *Cancer Res.* 2006;66:5781-5789.

Panobinostat Overcomes the Growth Stimulus of the Bone Marrow Microenvironment in Myeloma



Catley L, et al. *Blood*. 2006;108:3441-3449

HDAC Inhibitors Have Synergistic or Enhanced Cytotoxic Effects With Multiple Therapies

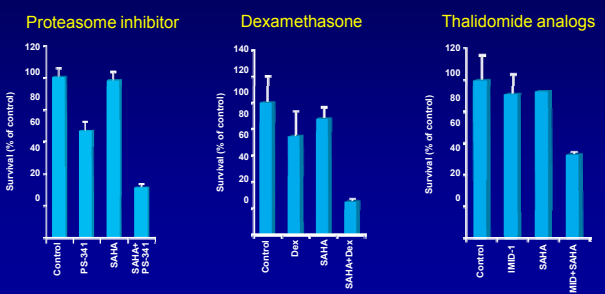
Synergistic or enhanced cytotoxicity when combined with vorinostat*

Therapeutic class	Therapy
Proteasome inhibitors[1-3]	Bortezomib
Immunomodulatory drugs (IMiDs)[3,4]	Thalidomide derivative IMiD-1
Alkylating agents[4,5]	Melphalan
Steroids[3,4]	Dexamethasone
DNA methyltransferase inhibitors[5-7]	Azacytidine, decitabine
Mammalian target of rapamycin (mTOR) inhibitors[8-10]	Temsirolimus, everolimus
Radiotherapy[11-14]	Ionizing radiation

HDAC=histone deacetylase
* Demonstrated in MM cells or disease models except mTOR inhibitors and radiotherapy

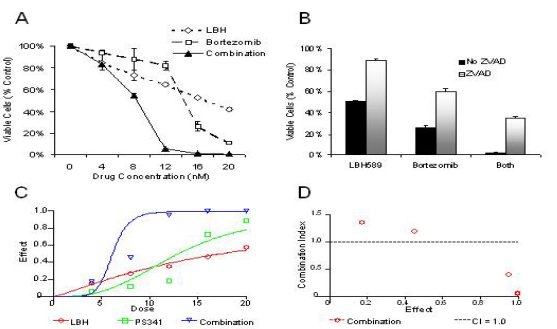
1. Pei et al. Clin Cancer Res. 2004;10(11):3839-3852
2. Maharaj et al. *Blood*. 2006;108(11):2604
3. Mitsiades et al. *Clin Lymph Myeloma*. 2009;9:Abstr B257
4. Mitsiades et al. Proc Natl Acad Sci. 2004;101(2):540-545
5. Campbell et al. J Clin Oncol (ASCO Annual Meeting). 2008;Abstr 733
7. Cameron et al. Nat Genet. 1999;21:103-107
8. Yazbeck et al. *Blood*. 2006;108(11): 2493
9. Haritunians et al. *Leukemia*. 2007;21(2):333-339
10. Yazbeck et al. Exp *Hematol*. 2008;36(4):443-450
11. Chinnaiyan et al. *Int J Radiat. Oncol Biol Phys* 2005;62(1):223-229
12. Munshi et al. *Mol Cancer Ther*. 2006;5(8):1967-1974
13. Baschnagel et al. *Mol Cancer Ther*. 2009;8(6):1589-1595
14. Blattmann et al. *Int J Radiat Oncol Biol Phys*. 2010;78(1):237-245

Vorinostat Enhances Sensitivity of MM to Conventional and Novel Agents



Mitsiades CS. *Proc Natl Acad Sci USA*. 2004;101:540-545

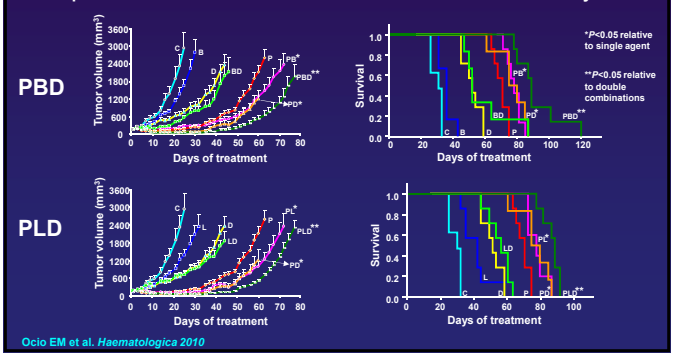
LBH589 (Panabinostat) is Selectively Synergistic With Bortezomib Against MM Cells



Catley et al. Blood 2006

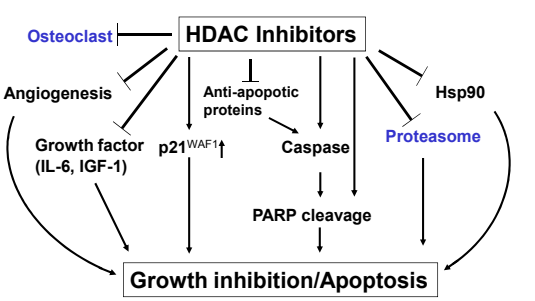
In vivo Anti MM Activity of Panobinostat with Dex, Lenalidomide, and/or Bortezomib

- Double combination with Bort, Len, or Dex is better than single agents
- Triple combination of PAN + Dex + either Bort or Len better than any doublet



Ocio EM et al. *Haematologica 2010*

Possible Mechanisms of Action of HDAC Inhibitors in MM Cells



Transcriptional (via histones) vs non-transcriptional

Monotherapy with Vorinostat in MM

- 13 heavily pre-treated patients with relapsed/refractory myeloma (12 had >3 treatments; 8 had prior BMT).
- 1 confirmed minor response (MR) and 9 stable diseases were observed.
- Of 9 patients with SD, 5 (55.6%) patients were progression free by 3 months (4 cycles or 12 weeks), and 1 (11.1%) was progression free by 6 months (8 cycles or 24 weeks)
- Generally well tolerated
- Early termination (not due to safety concerns)

Richardson et al Blood 2004; 104: abs 1503 [13]
Richardson et al, Leukemia and Lymphoma, 2007

Single-Agent Panobinostat in MM

- 38 pts: all refractory on most recent therapy
- Prior lines of therapy: 5 (range 2-12)
  - 25 out of 38 pts had received bortezomib , lenalidomide, and thalidomide, and 31 at least bortezomib and one IMiD
- Single-agent dose of 20 mg three times a week, QW suboptimal, however:
  - Interesting observations of activity:
    - 1 VGPR and 1 MR
    - Both pts remained stable on panobinostat for > 15 months
  - Tolerability:
    - Only few discontinuations due to AEs (cytopenia, GI, fatigue)
    - Few QTc interval prolongations, not clinically significant

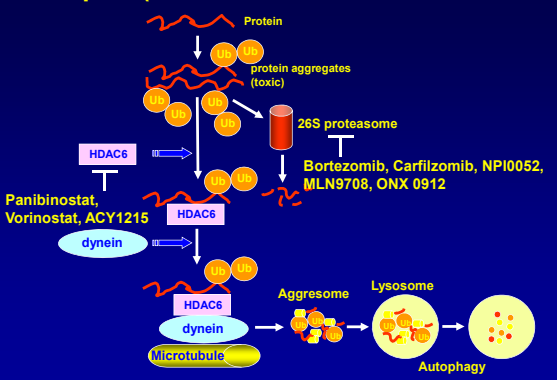
Activity of HDAC Inhibitors in MM Monotherapy

	N	ORR	Responses
Vorinostat[1] (SAHA)	10	0%	1 MR, 9 SD
Panobinostat[2] (LBH589)	38	3%	1 PR, 1 MR, 3 SD
Givinostat[3] (ITF2357)	19	0%	5 SD
Romidepsin[4] (FK228)	12	0%	4 SD

MR=minimal response; ORR=objective response rate (≥MR); PR=partial response; SD=stable disease

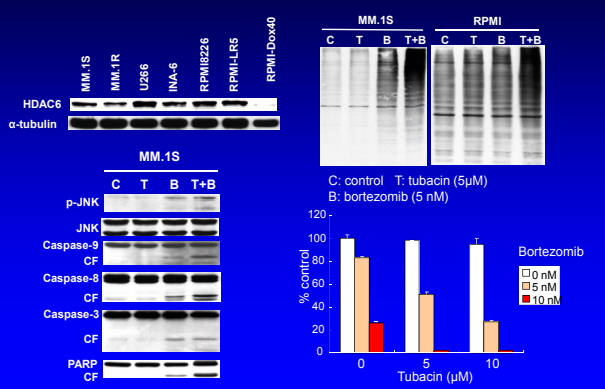
1. Richardson et al. *Leuk Lymphoma*. 2008;49(3):502-507
2. Wolf et al. ASH Annual Meeting 2008;Abstract 2774
3. Galli et al. *Ann Hematol*. 2010;89(2):185-190
4. Niesvizky et al. *Cancer*. 2011;117(2):336-342

Development of Rationally-based Combination Therapies (HDAC and Proteasome Inhibitors)



Hideshima et al. *Clin Cancer Res*. 2005;11:8530.Catley et al. *Blood*. 2006;108:3441-9.

Targeting Proteasome and Aggresome Triggers Synergistic MM Cytotoxicity

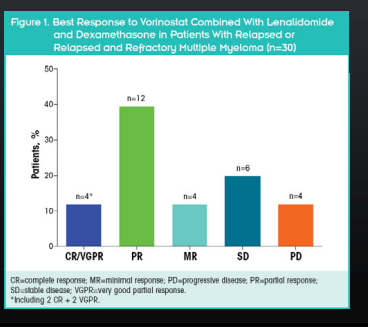


Hideshima et al. PNAS 2005; 102: 8567.

Phase I Study of Vorinostat, Lenalidomide, Dexamethasone

Of the 30 pts evaluable for efficacy, 26 pts (87%) had clinical benefit (complete response [CR] + partial response [PR] + minimal response [MR] + stable disease [SD]) on treatment.

Best single responses



Richardson et al , ASCO 2010

Bortezomib Vorinostat Phase I Trials

Trial 1

Cohort	Vorinostat po mg (Days 1-14)	Bortezomib mg/m² IV		n	DLT
1	200 bid	0.7	Day 4,8,11,15	3	-
2	200 bid	0.9	Day 4,8,11,15	3	-
3	400 qd	0.9	Day 1,4,8,11	6	Transient AST elevation (Grade 3)
4	400 qd	1.1	Day 1,4,8,11	6	-
5	400 qd	1.3	Day 1,4,8,11	6	Thrombocytopenia (Grade 4)
6	300 qd	1.3	Day 1,4,8,11	10	-

Trial 2

Cohort	Vorinostat po mg (Days 4-11)	Bortezomib mg/m² IV		n	DLT
1a	100 bid	1.0	Day 1,4,8,11	3	-
1	100 bid	1.3	Day 1,4,8,11	3	-
2	200 bid	1.3	Day 1,4,8,11	3	-
3	400 qd	1.3	Day 1,4,8,11	11	(3 + 8) -
4	500 qd	1.3	Day 1,4,8,11	3	Long QT interval; fatigue (both Grade 3)

I.V. intravenous; AST, aspartate aminotransferase

Weber DM et al. *Blood* (ASH Annual Meeting) 2008;112:Abstr 871
Badros A et al. *Clin Cancer Res* 2009;15:5250–5257

Vorinostat-Bortezomib Phase I Trials

Weber et al ASH 2008 Abstr 871

Effective for treatment of relapsed/refractory MM
- Overall response (PR + CR) ~38-43%
- ≥ SD ~90%

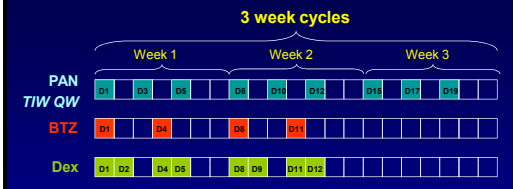
Effective despite prior bortezomib therapy
- Overall response ~29-35%
- SD ~41-53%
- Overall response refractory pts ≥ PR ~29-38%
- SD refractory pts ~42-50%

Well Tolerated Fatigue, Diarrhea, thrombocytopenia

Phase III trial of Bortezomib and Vorinostat versus Bortezomib in relapsed MM for FDA approval

Panobinostat Bortezomib in Rel or Rel & Ref MM pts

Dose Escalation Phase of LBH589B2207 Study - Treatment Scheme



8 Cycles with BTZ +PAN

PAN every week schedule & continued until progression

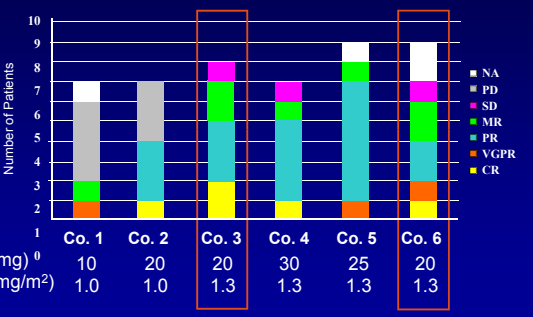
TIW QW: three times a week, every week

- Drug dose levels used in dose escalation phase
  - PAN: 10 mg, 20 mg, 25 mg, and 30 mg
  - BTZ: 1.0 mg/m², 1.3 mg/m²
  - (Dex : 20 mg fixed dose added at Cycle 2 in suboptimal responders)
- Pts with MM relapsed after ≥ 1 line of therapy, or relapsed and refractory, and suitable for treatment with BTZ

Panobinostat + Bortezomib Best Response

Dose Escalation B2207 Study in Relapsed MM Patients

Clinical benefit (≥ MR) in 13/17 (76%) at cohort 3 and 6 dose level



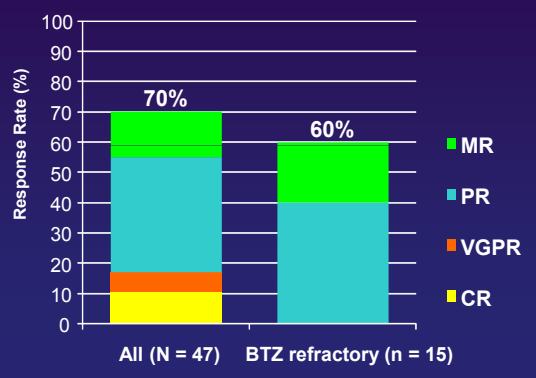
	Co. 1	Co. 2	Co. 3	Co. 4	Co. 5	Co. 6
PAN (mg)	10	20	20	30	25	20
BTZ (mg/m²)	1.0	1.0	1.3	1.3	1.3	1.3

PAN panobinostat; BTZ bortezomib.

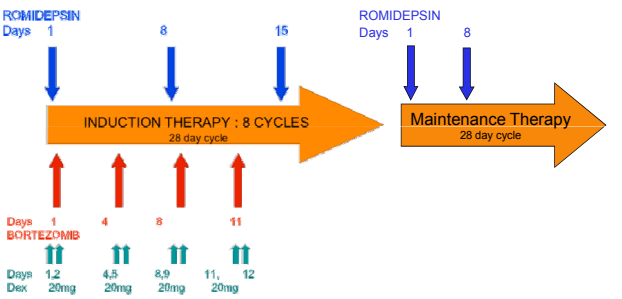
CR, IF-negative CR; VGPR, very good PR; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease; NA, no assessment.

Panobinostat + Bortezomib Efficacy

San Miguel et al, ASCO 2010
Panorama Phase III trial of Pan/Bort vs Bort Ongoing



Romidepsin + Bortezomib in Relapsed/Refractory MM: Harrison et al, Blood 2011

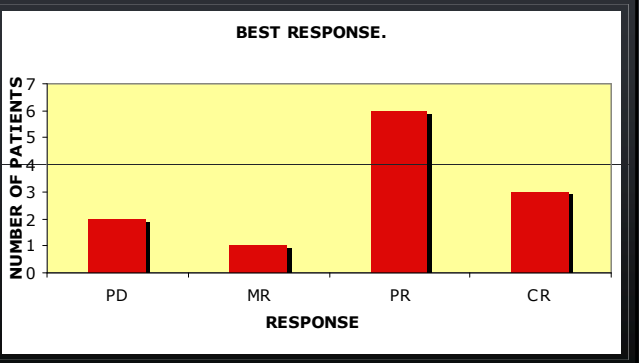


Romidepsin + Bortezomib in Relapsed/Refractory MM

Harrison et al, Blood 2011

- Bortezomib + Romidepsin induction is safe.
- Maintenance romidepsin proved feasible
  - 12 patients received a median of 7.5 (1- 29) cycles.
- The major toxicities were;
  - Neuropathy 76% (n = 19) (grade ≥ 3, 8%)
  - thrombocytopaenia (64%)
- OR (≥MR) was seen in 18/25 patients (72%)
- 2 (8%) CR, 7 (28%) VGPR, 6 (24%) PR
- Median TTP was 7.2 (5.5 – 19.6) months
- Median OS was >36 months.

Romidepsin + Bortezomib in Relapsed/Refractory MM



Harrison et al, Blood 2011

Efficacy of HDAC Inhibitors + Bortezomib

	Vorinostat[1]	Vorinostat[2]	Panobinostat[3*]	Romidepsin[4**]
Patients, n	23	34	62	25
Median prior regimens, n	**4**	**7**	**2**	**2**
≥PR, %	43%	47%	55%	60%
Prior bortezomib, %	83%	38%	63%	NR
Bortezomib–refractory, %	39%	NR	31%	NR
Prior IMiD (≥MR), %	NR	NR	NR	33%

*MTD=Panobinostat 20 mg thrice weekly (TIW) + bortezomib 1.3 mg/m² ± dexamethasone on a 4-week cycle

**MTD=Romidepsin 10 mg/m² once weekly (3 weeks on, one off) + bortezomib 1.3 mg/m² twice weekly (2 weeks on, 2 off) + 20 mg dexamethasone on a 4-week cycle

1. Badros et al. Clin Cancer Res. 2009;15:5250–5257
2. Weber et al. IMW Meeting 2011; Abstr 246, 248
3. San Miguel et al. IMW Meeting 2011; Abstract P-238
4. Harrison et al. Blood. 2011 Sep 12.

Comparison of Safety: HDAC Inhibitor + Bortezomib ± Dexamethasone

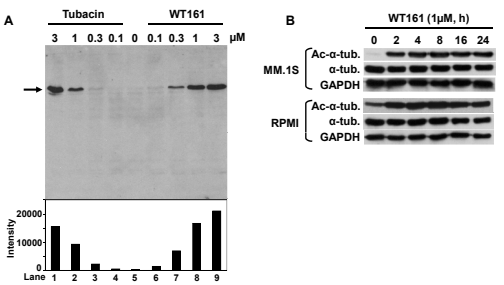
	Vorinostat[1] N=23		Vorinostat[2] N=34		Panobinostat[3] N=62		Romidepsin[4] N=25	
Median prior regimens, n	4		7		2		2	
Hematologic, %	All	Gr 3–4	All	Gr 3–4	All	Gr 3–4	All	Gr 3–4
Thrombocytopenia	74	**57**	59	**42**	87	**79**	NR	**64**
Neutropenia	30	13	18	9	71	**55**	NR	**36**
Anemia	70	22	24	0	52	18	NR	**36**
NonNonhematologic, %								
Diarrhea	**48**	9	74	9	**73**	14	NR	4
Nausea	**52**	0	74	9	**61**	3	NR	-
Fatigue	**48**	**22**	68	21	**52**	**10**	NR	**20***
Pyrexia	17	0	29	0	47	6	NR	-
Asthenia	-	-	-	-	44	6	NR	-
Anorexia	-	-	-	-	**44**	**26**	NR	-
Peripheral neuropathy	61	4	29	12	37	3	**76**	**8**

*includes fatigue, asthenia, lethargy, and malaise.

1. Badros et al. Clin Cancer Res. 2009;15:5250–5257
2. Weber et al. 2011; manuscript in preparation
3. San Miguel et al. IMW Meeting 2011; Abstract P-238
4. Harrison et al. Blood. 2011 Sep 12.

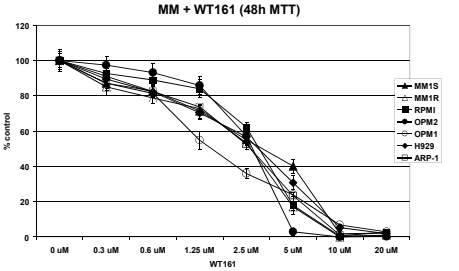
Prototype (Tubacin) vs New (WT161) HDAC6 Selective Inhibitor Induce Acetylation of Tubulin

Hideshima et al, 2011

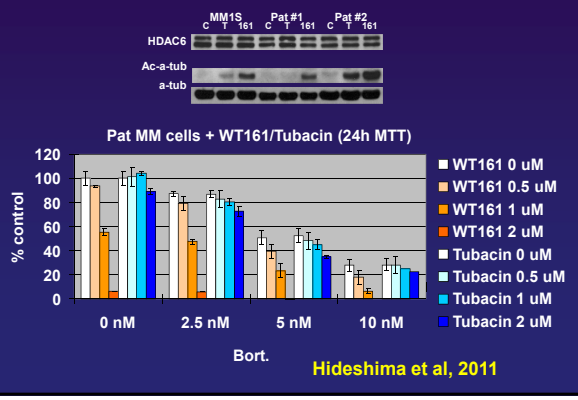


HDAC 6 Selective Inhibitor WT161 Inhibits MM Cell Growth

Hideshima et al, 2011

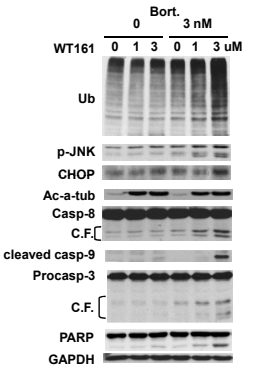


HDAC 6 Selective Inhibitors Tubacin and WT161 Enhances Bortezomib-Induced Cytotoxicity in Patient MM Cells



Hideshima et al, 2011

WT161 Enhances Bortezomib-Induced Apoptosis



Bench to Bedside Translation of HDAC 6 Selective Inhibitor ACY 1215

Orally bioavailable, highly potent, selective inhibitor of HDAC 6 synthesized in fall 2009

Synergistic MM cytotoxicity with Bortezomib in vitro and in vivo

Favorable PK/PD, toxicity profile

Highly favorable FDA regulatory process from pre-IND through IND allowance

Phase Ia/Ib/II clinical trial of ACY1215, alone and with Bortezomib, is ongoing

HDAC Inhibitors in MM: Summary

- Epigenetic agents which cause cell cycle arrest, trigger an apoptotic response, and have a key role in autophagy
- Dose-limiting toxicities include myelosuppression, nausea, diarrhea, fatigue
- Dose-dependent abnormalities in QT can occur, but rarely clinically important in MM to date
- Single agent activity is limited
- Selective HDAC 6 selective inhibitors developed to maintain efficacy and avoid toxicity
- Ongoing combination clinical trials of HDACi with Bortezomib or lenalidomide promising.

United Nations Against Myeloma:

Jerome Lipper and Lebow Bench to Bedside Research Team

USA
Kenneth Anderson
Paul Richardson
Nikhil Munshi
Robert Schlossman
Irene Ghobrial
Steven Treon
Jacob Laubach
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Karin Anderson
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Samantha Pozzi
Loredana Santo
Claire Fabre
Anuj Mahindra
Rao Prabhala
Jake Delmore
Puru Nanjappa
Michael Sellito
Avani Vaishnav

Canada

Germany

Austria

China

Greece

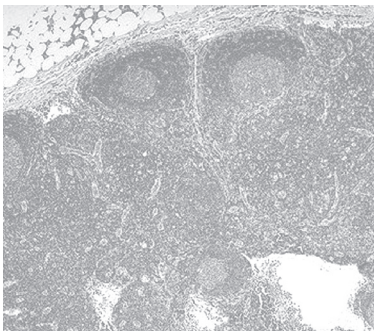
Taiwan

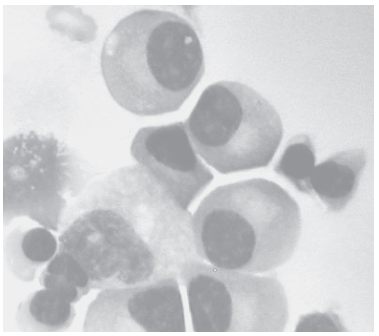
Turkey

Australia

Ireland

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





New treatments and how best to use them in lymphoma and myeloma: Bendamustine

Suzanne Lentzsch, MD, PhD

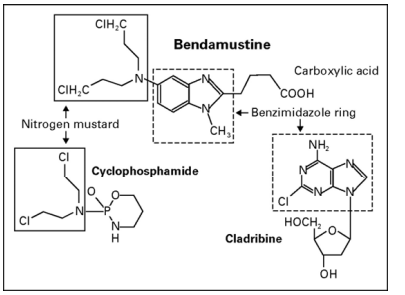
New treatments and how best to use them in lymphoma and myeloma:

Bendamustine

Suzanne Lentzsch, MD PhD
Director of the Multiple Myeloma Clinic
University of Pittsburgh Cancer Institute



Bendamustine

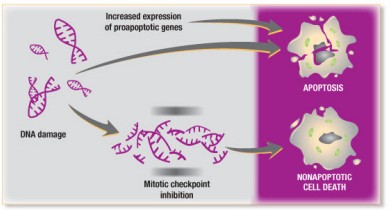


Bendamustine was synthesized as a unique chemical structure combining an alkylating group with a purine-like benzimidazole ring in 1963.

- The alkylating group contains mechlorethamine, which confers alkylating properties.
- The benzimidazole component contains a purine-like benzimidazole ring.

Cheson et al. JCO 2009; 27:1492-1501

Bendamustine HCl for Injection



Adapted with permission from Oncology NEWS International.

Bendamustine is active against both quiescent and dividing cells.

- The exact mechanism of action of bendamustine remains unknown.

FDA Approved Indications

- Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established
- Indolent B-cell non-Hodgkin's lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen
- Bendamustine has been used in over 67,000 patients in the US and Europe since 1994.

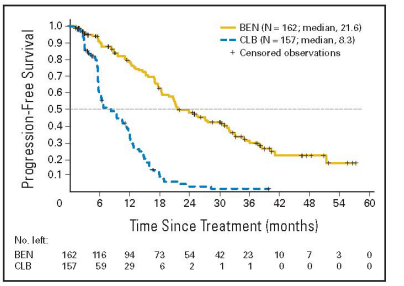
Chronic Lymphocytic Leukemia

Phase III Randomized Study of Bendamustine Compared With Chlorambucil in Previously Untreated Patients With Chronic Lymphocytic Leukemia

- Randomized, open-label, parallel-group, multicenter study designed to compare the efficacy and safety of bendamustine and chlorambucil in previously untreated patients with advanced (Binet stage B or C) chronic lymphocytic leukemia (CLL).
- Patients (≤75 years of age) randomly assigned to receive bendamustine 100 mg/m^2/d intravenously on days 1 to 2, or chlorambucil 0.8 mg/kg (Broca's normal weight) orally on days 1 and 15.
- 319 patients were randomly assigned (162 bendamustine, 157 chlorambucil).
- CR/PR were achieved in 110 (68%) of 162 bendamustine-treated and 48 (31%) of 157 chlorambucil-treated patients (P< .0001).
- CR for bendamustine 31% and chlorambucil 2%.

Knauf et al. J Clin Oncol 2009; 27:4378-4384.

Progression Free Survival



Progression-free survival based on the assessment of independent Committee for Response Assessment: intention-to-treat population.

BEN, bendamustine; CLB, chlorambucil

Knauf et al. J Clin Oncol 2009; 27:4378-4384.

Bendamustine Combined With Rituximab in Patients With Relapsed and/or Refractory Chronic Lymphocytic Leukemia: A Multicenter Phase II Trial of the German Chronic Lymphocytic Leukemia Study Group

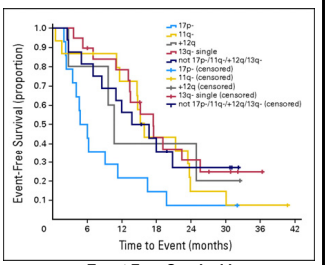
Patients and Methods

- 78 patients, including 22 patients with fludarabine-refractory disease (28.2%) and 14 patients (17.9%) with deletion of 17p.
- Bendamustine 70 mg/m^2 on days 1 and 2 combined with rituximab 375 mg/m^2 on day 0 of the first course and 500 mg/m^2 on day 1 during subsequent courses for up to six courses.

Fischer et al. J Clin Oncol. 2011;29:3559-66

Response and Overall Survival

Response	N (%)
Overall response	46 (59)
Complete response	7 (9)
Partial response / Nodal partial response	39 (50)
Stable disease	20 (26)
Progressive disease	5 (6)
Survival	**Median (months)**
Overall survival	33.9
Progression free survival	15.197
Event free survival	14.7



Event Free Survival in Cytogenetic Risk Groups

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Fischer et al. J Clin Oncol. 2011;29:3559-66

Authors' Conclusions

- Except for patients with del(17p), the combination therapy of BR offers an effective and safe treatment for patients with relapsed CLL.
- Further studies with well-defined patient populations need to be performed to validate these findings.
- Given the promising results obtained in this phase II trial, we initiated a further phase II trial evaluating the BR regimen as first-line therapy for patients with CLL.

Fischer et al. J Clin Oncol. 2011;29:3559-66

Non-Hodgkin Lymphoma

Bendamustine Is Effective Therapy in Patients With Rituximab-Refractory, Indolent B-cell Non-Hodgkin Lymphoma

- Multicenter, open-label, single-arm clinical trial
- Efficacy and safety of bendamustine in patients with rituximab-refractory, indolent B-cell NHL
- Bendamustine at a dose of 120 mg/m^2 IV Days 1 and 2 every 21 days
- 6 to 8 cycles as long as a response or stable disease (SD)

Kahl et al. Cancer 2010; 116:106-14

Patient Demographics and Disease Characteristics	No of Patients (%)
No. of patients treated	100
No. of men/women	65/35
Median age (range), years	60 (31-84)
Disease stage	
I	8 (8)
II	16 (16)
III	33 (33)
IV	43 (43)
Histology	
Follicular	62 (62)
Unknown	5 (5)
Small lymphocytic lymphoma	21 (21)
Lymphoplasmacytic lymphoma	1 (1)
Marginal zone	16 (16)
Follicular Lymphoma Prognostic Index, n = 62	
Low risk: 0-1 risk factor	18 (29)
Intermediate risk: 2 risk factors	26 (42)
High risk: 3-5 risk factors	18 (29)

Kahl et al. Cancer 2010; 116:106-14

Response Rates (in Percentages) According to Non-Hodgkin Lymphoma Histology

Histology	No of Patients	ORR	CR	Cru	PR	SD	PD	Unknown
Follicular	62	74	15	5	55	15	10	2
Small lymphocytic	21	71	5	0	67	19	5	5
Lymphoplasmacytic	1	100	0	0	100	0	0	0
Lymph node marginal zone	9	78	11	0	67	22	0	0
Extralymph node marginal zone	7	86	43	0	43	14	0	0
Total	100	75*	14	3	58	16	7	2

ORR indicates overall response rate (complete responses plus unconfirmed complete responses plus partial responses); CR, complete response; CRu, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease.

* The 95% confidence interval was from 65% to 83%.

Kahl et al. Cancer 2010; 116:106-14

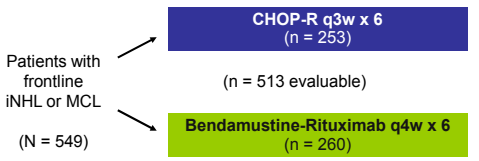
Median Response Duration in Responders and Subgroups*

Patient Group	No of Responders	Duration of Response (95% CI), months
Overall	75	9.2 (7.1-10.8)
Chemosensitive	45	10.0 (8.4-11.7)
Chemorefractory	23	6.3 (4.9-NA)
Alkylator sensitive	44	9.7 (8.3-11.7)
Alkylator refractory	18	7.7 (4.9-NA)

* Subgroups do not total 75 patients, because some patients could not be characterized as sensitive versus refractory.

Kahl et al. Cancer 2010; 116:106-14

StiL: Bendamustine + Rituximab vs CHOP-R in Frontline NHL



Rituximab 375 mg/m^2 on Day 1; (bendamustine 90 mg/m^2 on Days 1-2 q28 days) or (standard CHOP q21 days) x 6

Rummel MJ, et al. ASH 2009. Abstract 405.
http://www.clinicaloptions.com/Oncology

StiL: Results

Median observation time: 32 mos

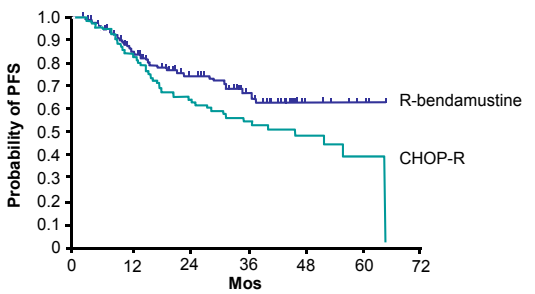
Outcome	CHOP-R	R-Bendamustine	*P* Value
ORR, %	92.7	91.3	--
CR, %	30.8	40.1	.0323
PFS, mos	34.8	54.9	.00012
EFS, mos	31	54	.0002

- Significant PFS benefit for MCL, WM, follicular lymphoma subtypes
- Significant TTNT benefit overall (*P* = .0002)

Rummel MJ, et al. ASH 2009. Abstract 405.
http://www.clinicaloptions.com/Oncology

StiL: PFS for FL Patients

R-bendamustine: not reached vs CHOP-R: 46.7 mos (median)
HR: 0.63 (95% CI: 0.42-0.95; *P* = .0281)



Rummel MJ, et al. ASH 2009. Abstract 405.
http://www.clinicaloptions.com/Oncology

StiL: Adverse Events for R-Bendamustine vs R-CHOP

Adverse Event	R-Bendamustine	R-CHOP	*P* Value
Grade 3/4, % of cycles	(n = 1450)	(n = 1408)	--
• Neutropenia	10.7	46.5	< .0001
• Leukocytopenia	12.1	38.2	< .0001
All grades, n of patients	(n = 260)	(n = 253)	
• Alopecia	-	+++	< .0001
• Infectious complications	96	127	.0025
• Paresthesias	18	73	< .0001
• Stomatitis	16	47	< .0001
• Rash	42	22	.0122

Rummel MJ, et al. ASH 2009. Abstract 405.
http://www.clinicaloptions.com/Oncology

T-Cell Lymphoma

Preliminary Results from an Open-Label, Multicenter, Phase II Study of Bendamustine in Relapsed or Refractory T-Cell Lymphoma from the French Goelams Group: The Bently Trial

Objective

- Phase II, single-arm, open-label study
- Evaluate the activity of bendamustine in patients with progressive or relapsed T-cell lymphoma
- Confirmed T-cell lymphoma (PTCL nos, AILD, ALCL, other subtypes) or Mycosis Fungiode (MF) ≥ stage IIB who failed or were refractory to ≥ 1 prior systemic therapy, and had measurable disease and ECOG performance status ≤3
- Bendamustine at the dosage of 120 mg/m^2 as a 1 hr IV infusion on days 1-2, every 21 days for 3 cycles

Efficacy and Safety

- 38 patients who received at least 1 cycle of bendamustine were analyzed
- ORR was 47% including CR+CRu in 11 patients (29%)
- PR in 7 patients (18%)
- 20 patients experienced PD (53%)
- Median duration time for responder patients was 157 days (14-350).

Conclusion

- Complete and durable responses were observed with bendamustine used as a single agent in patients with relapsed or refractory PTCL.

Damaj et al. Abstract 126. Presented at the 11th International Conference on Malignant Lymphoma, June 2011, Lugano, Switzerland.

Hodgkin's Lymphoma

Phase II Trial of Bendamustine in Relapsed and Refractory Hodgkin Lymphoma

- Bendamustine 120 mg/m2 day 1 and 2 of 28 day cycles; maximum 6 cycles
- Pegfilgrastim with each cycle

	All Patients* (N=34)	Allo-SCT Eligible † (N=25)	Previous Allo-SCT (N=6)	Previous Auto-SCT (N=27)
Overall Response Rate (CR + PR), N (%)	20 (59)	15 (60)	4 (66)	17 (63)
Complete Response (CR), N (%)	12 (35)	9 (36)	2 (33)	10 (37)
Partial Response (PR), N (%)	8 (24)	6 (24)	2 (33)	7 (26)
Median Remission Duration, months	5			

* 36 patients enrolled; 2 not evaluable due to 1 withdrawal after 1 cycle and 1 death in a car accident before first re-staging. Both were clinically responding to treatment.

† 5 patients proceeded to allogeneic stem cell transplant following bendamustine, representing 20% of the initially transplant eligible population

Moskowitz et al. Abstract 288, 11th International Conference on Malignant Lymphoma, June 2011, Lugano, Switzerland.

Authors' Conclusions

- Bendamustine was active and well tolerated in this heavily pre-treated patient population with R/R Hodgkin lymphoma
- Prior autologous or allogeneic stem cell transplant did not appear to impact response to bendamustine
- 5 patients proceeded to allogeneic stem cell transplant following bendamustine, representing 20% of the initially transplant eligible population
- Progression of disease was the most common reason for failure to proceed to allogeneic stem cell transplant
- Studies evaluating bendamustine in combination with novel agents in relapsed and refractory Hodgkin lymphoma are needed to improve response duration and increase the rate of referral to allogeneic stem cell transplant.

Moskowitz et al. Abstract 288, 11th International Conference on Malignant Lymphoma, June 2011, Lugano, Switzerland.

Multiple Myeloma

Historical Response and Survival Rates Bendamustine in Multiple Myeloma

AGENT/ REGIMEN	Study First Author	N 28-68	CR/nCR (%) 0-32	ORR* (%) 55-96	Median PFS or TTP (mos)	Median OS (mos) 20-33
Relapsed/Refractory Multiple Myeloma						
Bendamustine	Knop	31	6	55	6-PFS	NR
Bendamustine plus Thalidomide, Prednisolone	Ponisch	28	14	89	50% at 1 yr PFS	92% at 1 year
Bortezomib (V)+/- Dexamethasone (D)+/- Bendamustine (B)	Fenk	23 (V) 20 (VD) 7 (BVD)	18 0 0	95 70 86	8-PFS (All)	20 (All)
Bendamustine plus Bortezomib	Hrusovsky	40	0	85	NR	NR
Newly Diagnosed Multiple Myeloma						
Bendamustine plus Prednisone (BP) vs Melphalan plus Prednisone (MP)	Ponisch	BP 68 MP 63	32 13	75 70	14-TTP 10-TTP	32 33

Knop et al. Haematologica. 2005;90(9):1287-1288; Pönisch et al. BJM. 2008;191-200; Fenk et al. Leukemia and Lymphoma. 007;48:2345-2351; Hrusovsky et al. Blood. [ASH Abstract #4851] 2007; Pönisch et al. J Cancer Res Clin Oncol. 2006;132:205-212

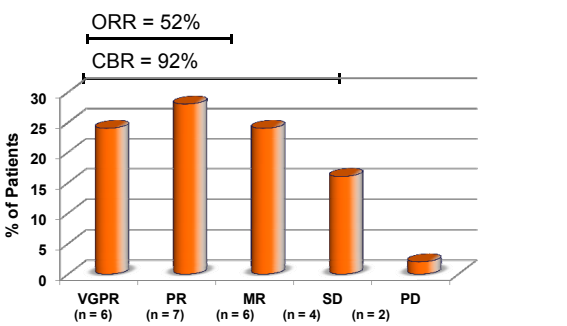
Combination of Lenalidomide, Bendamustine, and Dexamethasone in Patients with Refractory or Relapsed MM



- Phase 1/2, open-label, multicenter, nonrandomized study
- Escalating doses of bendamustine (75, 100 mg/m2) in combination with lenalidomide (5, 10 mg) with a fixed dose of dexamethasone)
- Standard 3+3 dose escalation design
- 12-patient expansion cohort enrolled at the MTD

Lentzsch et al. 2010 ASH Annual Meeting, Abstract 989, Orlando, FL

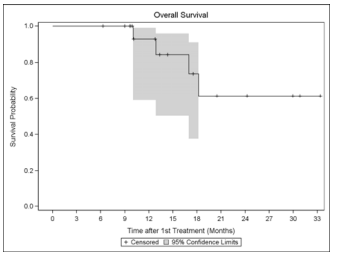
Best Response After 2 or More Treatment Cycles (N = 25 patients evaluable)



Lentzsch et al. 2010 ASH Annual Meeting, Abstract 989, Orlando, FL

Outcome

- As per June 1, 2011, median follow up for patients who are alive was 13 months. 4 patients have died.
- Time to next treatment 5.8 months (95% CI; 2.5-8.7)
- Time to best response 1.6 months (95% CI; 1.6-3.5)
- Progression free survival 6.1 months (95% CI; 3.7-9.4)
- Median Overall survivalhas not been reached
- Estimated 1 year OS 93% (95% CI; 59-99%)



Lentzsch et al. 2010 ASH Annual Meeting, Abstract 989, Orlando, FL

Authors' Conclusions

- This is the first phase I study to assess safety and antitumor activity of BLD
- BLD is generally well tolerated in patients with relapsed/refractory MM
  - Grade 3/4 AEs are mainly myelosuppressive
  - No unanticipated DLT
  - Tolerated in older patients up to 81 years
  - May be well suited for patients with a history of peripheral neuropathy
- BLD is highly active in relapsed/refractory MM
  - PR/VGPR rate of 65%
  - Active in heavily pretreated patients

Lentzsch et al. 2010 ASH Annual Meeting, Abstract 989, Orlando, FL

An Open-label, Phase 1/2 Trial of Bendamustine Plus Bortezomib in Patients With Relapsed or Refractory Multiple Myeloma

Trial design

- Phase 1/2, open-label, multicenter, nonrandomized study
- 3 dose levels of bendamustine (50, 70, 90 mg/m^2) in combination with a fixed dose of bortezomib (1.0 mg/m^2), with 3-6 patients enrolled at each dose level
- A standard 3+3 approach was used to determine the MTD; the MTD dose cohort was subsequently expanded until a total of 40 patients was enrolled.

Patients

- An interim analysis was conducted on 38 safety-evaluable and 36 efficacy-evaluable patients
- Median prior therapies 3 (1-9)

Berenson et al. 16th Congress of the European Hematology Association, London, United Kingdom, June, 2011

Efficacy and Safety

Efficacy

- Among 36 evaluable patients, the ORR was 47%, including 1 VGPR (3%), 6 PR (17%), and 10 MR (28%).
- An additional 17 patients (47%) had SD, corresponding to a clinical benefit rate (CBR) of 94%.
- In patients administered bendamustine at 90 mg/m^2 (n = 27), the ORR was 52%.
- In patients previously treated with bortezomib (n = 27) or alkylators (n = 26), the ORR was 37% and 40%, respectively.
- Median time to first response was 1.4 and 1.9 months across all doses and the 90 mg/m^2 bendamustine dose, respectively (range 0.7-3.8 months).
- 3 of 17 responding patients have experienced disease progression.
- Median DOR has not been reached.
- Median TTP has not been reached after a median follow-up of 3.0 months.

Safety

- No DLT was observed at any dose level.
- The maximum dose of bendamustine (90 mg/m^2) was well tolerated in combination with bortezomib 1.0 mg/m^2 and was designated as the MTD.
- Enrollment in the MTD expansion cohort has been completed.

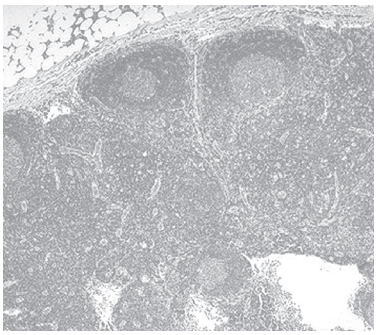
Berenson et al. 16th Congress of the European Hematology Association, London, United Kingdom, 2011

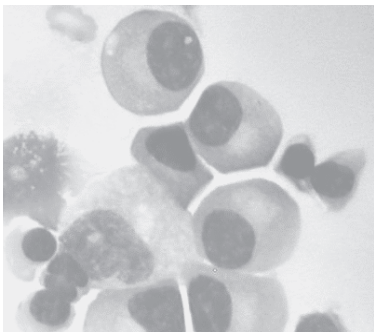
Authors' Conclusions

- Bendamustine 90 mg/m^2 plus bortezomib 1.0 mg/m^2 was well tolerated and demonstrated activity for patients with relapsed/refractory MM (52% ORR).
- Efficacy was observed in a heavily pretreated population across all dosing cohorts (47% ORR), including patients previously exposed to bortezomib and alkylator therapy (ORR = 37% and 40%, respectively).
- The modified bortezomib regimen used in the study was associated with a low risk of treatment-emergent PN.
- Further analysis of this study will be conducted.

Berenson et al. 16th Congress of the European Hematology Association, London, United Kingdom, 2011

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





The Prince Family lecture: Is a cure on the horizon?

Michael J. Keating, MD

Prince Family Lecture
CLL—Is cure on the horizon?

Michael J. Keating M.B.,B.S.
Professor of Medicine
Department of Leukemia
Division of Cancer Medicine
U.T. M.D. Anderson Cancer Center
Houston, TX USA

Newer Prognostic Factors Associated With Inferior Survival in CLL

Unmutated (<2% homology with germline IgV_H)

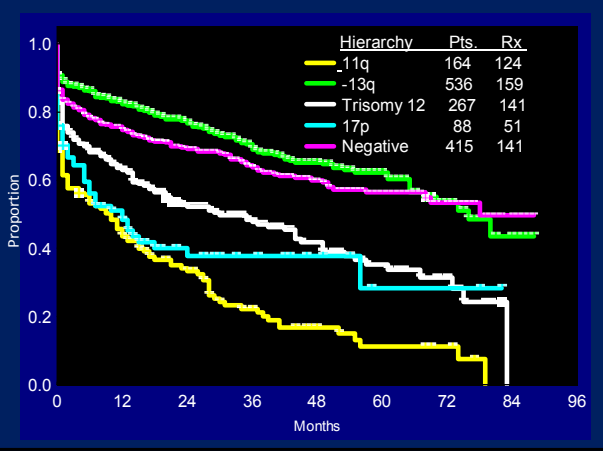
FISH cytogenetic abnormalities

- 17p deletion or 11q deletion
- Complex abnormalities

Expression of ZAP-70 (≥ 20% positive)

Expression of CD38 (≥ 30% positive)

Time to Treatment by FISH 2004-11 (1470 pts)



Frontline therapy for CLL

FC + Rituximab Schedule In CLL

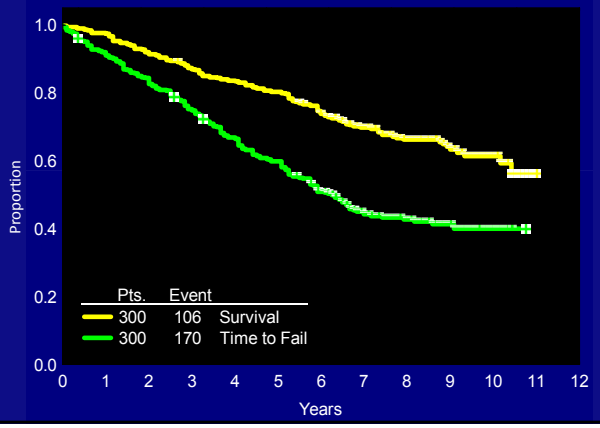
Drug	Dose (mg/m^2)	Days of Course C #1	Days of Course C #2 - 6
Rituximab	375	1	
	500		1
Fludarabine	25	2 – 4	1 – 3
Cyclophos.	250	2 – 4	1 – 3

(Allopurinol 300mg/day)

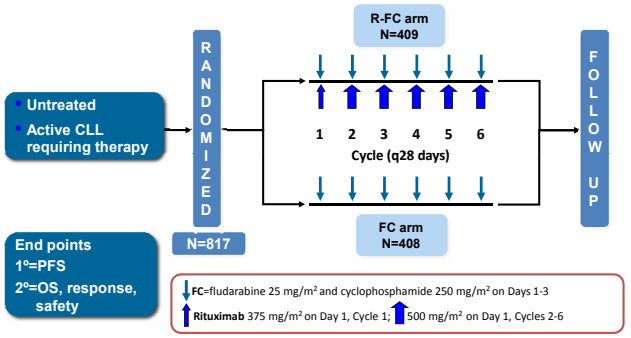
Response to FC + Rituximab (NCI-WG: 300 Patients)

Response	# Pts.	(%)	
CR	217	(72%)	95%
Nodular PR	31	(10%)	
PR	37	(12%)	
No Response	13	(4%)	
Early Death	2	(1%)	

FCR-300 Survival and Time to Fail



CLL-8: Study Schema



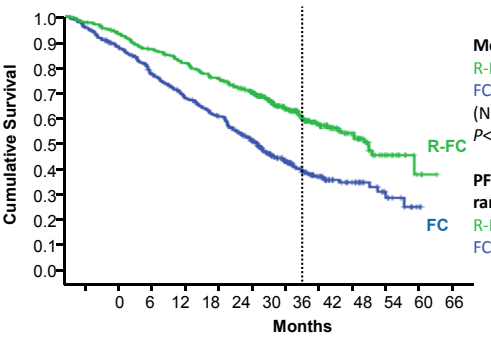
Hallek M, et al. Presented at: American Society of Hematology 2008; December 6-9, 2008; San Francisco, CA. Abstract 325.

Best Response to Treatment

		FC	R-FC
CR[a,b] [P<.01]		21.8%	44.1%
PR		66.6%	51.0%
ORR [P<.01][b]		88.4%	95.1%
All included in PR	CR_u	4.6%	3.6%
	CR_i	1.9%	2.3%
	nPR	5.7%	3.4%
SD		7.8%	3.9%
PD		3.8%	1.0%

[a]P<.01.
[b]Hallek M, et al. Updating the National Cancer Institute- Working Group (NCI-WG) 1996 guidelines. Blood. 2008.
According to 2008 NCI WG Criteria, confirmatory BM assessment performed up to 6 months after final restaging.
Hallek M, et al. Presented at: ASH Annual Meeting 2009; December 5-8, 2009; New Orleans, LA. Abstract 535.

Progression-Free Survival

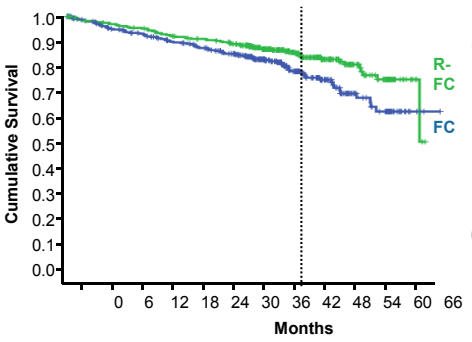


Median PFS:
R-FC: 51.8 months
FC: 32.8 months
(N=790; HR 0.563, *P*<.001)

PFS rate 3 years post-randomization:
R-FC: 64.9%
FC: 44.7%

Hallek M, et al. Presented at: ASH Annual Meeting 2009; December 5-8, 2009; New Orleans, LA. Abstract 535.

Overall Survival



Overall survival 3 years post-randomization:
R-FC: 87.2%
FC: 82.5%
(n=817, HR 0.664, *P*=.012)

Hallek M, et al. Presented at: ASH Annual Meeting 2009; December 5-8, 2009; New Orleans, LA. Abstract 535.

Is FCR good for everyone ?

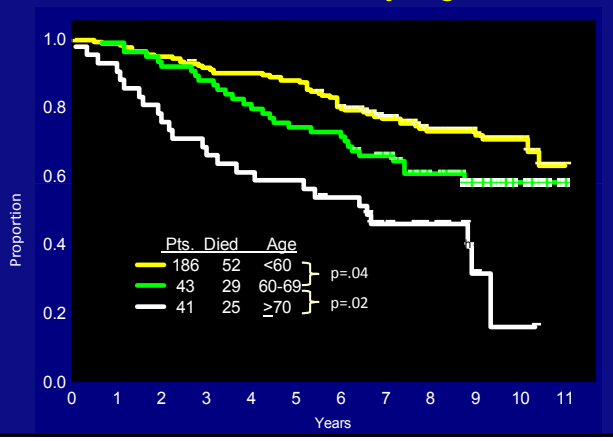
Age greater than 70 years?

Mutation status?

17p– (p53 mutation)?

11q- (ATM deletion)

Survival FCR by Age



Lenalidomide in Elderly CLL: Treatment Schedule

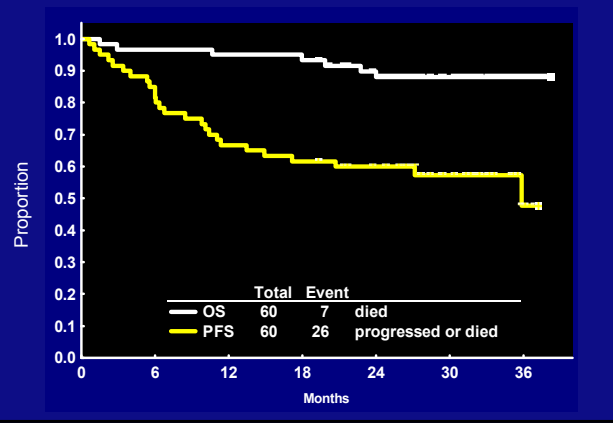
- Lenalidomide
  - 5 mg orally daily x 2 cycles (56 days)
  - Increase by 5 mg/cycle (28 days) to maximum 25 mg daily
  - Treatment continued until progression

--Allopurinol 300 mg d 1-14

--No mandated antibiotic or anti-viral prophylaxis, DVT prophylaxis or tumor flare prophylaxis

MD Anderson Cancer Center

Lenalidomide in Elderly CLL: Overall and Progression-free Survival

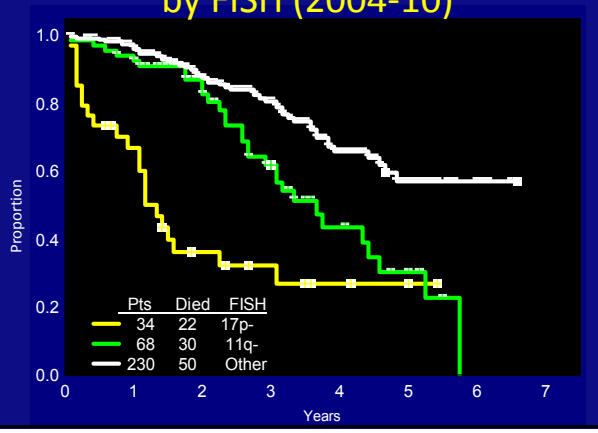


FISH CYTOGENETICS

Prospective Evaluation of Prognostic Factors Post FCR Study (2004-2010)

Prognostic Factor	Value	Pts.	%CR	%nPR	%OR
FISH	-17p	37	35	5	76
	-11q	75	76	9	97
	Trisomy 12	66	80	11	98
	-13q	100	66	8	98
	Negative	70	71	11	96

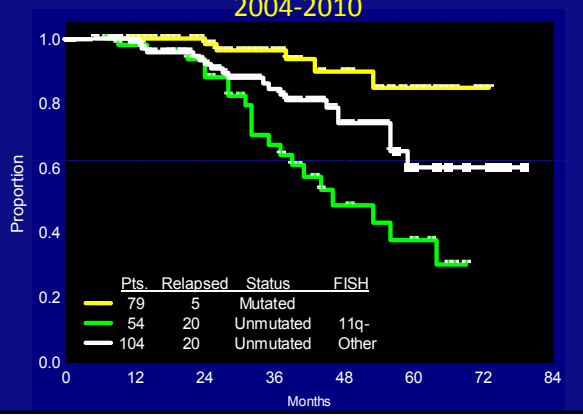
Time to Fail Untreated CLL Age <70 by FISH (2004-10)



Prospective Evaluation of Prognostic Factors Post FCR Study (2004-2010) Recent

Prognostic Factor	Value	Pts.	%CR	%nPR	%OR
Mutation Status	Mut	97	64	11	97
	Unmut	215	70	9	94
ZAP 70 (UCSD)	<20	87	66	8	95
	≥20	111	73	11	98
ZAP 70 (IHC)	Negative	102	70	10	96
	Positive	177	66	9	92

Time to Progression FCR Based responders by Mutation Status and FISH 2004-2010



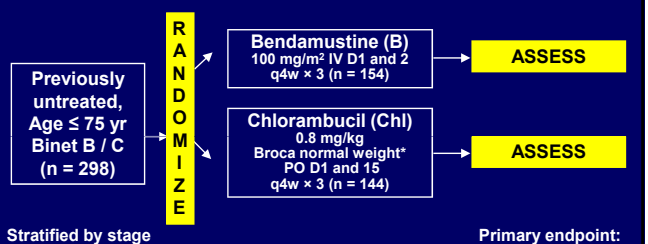
New Treatments for CLL - 2011

1. Lenalidomide , Flavopiridol, SCH-727965
2. Ofatumumab, GA-101, Abt-263, etc
3. Bendamustine, Nelarabine
4. CAL 101(PI3-K Delta inhibitor), BTK Inhibitor, etc
5. PEITC (Huang), Sapacitabine (Plunkett)
6. Immuno-therapy (CARs)
7. OFAR (Oxaliplatin)—Richter's
8. Non –ablative allo transplant.

Are we ready to assign treatment of CLL by genetics (The AML Model)

- 17p- p53 mutation—Resistant to Chemotherapy but sensitive to antibodies, BCR antagonists .
- 11q- ATM deletion and DNA repair defect. High CR rate (Candidate for consolidation therapy)
- Trisomy 12. High expression of CD20, (Lymphoma karyotype)
- 13 q- Mir 15/16. High response rate. Cri common
- Others to be discovered by CGH and SNP arrays

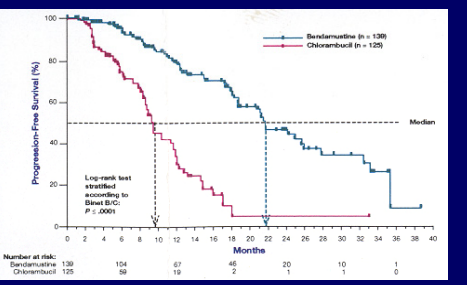
Untreated CLL: Chlorambucil vs Bendamustine



*Broca normal weight in kg (men) = height in cm–100.
Broca normal weight in kg (women) = 0.9 (height in cm–100).

Knauf WU, et al. *Blood.* 2007:110. Abstract 2043.

Untreated CLL: Chlorambucil vs Bendamustine Progression-Free Survival



Knauf WU, et al. *Blood.* 2007:110. Abstract 2043 and poster at American Society of Hematology Annual Meeting 2007.

Bendamustine +Rituximab Treatment Schedule

R B B R B B R B B R B B R B B R B B

B = Bendamustine 90 mg/m^2 day 1-2, cycle 1-6, q4wks

R = Rituximab 375 mg/m^2 day 0, cycle 1,
500 mg/m^2 cycle 2-6, q4wks

Bendamustine + rituximab-- Ph 11 CLL2M Frontline therapy for CLL

- Patients 117
- CR (%) 27(23%)
- PR (%) 74(63%)
- Median EFS 34 months
- Fischer et al. ASH 2009: Abstract 205

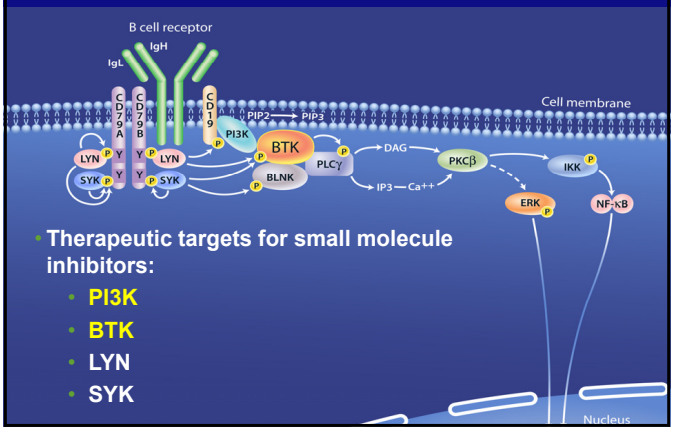
Phase II CLL2M Bendamustine + Rituximab: Response by Genetics

Category	n	ORR (%)	CR (%)
+12	19	17 (89.5)	3 (15.8)
11q del	21	19 (90.5)	9 (42.9)
17p del	7	3 (42.9)	-
IGHV unmutated	63	56 (88.9)	25 (39.7)

Stephan Stilgenbauer, Ulm

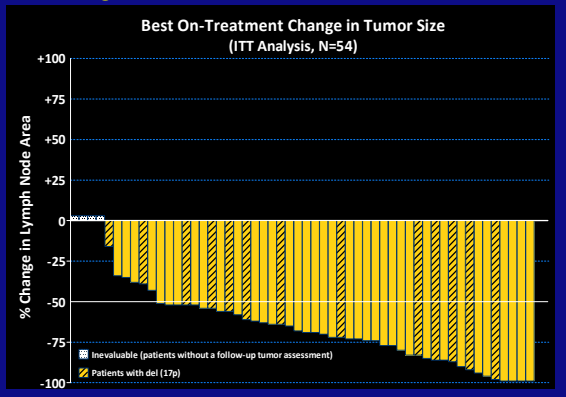
Fischer et al. ASH 2009; Abstract 205.

B Cell Receptor Signaling Pathway



- **Therapeutic targets for small molecule inhibitors:**
  - **PI3K**
  - **BTK**
  - **LYN**
  - **SYK**

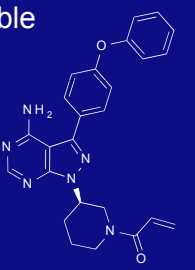
Single-Agent CAL-101 Resulted in Nodal Shrinkage in All Evaluable Patients with CLL



Furman et al. ASH 2010, Abstract 55

PCI-32765 Novel Small Molecule Btk Inhibitor

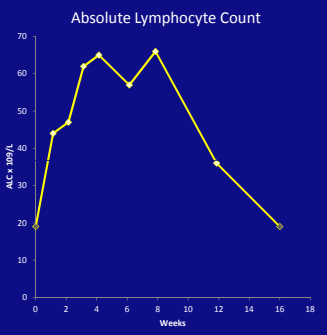
- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent Btk inhibition
  - IC_{50} = 0.5 nM
- Orally available

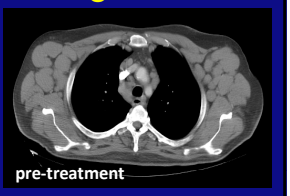


PCI-32765

Burger et al. ASH 2010, Abstract 57

ALC versus LN Response: Continuous Dosing







3

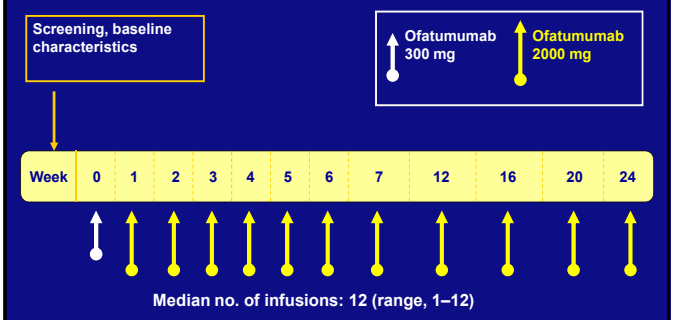
Response Characteristics of PCI 32765 (BTK Inhibitor) in del 17p

CR Nodes	7 / 7*
Final Hgb > 11G%	7 / 9
Final Platelets >100 K	9 / 9
Final ALC <4000/μl	3 / 9

* Evaluable

Ofatumumab in refractory CLL Study design

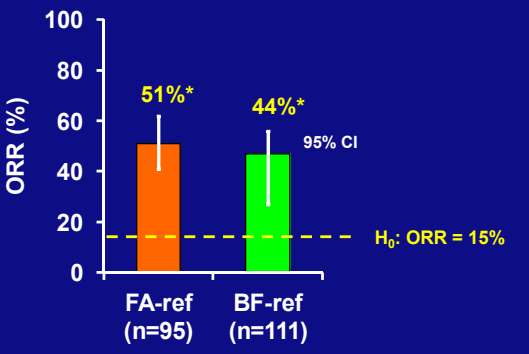
- **Prednisolone 100 mg IV with initial courses**



Median no. of infusions: 12 (range, 1–12)

Wierda et al. ASH 2010, Abstract 921

Ofatumumab in refractory CLL Objective responses by IRC evaluation

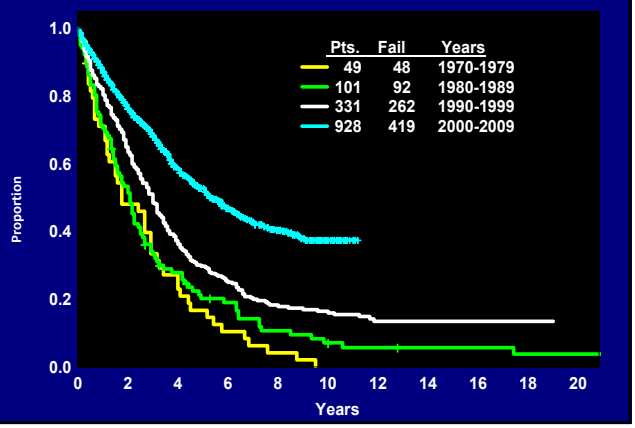


*P<0.0001 versus H_0 (two-sided exact test)

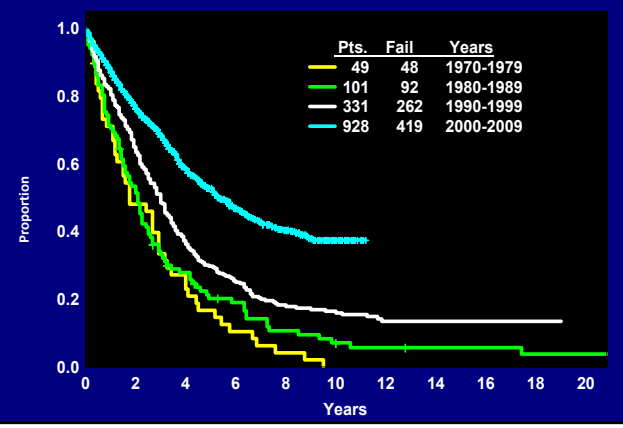
CI, confidence interval

Wierda et al. ASH 2010, Abstract 921

CLL 5 year + 10 year Time to Fail by Decade

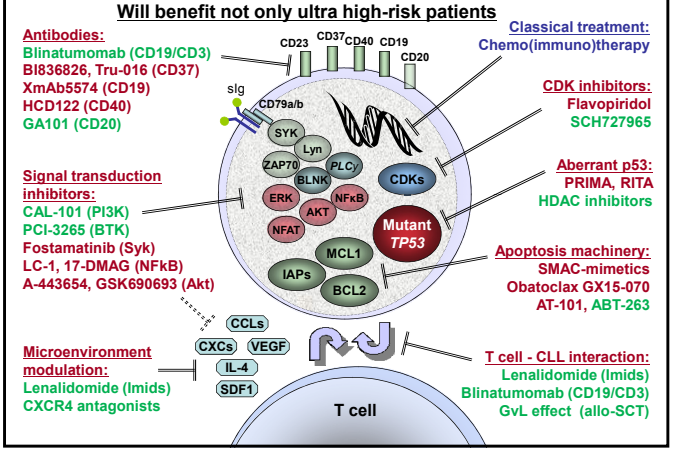


CLL 5 year + 10 year Time to Fail by Decade



Future Treatment Approaches (e.g.)

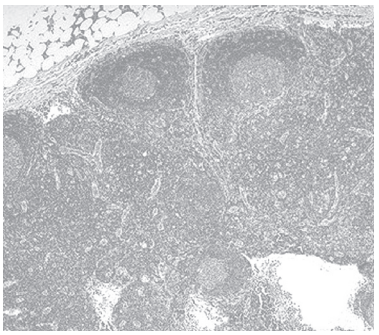
Will benefit not only ultra high-risk patients

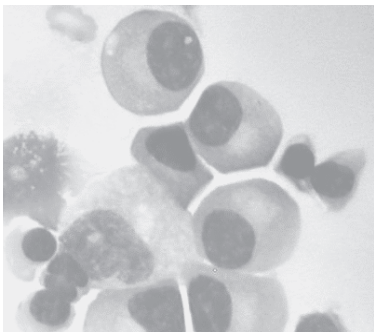


Frontline treatment of CLL 2015

- Induction with BCR Tyrosine kinase inhibitor
- Test for MRD with flow, plasma DNA,Mirs and other serum markers
- Consolidation with CARs or genetic specific therapies
- NST allogeneic transplants later.

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies

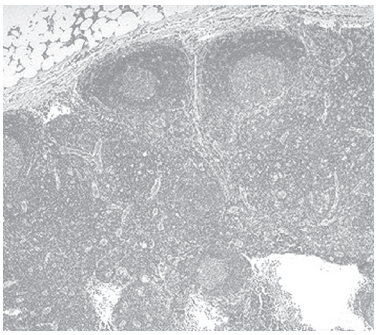


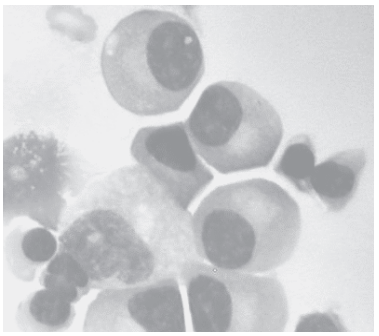


Molecular pathogenesis and therapy of CLL

Thomas J. Kipps, MD, PhD

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Transplantation in CLL: How major a role?

Edwin Alyea, MD

Role of Transplantation in the Treatment of CLL

Edwin P. Alyea
Associate Director
Stem Cell Transplant Program
Dana Farber Cancer Institute

Associate Professor of Medicine
Harvard Medical School

Transplantation for CLL

- Autologous Transplantation
- Allogeneic Transplantation
  - Eligible patients
  - Reduced Intensity Conditioning Transplantation
  - Role of T cell Depletion
  - Related versus unrelated donor
  - Methods to Prevent and Treat of Relapse

ASCT versus chemotherapy in CLL
randomized trial

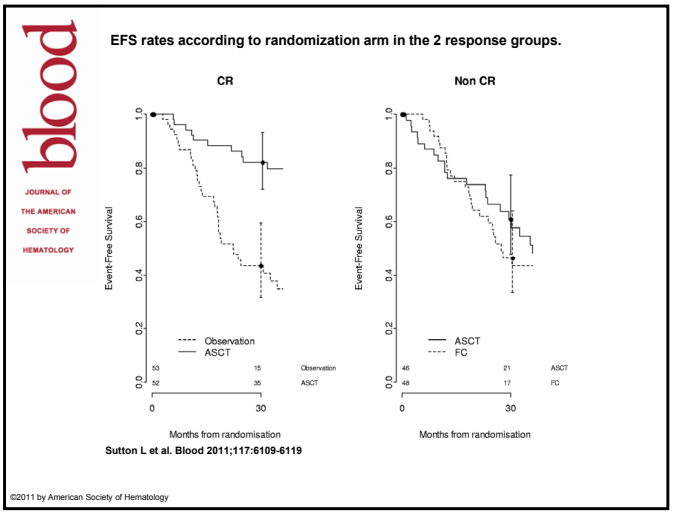
- untreated CLL patients
- 241 patients < 66 years of age with Binet stage B or C CLL
- 3 courses of mini-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone) and then 3 courses of fludarabine.
- Treatment:
  - **complete response (CR) were then randomized to:ASCT or observation,**
  - **other patients were randomized DHAP salvage followed by either ASCT or 3 courses of fludarabine plus cyclophosphamide (FC)**
- The primary end point was event-free survival

Sutton L et al. Blood 2011;117:6109-6119

ASCT versus chemotherapy
randomized trial results

- 105 patients entered CR and were randomized between ASCT (n = 52) and observation (n = 53)
- 3-year EFS rates were 79.8% and 35.5%
- 94 non-CR patients were randomized between ASCT (n = 46) and FC (n = 48);
- 3-year EFS rates were 48.9% and 44.4%
- No difference in overall survival was found between the 2 response subgroups.
- No difference was observed between ASCT and FC in patients requiring salvage.

Sutton L et al. Blood 2011;117:6109-6119



2.

Autografting CLL: the game is over!

Editorial by Moteserrat and Gribben
***Blood* 2011**

- Reviewed the results of 2 randomized trials comparing autologous transplantation with chemotherapy
- Prolonged EFS and PFS following autologous transplantation
- No improvement in OS
- Negative impact of p53 not overcome by autologous transplant
- ASCT is not an effective salvage therapy

EBMT CLL Working Group
Candidates for Allogeneic Transplantation

- Allo-SCT is a reasonable treatment option for eligible patients with previously treated, poor-risk CLL
  - non-response or early relapse (within 12 months) after purine analogue-containing therapy
  - relapse (within 24 months) after purine analogue combination therapy or treatment of similar efficacy or autologous SCT
  - p53 deletion/mutation (del 17p13) requiring treatment).

Dreger et al., Leukemia, 2007

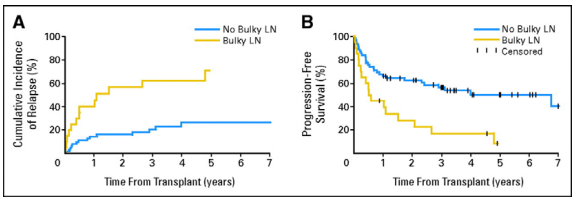
Five-Year Follow-Up of Patients With Advanced Chronic Lymphocytic Leukemia Treated With Allogeneic NST

- 82 patients with fludarabine-refractory CLL
- 2 Gy total-body irradiation alone or combined with fludarabine followed by HCT from related (n = 52) or unrelated (n = 30) donors.
- CR and PR were achieved in 55% and 15% of patients, respectively.
- Higher CR rates were noted after unrelated HCT (67% *v* 48%).
- 5-year incidences:
  - nonrelapse mortality (NRM) 23%
  - progression/relapse 38%
  - overall survival 50%
  - progression-free survival 39%
- 24% of surviving patients continue to receive immunosuppression for chronic graft-versus-host disease
- Lymphadenopathy ≥ 5 cm, but not cytogenetic abnormalities at HCT, predicted relapse.

Sorror M L et al. JCO 2008;26:4912-4920

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Incidence of relapse and progression-free survival stratified by lymph node (LN) diameter.



Sorror M L et al. JCO 2008;26:4912-4920

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JOURNAL OF CLINICAL ONCOLOGY

Multivariate Analysis Predicting Outcome after NST

	PFS	OS
	HR (p)	***HR (p)***
Disease status (no CR/PR)	3.18 (.01)	4.56 (.02)
Number previous therapies	1.39 (.002)	1.32 (.02)
Time to NST	0.99 (.91)	0.99 (.85)
Adverse cytogenetics	2.33 (.10)	2.63 (.15)
Bone marrow > 5% CLL	8.0 (.0002)	2.96 (.06)
BM involvement (continuous)	1.02(.011)	.03 (.0007)

Brown et al., BBMT 2006

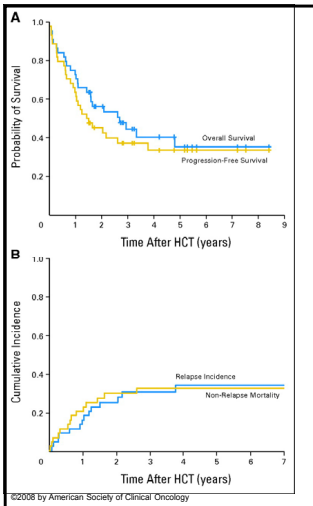
17p Deletion

- 44 patients with 17p CLL
- matched sibling (n = 24) or an alternative donor (n = 20).
- At transplant 53% of patients were in remission.
- Reduced-intensity conditioning in 89% of patients.

- 3 year overall survival and progression-free survival rates were 44% and 37%
- The cumulative incidence of progressive disease at 4 years was 34%
- No late relapse occurred in nine patients with a follow-up longer than 4 years.
- Multivariate analysis maximum Binet stage, number of prior chemotherapy regimens, and T-cell depletion were associated with decreased PFS

- **Conclusion** Allogeneic HCT has the potential to induce long-term disease-free survival in patients with 17p CLL.

Schetelig J et al. JCO 2008;26:5094-5100



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17p deletion:
OS and risk of relapse

Schetelig J et al. JCO 2008;26:5094-5100

JOURNAL OF CLINICAL ONCOLOGY

Does RIC confer a survival advantage to patients with poor prognosis chronic lymphocytic leukaemia?

A case–control retrospective analysis

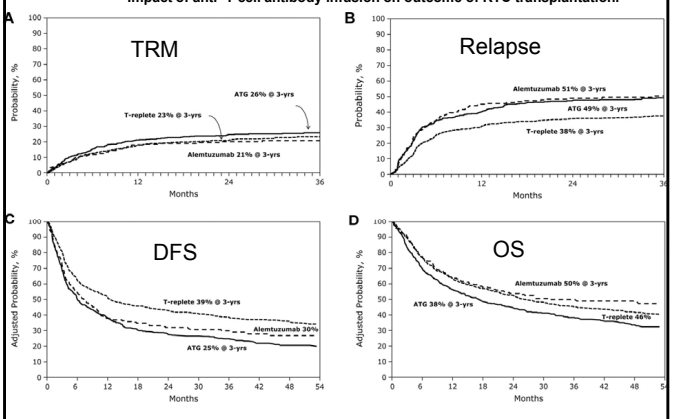
- 37 patients who underwent RIC allo-HCT were compared with 43 patients from the same institutions who received conventional therapy only
- Matching variables were age at diagnosis and time to first CLL-specific therapy.
- groups were well balanced in terms of cytogenetics by FISH, CD38 and ZAP-70 expression, and immunoglobulin heavy-chain variable region mutational status
- Median overall survival was 113 months for HCT patients and 85 months for controls when calculated from time of diagnosis ($P = 0.072$) and 103 and 67 months, respectively, when calculated from time of first therapy ($P = 0.041$).
- **Conclusion:** RIC allo-HCT is a reasonable option for patients with high-risk CLL.

Delgado J et al. Ann Oncol 2009;20:2007-2012

Conditioning regimens and GVHD Prevention
role of T cell depletion

- No conditioning regimen noted to be superior to other regimens
- Chronic GVHD remains a significant barrier to successful transplantation
- ATG and alemtuzumab have been used to:
  - Reduce risk of graft rejection
  - Reduce incidence of both chronic and chronic GVHD
- Concern that these agents may increase risk of relapse

Impact of anti–T-cell antibody infusion on outcome of RTC transplantation.

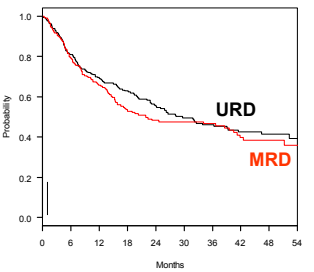


Soiffer R J et al. Blood 2011;117:6963-6970

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Impact of Donor type
MRD vs. URD

Overall Survival



OS	+100	1-yr	2-yr
MRD	90%	66%	48%
URD	92%	70%	56%

P = 0.33

Competing risk regression- NRM vs. Relapse

	NRM		Relapse	
Variable	**HR**	**p**	**HR**	**p**
Donor type, MRD vs. URD	1.15	0.65	1.4	0.006
Pt Age (Continous variable)	1.00	0.87	1.00	0.86
Prior Auto Transplant	1.44	0.37	1.25	0.14
Disease Risk, High vs. Low	1.41	0.47	1.49	0.03
F/M Donor-recipient gender	0.56	0.14	0.88	0.36
Siro containing GHVD prophylaxis	0.99	0.97	0.82	0.18
Diagnosis, AML/MDS vs. other	1.40	0.32	1.62	0.0009
Year of Transplant	0.82	0.068	1.01	0.74
CMV, Positive vs. Negative	0.72	0.54	1.16	0.56
RIC Regimen, FLU/BU2 vs.FLU/BU1	1.58	0.35	0.62	0.03

Current National Trial in CLL
Collaboration between CALGB and CTN

- Primary Objective
  - In early high-risk cohort
  - 2-year PFS ≥70% vs 50%
  - Accrual = 39
- Secondary Objectives
  - In relapsed/refractory cohort
  - 2-year PFS ≥ 50% vs 30%
  - Accrual = 39
- Other objectives
  - Response
  - GVH
  - TRM
- Donors
  - 6/6 sib
  - 8/8 MUD (molecular for A, B, C, DR)

Eligibility - Early cohort

- Diagnosis of B-CLL or B-SLL
- High-risk features
  - FISH showing 17p (≥20%) either alone or in combination
  - FISH showing 11q alone or in combination unless a complete remission with initial therapy
  - Failure to achieve PR to initial therapy
- Initial therapy
  - At least 2 cycles of fludarabine-based therapy
  - No more than 2 regimens prior to transplant (I.e. PR to initial therapy, second regimen to improve response)
- Disease status
  - No prior progression
  - Stable or better to most recent therapy
  - Nodes < 5cm, marrow < 50% lymphs

Eligibility - Advanced cohort

- Diagnosis of CLL or SLL
- High-risk features
  - First progression < 24 mo after purine analog based therapy
  - Second or subsequent progression
- Disease status
  - Stable or better to most recent therapy
  - Nodes < 5cm, marrow < 50% lymphs

Preparative Regimens

Fludarabine 30 mg/m2 x 4 days -5 to -2
Busulfan 0.8 mg/kg daily x 4 days -5 to -2

Fludarabine 30 mg/m2 x 4 days -7 to -3
Cyclophosphamide 1000 mg/m2 days -5 to -3
For MUD patients:
Rabbit ATG total 6 mg/kg (1.5 mg/kg day -6, 2 mg/kg day -5, 2.5 mg/kg day -4)

Both:
Rituximab 500 mg/m2 x 4 days -7, -1, +7, +14

Rituximab Maintenance

Rituximab 500 mg/m2 as a single infusion for 4 courses
given 3, 6, 9, 12 mo after transplant

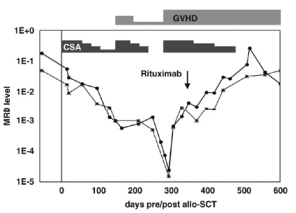
GVHD Prophylaxis Regimens

Tacrolimus	day -3
MTX 10 mg/mn2	days +1, +3, +6
Tacrolimus	day -3
Sirolimus	day -3
MTX 5 mg/mn2	days +1, +3, +6

Taper both tac/sirolimus by 1/3 day +60 to +90
Then taper to off by day +180

Durability of GVL

Can GVL immunity be maintained?

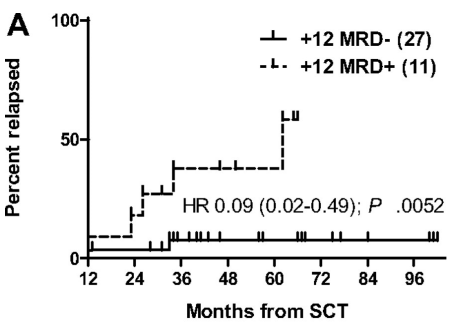


MRD kinetics in a patient acquiring GVL resistance:
-Bold line, MRD by RQ-PCR
-Thin line MRD by MRD-flow.

M Ritgen et al., Leukemia 2008

Dreger, P. et al. Blood 2010;116:2438-2447

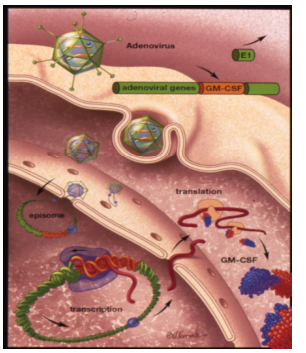
Outcome according to MRD status 1 year after SCT
GCLLSG CLL3X trial



Current Trials

- Lenalidomide maintenance
  - Phase 1 after RIC
  - Randomized trial, goal 80 CLL patients
- Sirolimus
  - Randomized trial
- Rituximab post transplant
  - 2 studies with rituximab early post transplant
  - CALGB/CTN study with rituximab maintenance
- Autologous followed by RIC
- DLI post transplant
  - Activated DLI
- Post transplant vaccines
  - GVAX

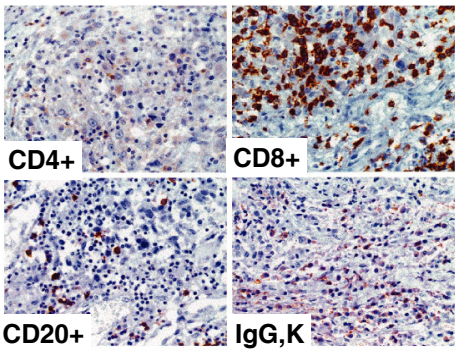
GVAX®: GM-CSF Secreting Tumor Cell Vaccine



- **Autologous tumor cell**
- **GM-CSF transduction (E1, E3 deleted Adenovirus serotype 5 vector)**
- **Irradiation (10,000 rads)**
- **No proliferation potential**
- **GM-CSF secretion maintained 7 days in vitro**
- **Biologic activity observed in melanoma, lung cancer, MDS/AML human trials**

GVAX

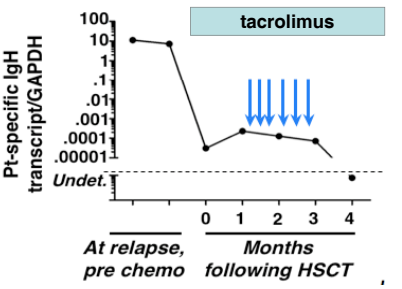
Local production of GM-CSF improves tumor antigen presentation



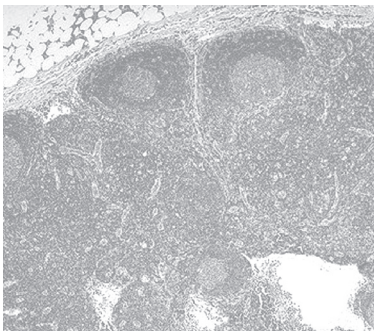
- Intense localized skin reactions at the injection sites
- Associated with new influx of immune mediators
- Associated with subsequent immune mediated tumor rejection at distant metastatic sites

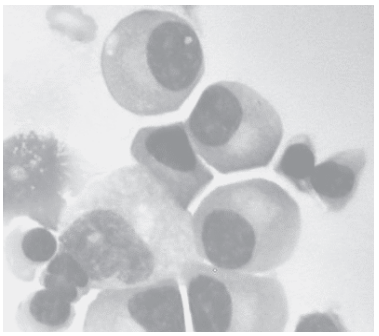
Stoffer, JCO 2003

Biologic activity of the vaccine



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Treatment of the elderly: How gentle should it be?

Neil E. Kay, MD

Treatment of The Elderly: How Gentle Should It Be?

Neil E Kay, M.D.
2011
Kay.neil@mayo.edu

Case Study

- 90 year old Woman with CLL
- Warned me not to “disturb” her CLL
- Placed her on Chlorambucil for ≥ 400 WBC
- Became cytopenic and mean
- I stopped treatment
- 8 years later she is still visiting me!

Learning Objectives

- Who is elderly ?
- What is the survival data in elderly?
- Should we treat the elderly CLL?
- How do we counsel the elderly?
- Should we use “standard therapies” ?
- Treatment options for your patient
  - Based on published / evidence based data

Who is Elderly?

CLL Demographics in The Elderly

- Age (median)
  - Diagnosis around age 70
  - Almost 70% of CLL patients are older than 65 years
    - 13% are older than 85 y.
  - 1st Therapy is often in 75 or older
  - Median age at death is 79 years.

Blood. **2010 January 14; 115(2): 187–197.**

What is The Survival Data in Elderly?

CLL Demographics in The Elderly

- Incidence (United States/yr)
  - 5-6:100,000 (15-20,000)
  - ≥ 70 years of age= 20-30:100,000
  - Males predominate (60-70%)

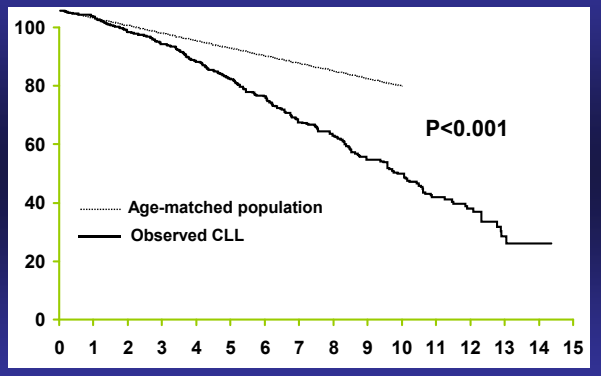
1)Blood. 2010 January 14; 115(2): 187–197.
2) SEER cancer statistics review, 1975-2007. Bethesda (MD): National Cancer Institute [online]. URL: http://seer.cancer gov/statfacts/html/clyl.html [Accessed 2010 Aug 1]

CLL Demographics Age and Survival

- Entire CLL Cohort
  - Median 10 year survival
  - But the range is wide (≤ 2 to ≥ 20 yr)
- Older patients
  - 65- 74 yr have decreased survival
  - ≥ 75 yr worse survival particularly for males

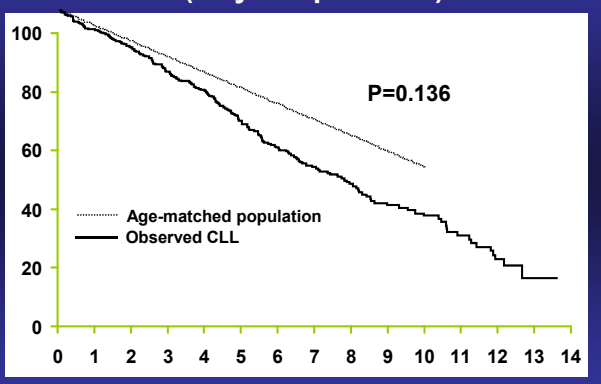
Leuk Res 2009;33:1463.
Blood 2009 113:4188
Blood 2009;114:2044.

CLL Survival: Diagnosis 65-74 yr (Mayo Experience)



Blood 2009;114:2342

CLL Survival: Diagnosis ≥75 yr (Mayo Experience)



Blood 2009;114:2342

Why Inferior Survival?

- Co morbidities(89% had more than 1)
- Age related health problems
- Increased "frailty" (multisystem reduction in physiological capacity)

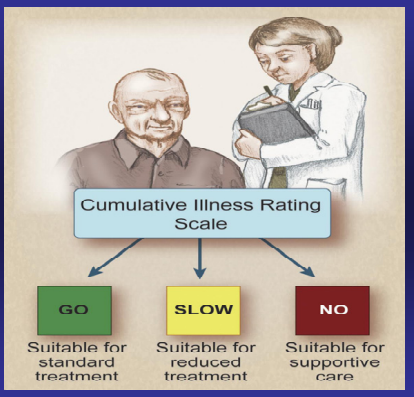
Thurmes, Leuk Lymph, 49:49-56,2008

Should We Treat Older CLL Patients ?

- German Experience
- CLL4 or CLL5 trials by the GCLLSG
  - CLL was the cause of death in more than two-thirds of the patients.
  - Death causes were not significantly different in younger and older patients.
- CLL is the primary cause of death in older patients
- "There is no justification for withholding treatment from these patients on the basis of their age alone."

1) Cramer P, [abstract no. 2840]. Blood 2006; 108 (11)
2) Zenz, Clin Oncol. 2010 Oct 10;28(29):4473-9. Epub 2010 Aug 9.

To Treat or Not

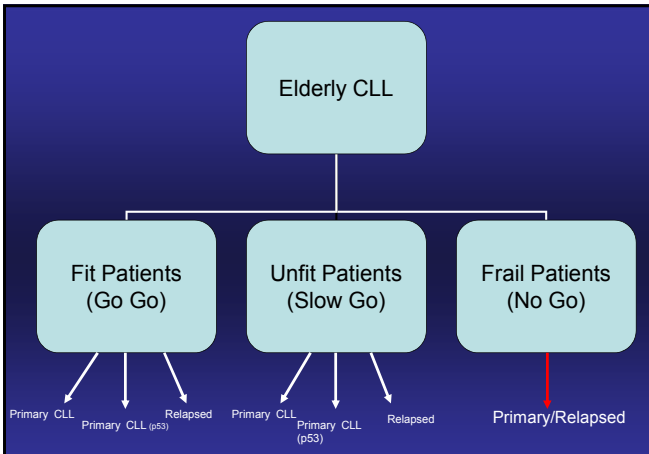


Gribben, Blood 114:3359

What is the CIRS?

- **Description of Instrument :**
  - **Assessment of physical impairment based on function of 13 organ areas.**
- **Scale Format :**
  - **5-point Likert scale measuring degree of severity. "none" to "extremely".**
- **Administration Technique:**
  - **Health provider completed is based on clinical assessment/ judgment.**

Linn BSJ Am Geriatr Soc. 1968 May;16(5):622-6
J Am Acad Nurse Pract. 2004 Aug;16(8):343-52



Modified from Goede, Drugs Aging 2011; 28 (3): 163-176

Conclusions to Date

- Elderly CLL= Male over 75
- Survival for the elderly
  - Is compromised and can be related to CLL
- Should treatment be considered in the elderly?
  - Would seem to be yes----
  - Especially if the individual is fit

How Do We Counsel Elderly CLL?

- Patients with early-stage CLL (EVEN the elderly) will have cohorts that rapidly progress.
- Little data on predictive impact of prognostic factors in elderly
- IGHV and FISH cytogenetics predicted survival in younger patients (age 55–74 years)
  - but had no prognostic value in patients over 75 years.
- Standard method of risk assessment at diagnosis might be less valuable in elderly patients with CLL

Shanafelt ,TD ,Cancer 2010 Oct 15; 116 (20): 4777-87

Should We Use "Standard Therapies"?

Can we use Pivotal Phase III Therapy Trials for Recommendations in the Elderly CLL Patient?

- Trial results favoring novel treatments were derived from clinical studies that enrolled younger patients
- The median patient age in these trials was 62 years
- "Thus recommendations for elderly CLL patients based on phase 3 trials is difficult to assess"

1.Johnson S., Lancet 1996 May 25; 347 (9013): 1432-82.
2. Leporrier M, Blood 2001 Oct 15; 98 (8): 2319-25
3. Rai KR, N Engl JMed 2000 Dec 14;343 (24): 1750-7
4. Eichhorst BF, Blood 2006 Feb 1; 107 (3): 885-91
5. Catovsky D, Lancet 2007 Jul 21; 370 (9583): 230-9
6. Flinn IW. J Clin Oncol 2007 Mar 1; 25 (7): 793-8
7. KnaufWU., J Clin Oncol 2009 Sep 10; 27 (26): 4378-84
8. Hillmen P., J Clin Oncol 2007 Dec 10;25 (35): 5816-23
9. Hallek M, Blood 2009; 114 (22)
10. Eichhorst BF, Blood 2009 Oct 15; 114 (16): 3382-91

Therapy Options for Elderly CLL (Upfront Therapy)

- Chemoimmunotherapy (CIT) should be first choice
  - FCR, FR, PCR
- But patients must have:
  - low burden of co-morbidity
  - level of physical fitness comparable with to younger patients
- Benefit from the therapy to the same degree as younger patients.
- Modern CIT therefore is the treatment of choice
- Should not be withheld "just" because of age

Hallek M., *Lancet*. 2010;376(9747):1164-1174.
Kay N, Blood 2007 Jan 15; 109 (2): 405-11

Therapy Options for Elderly CLL (Upfront Therapy)

- CLL8 trial comparing FCR to FC
  - FCR regimens showed improvements in survival in younger patients
    - CR rates of 44% and PFS of 52 months
  - CIT benefit was noted in patients younger than 65 years and 65 years or older for:
    - response rates and time to progression but not survival time
  - Age was not an independent predictor of PFS or overall survival
- CLL8 trial - no significant difference in toxicity rates between younger patients and older patients (age 70–80 years) for FCR.

Hallek M,. *Lancet*. 2010;376(9747):1164-1174.
Kay N, Blood 2007 Jan 15; 109 (2): 405-11

Therapy Options for Elderly CLL (Upfront Therapy)

- Chlorambucil
  - Not popular in the United States
  - Randomized trials show 70% OR but few CR
    - Usually partial remissions are short lived
  - Attractive features:
    - Low toxicity and oral administration

Blood 2009 Oct15; 114 (16): 3382-91
Cramer P, [abstract no.2840]. Blood 2006; 108 (11)
Goede, Drugs Aging. 2011 Mar 1;28(3):163-76.

Therapy Options for Elderly CLL (Upfront Therapy)

- Randomized trial by the GCLLSG (F vs Chlor)
  - Median age 71 years
  - Chlorambucil had a median PFS of 18 months vs. 19 months in patients treated with fludarabine.
  - Front line therapy with chlorambucil was not disadvantageous in terms of overall survival
    - Even for co morbid patients

Blood 2009 Oct15; 114 (16): 3382-91
Cramer P, [abstract no.2840]. Blood 2006; 108 (11)
Goede, Drugs Aging. 2011 Mar 1;28(3):163-76.

Therapy Options for Elderly CLL (Upfront Therapy)

- Bendamustine vs chlorambucil as initial therapy (Ph-3)
- Bendamustine induced CRs in 31 % of subjects
  - the median PFS was 22 months.
- Younger patients (age 35–65 years) and older patients (age 66–78 years) benefit equally with bendamustine
  - Median age of patients was 63 years
  - Number of enrolled patients of more advanced age (i.e. age >70 years) was relatively small.
- Grade 3 to 4 adverse events were more common with bendamustine than with chlorambucil
  - 40% *v* 19% of patients.

Knauf,J.CO.O:2009;27:4378 -4384

Therapy Options for Elderly CLL (Upfront Therapy)

- Regimens that have evidence for efficacy
  - Dose-reduced purine analogue CIT trials such as the "FCR-Lite"
    - Single study with many early stage patients
    - PFS was only 22 months
  - Pentostatin, cyclophosphamide and rituximab (PCR)
    - reduced myelotoxicity and improve tolerability in the elderly
    - PFS is 31 months and OS is 80 + months
  - Bendamustine plus Rituximab
    - Small study that needs more data

Foon KA, Boyiadzis M, Land SR. *J Clin Oncol*. 2009;27(4):498-503.
Shanafelt TD, Lin T, Geyer SM,. *Cancer*. 2007;109(11):2291-2298.
Inanitto E, Br J Haematol. 2011 Mar 4.
Knauf, J Clin Oncol. 2009 Sep 10;27(26):4378-84. Epub 2009 Aug 3.

Therapy Options for Elderly CLL (Upfront Therapy)

- Neutropenia the most common grade 3-4 treatment-related toxicity
  - 34% of treatment cycles.
- Major infections or neutropenic fever occurred in 12% of patients.
- Noted an increase in serum Immunoglobulin levels across all classes

X. C. Badoux, Blood 2011 118 (13)

Therapy Options: Elderly CLL with High Risk or Relapsed/Refractory Status

- Treatment of relapsed/refractory CLL in fit patients of advanced age is usually not different from the salvage therapy for younger patients.
- No broadly accepted standard therapy but the use of aggressive regimens and/or allogeneic SCT can be an option up to age 70
  - IF there are no restrictions regarding physical fitness or co-morbidities that conflict with such approaches.

Dreger P. Hematology Am Soc Hematol Educ Program 2009: 602-9
Toze CL, [abstract no. 3305]. Blood 2008; 112 (11)

High Risk or Relapsed/Refractory Status

- Bendamustine plus Rituximab
- Median age =66.5
- ORR = 59.0%
  - CR, PR, and nodular PR were achieved in 9.0%, 47.4%, and 2.6%
- ORR 45.5% in fludarabine-refractory patients and 60.5% in fludarabine-sensitive patients.

Fischer J Clin Oncol.2011 Sep 10;29(26):3559-66. Epub 2011 Aug 15.

High Risk or Relapsed/Refractory Status

- Genetic subgroup ORR:
  - 92 % with del(11q)
  - 100% with trisomy 12
  - 7 % with del(17p)
  - 59 % with unmutated IGHV status
- Severe infections occurred in 12.8% of patients.
- Grade 3 or 4 neutropenia, thrombocytopenia, and anemia in 23.1%, 28.2%, and 16.6%.

Fischer J Clin Oncol.2011 Sep 10;29(26):3559-66. Epub 2011 Aug 15.

High Risk or Relapsed/Refractory Status

- Ofatumumab
- Monotherapy for 2 cohorts
  - refractory to fludarabine and alemtuzumab (FA-ref)
  - refractory to fludarabine with bulky (>5cm) lymph nodes (BF-ref).
- "ad hoc retrospective analysis" in the final 96 FA-ref and 111 BF-ref patients.
- Prior Rituximab or not
  - Median age- 63 (41–85) vs 64 (44–87)

Wierda, Blood.2011 Aug 19. [Epub ahead of print]

High Risk or Relapsed/Refractory Status (Ofa)

- RituximabTreated-ORR-43%,PFS-5.3, PFS-15.5
- Rituximab Refractory- ORR-44%,PFS-5.5,OS-15.5
- Rituximab Naïve patients- ORR 53% ,PFS-5.6.OS-20.2
- Ofatumumab monotherapy - effective in patients with fludarabine-refractory CLL, including patients with previous rituximab exposure

Wierda, Blood.2011 Aug 19. [Epub ahead of print]

Therapy Options for Elderly CLL (Novel Agents: Upfront Therapy)

- Lenalidomide
- Sixty patients with CLL age 65 years and older
  - Lenalidomide 5 mg daily for 56 days, then titrated up to 25 mg per day as tolerated.
- Results:
  - 2-year progression-free survival is 60%.
- ORR is 65%
  - 10% CR, 5% CR with residual cytopenia, 7% nodular PR, and 43% PR.

X. C. Badoux, Blood 2011 118 (13)

Therapy Options for Elderly CLL (Novel Agents: Upfront Therapy)

- PCI32765 (Btk inhibitor)
- Oral agent –small molecule inhibitor
- Phase 1b/11 trial for CLL/SLL
  - Median age 68
  - R/R CLL and previously untreated
  - Oral for 28 days until progression
- Response levels = 64% for untreated
- Responses even in high risk genetic / IgVH cohorts

Burger, Blood,2010 ASH Abstract 57

Other Therapy Options for Elderly CLL

- Clinical Options
  - Low dose CIT approaches
  - Abbreviated CIT trials
  - Chlorambucil plus Rituximab
  - Lenalidomide
    - Combinations with L including Bendamustine
  - Alemtuzumab and Rituximab
  - Oral signal inhibitors
    - Akt
    - PI3Kinase (in combination)
    - BTK inhibitors

Cancer 2009 Jul 1; 115 (13): 2824-36
Blood 2006 Feb 15; 107 (4): 1276-83
Leuk Lymphoma 2009 Mar; 50 (3): 510-3

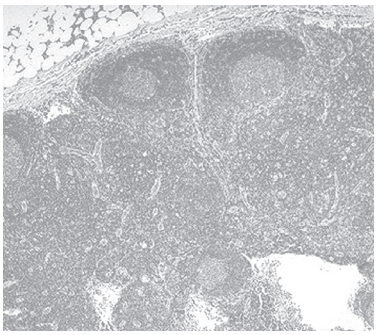
Therapy Options for Elderly CLL

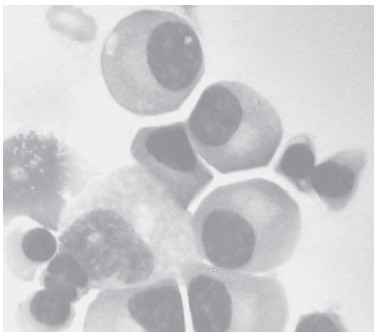
- Workup of the Elderly
  - Cumulative Illness Rating Scale
  - Reproducible geriatric functionality tests
  - Traditional performance status assessment
- Age Plus Performance Status impacts on tolerability and applicability of CLL Therapies !

Cancer 2009 Jul 1; 115 (13): 2824-36
Blood 2006 Feb 15; 107 (4): 1276-83
Leuk Lymphoma 2009 Mar; 50 (3): 510-3

END

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Non-chemotherapeutic approaches: Can we avoid alkylators and purine analogues?

Susan O'Brien, MD

Non-chemotherapeutic Approaches: Can We Avoid Alkylators and Purine Analogs

No
Relapsed CLL

Relapsed CLL, In Particular, Non-chemotherapeutic Approaches

Susan O'Brien, MD

Response to First Salvage of Front Line FCR Relapsed/Refractory Patients

Total Patients	97	
CR	**16**	**(16%)**
Nodular PR	10	(10%)
PR	29	(28%)
NR	37	(38%)
Early death/LFU	5	(5%)

Response to First Salvage by Patient Characteristics (I)

Characteristic	Value	Pts.	%CR	%nPR	%OR
Age (years)	<60	47	19	13	55
	60-65	22	18	9	63
	>65	28	11	7	54
β_2M	≤4	44	32*	16	61*
	>4	31	0	10	42
Rai Stage	0-II	39	26	13	67*
	III	10	10	0	70
	IV	36	11	14	42

* p< .05

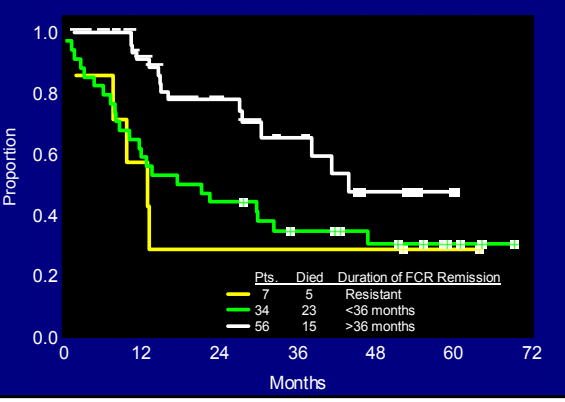
Response to First Salvage by Biologic Characteristics

Characteristic	Value	Pts.	%CR	%OR
Mutation Status:	Mutated	4	0	50
	Unmutated	28	11	43
FISH:	Negative	6	17	67
	+12, 13q-	8	0	25
	11q-	11	18	55
	17p-	19	5	10

Response to First Salvage by Patient Characteristics (II)

Characteristic	Value	Pts.	%CR	%nPR	%OR
Response to FCR as Initial Rx	CR	60	18	10	67
	nPR	12	25	33	75
	PR	18	6	0	33
	Fail	7	14	0	29
Time to FCR Fail/Relapse (Months)	<12	9	11	-	37
	12-36	32	9	19	47
	>36	56	21	7	66

Survival from First Salvage by Duration of Initial FCR Response



Response to First Salvage Regimen after FCR (Antibodies)

Regimen	Pts.	%CR	%nPR	%OR
Rit+ GMCSF	10	0	10	50
Rit + Methylpred.	7	14	0	57
Rit	7	0	0	14
Total Rituximab	24	4	4	42
Alemtuzumab (Alem)	4	0	25	50
Alem+Rit	12	42	8	75

Response to First Salvage Regimen after FCR (Chemo ± Antibodies)

Regimen	Pts.	%CR	%nPR	%OR
CFAR (FCR+Alem)	9	56	22	88
FCR± Lumiliximab	28	18	18	78
"CHOP-Like"	4	0	25	25
Misc	15	0	0	0

Alemtuzumab for Fludarabine-Refractory B-CLL: Study Results

- OR 33% (CR 2%, PR 31%)
- 59% of patients had stable disease
- Median TTP of responders 9+ months
- Fever, chills: 76% Gr 1-2, 20% Gr 3-4
- Grade 3-5 infections in 33% of patients

Keating et al. *Blood* 99 (10), 3554-61, 2002.

Local Injection-Site Reaction Following SC Alemtuzumab Administration

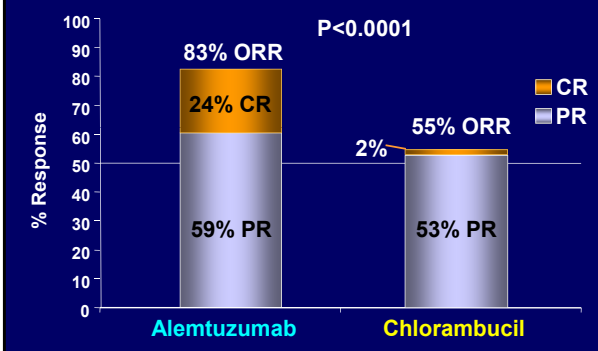
Disappeared within 2 weeks of continued therapy



Skin reactions appear to be much less pronounced in pretreated CLL patients

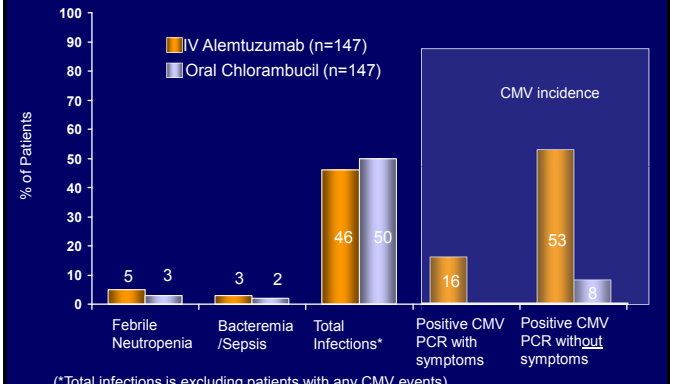
CAM307: Response to First-line Therapy With Alemtuzumab vs Chlorambucil (N = 297)

IRRP Response Rate to First-line B-CLL Therapy



Hillmen et al. JCO 2008;25:5616-5623.

CAM307: Safety
Summary of Infection-Related Adverse Events



(*Total infections is excluding patients with any CMV events)

Hillmen et al. JCO 2008;25:5616-23

CMV Viremia with Alemtuzumab

Trial No. Pts.	% Pts with CMV	Time of CMV	Organ Involv.	Deaths
Keating 93	8	on therapy	no	0
Nguyen 34	10	28 days	no	0
Ferrajoli 78	20	1st month	no	0
Lundin* 41	10	on therapy	no	0

*initial therapy

Keating et al Blood 99(10) 3554-3561 2002, Nguyen et al Clinical Lymphoma 3(2) 105-110, 2002, Ferrajoli et al Cancer 98:773-8 2003, Lundin et al Blood 100:768-773 2002

Prophylaxis Trial

Inclusion

Patients receiving alemtuzumab

Exclusion

Cr Cl calculated < 10 cc/min

Schema

1: 1 randomization

Valacyclovir **500 QD vs** Valganciclovir **450 BID**

12 weeks therapy endpoint

Results

	Total	CMV Reactivation	
Valacyclovir	20	7	p = .004
Valganciclovir	20	0	

O'Brien et al. Blood 2008;111(4):1816-19

Lymphadenopathy Predicts Poor Response to Alemtuzumab in Relapsed/Refractory CLL

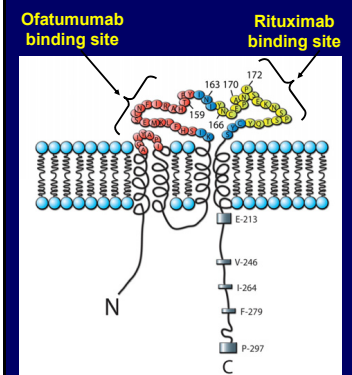
Response according to size of largest lymph node

% of patients

Largest node	No.	NCI Response CR	NCI Response OR	MRD-negative response
None	33	72	87	39
<5cm	47	17	40	11
>5cm	11	0	9	0

Moreton P et al. *J Clin Oncol.* 2005;23:2971-2979.

Ofatumumab: Characteristics



- Human CD20 mAb
- Binds a small-loop epitope of CD20
- Potent lysis of B cells
- More effective *in vitro* CDC versus rituximab
- Effective CDC of cells with low CD20 expression, including CLL cells
- Promising activity in pilot CLL study: ORR 50% in high-dose group (n=27)[3]

1. Teeling et al. *J Immunol* 2006: 177;362. 2. Teeling et al. *Blood* 2004: 104;1793. 3. Coiffier et al. *Blood* 2008; 111:1094.

Ofatumumab in Refractory CLL Objectives and Key Inclusion Criteria

- Multicenter, open-label, single-arm study: Europe and US
- Overall study objectives: efficacy and safety
- Patient population:

Double-Refractory (DR)	Bulky Fludarabine-Refractory (BFR)
• Refractory to fludarabine-containing regimen (≥2 cycles) • Refractory to alemtuzumab-containing regimen (≥12 doses)	• Refractory to fludarabine-containing regimen (≥2 cycles) • Inappropriate for alemtuzumab due to bulky nodes (>5 cm)

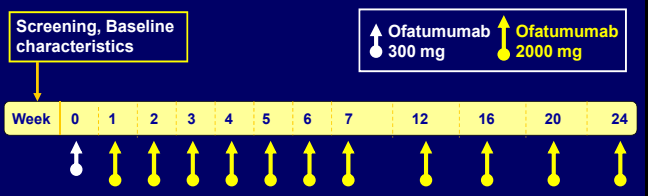
- No upper age limit
- ECOG performance status 0 to 2
- No exclusions for severe cytopenias

Wierda et al JCO 2010;28:1749-55

Ofatumumab in Refractory CLL
Baseline Characteristics (n=138)

Characteristic	DR n=59	BFR n=79
Male	75%	72%
Median age, yrs (range)	64 (41–86)	62 (43–84)
Rai stage III / IV	54%	70%
ECOG performance status 1 or 2	53%	67%
Lymph nodes >5 cm	93%	100%
Median number of prior therapies (range)	5 (1–14)	4 (1–16)
Prior rituximab exposure	59%	54%

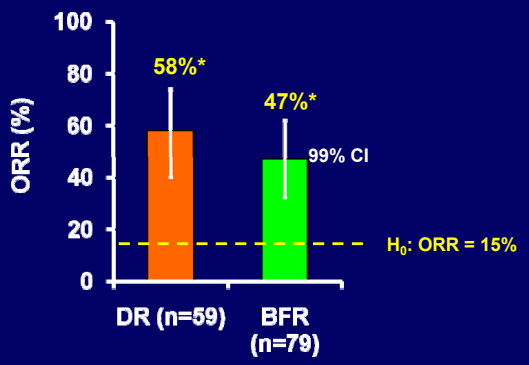
Ofatumumab in Refractory CLL
Treatment Schedule



- Pre-medication:
  - Paracetamol (acetaminophen) 1 g PO or eq.
  - Antihistamine (cetirizine) 10 mg PO or eq.
  - Glucocorticoid (prednisolone) 100 mg IV or eq.

Median no. of infusions: 12 (range, 1–12) for both groups

Ofatumumab in Refractory CLL
Objective Responses



*P<0.0001 versus H_0 (two-sided exact test).

Lenalidomide in CLL Salvage

	RPCI[1] N=45	MDACC[2] N=35
Dose (mg)	25	10
Response (%)		
CR	8 (18)[a]	2 (6)
N-PR		1 (3)
PR	18 (40)	10 (29)
OR	26 (58)	13 (37)
SD	6 (14)	10 (29)

*Molecular remission (PCR) in 3 pts

[1]Chanan-Khan AA et al. JCO 24:5343-5349, 2006 updated 2007; [2]Ferrajoli A et al. Blood 108(11):94a (Abstract #305), 2006

Lenalidomide: Adverse Events

	RPCI[1]		MDACC[2]	
Toxicity (%)	G < 3	G ≥ 3	G < 3	G ≥ 3
Fatigue	73	10	32	9
Flare reaction	50	8	30	7
Constipation	30	-	-	-
Diarrhea	33	-	11	5
Rash	40	3	32	-
DVT/PE	-	5	3	-
Neutropenia	8	70	-	25
Thrombopenia	33	45	5	20
Anemia	45	18	9	5

1Chanan-Khan AA et al. JCO 24:5343-5349, 2006; 2Ferrajoli A et al. Blood 108(11): 94a (Abstract #305), 2006

Tumor Flare Reaction



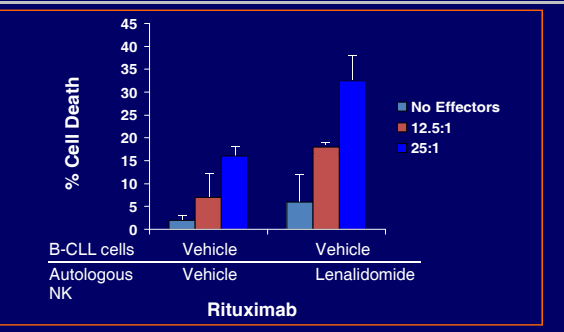
Combination Therapy with Lenalidomide and Rituximab in Patients with Relapsed Chronic Lymphocytic Leukemia

Alessandra Ferrajoli, Xavier Badoux, Susan O'Brien, William Wierda, Stefan Faderl, Manolo Pasia, Bang-Ning Lee, James Reuben, Hagop Kantarjian and Michael Keating

Department of Leukemia
The University of Texas, M.D. Anderson Cancer Center, Houston, TX.

ASH 2009 Abstract 206

Lenalidomide Enhances NK-Cell–Mediated Cytolysis of Rituximab-Coated CLL Cells

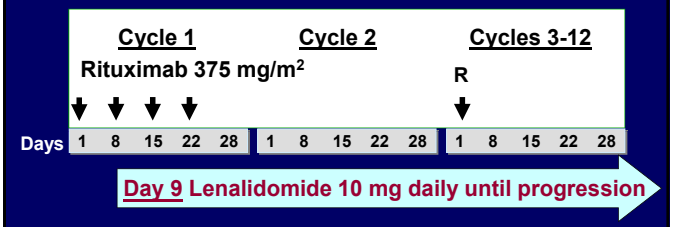


Lenalidomide treatment of autologous derived NK cells results in enhanced rituximab mediated ADCC of untreated CLL cells

Lapalombella et al. Blood 2008 ;112(13):5180-9

26

Lenalidomide-Rituximab: Dose and Schedule



Allopurinol 300 mg day 1 -14 of cycle 1

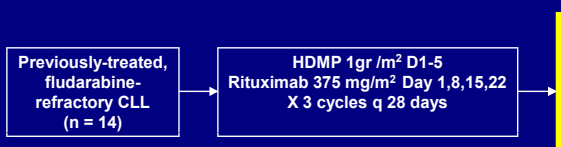
Ferrajoli et al; ASH 2009 Abstract 206: Lenalidomide and rituximab

Lenalidomide and Rituximab in Relapsed CLL: Responses (ITT)

Time on therapy Evaluable	Cycle 6 44	Cycle 12 22
Complete Response, N (%)	-	2 (9)
Nod. Partial Response, N (%)	7 (16)	4 (18)
Partial Response, N (%)	21 (48)	8 (36)
Overall Response, N (%)	28 (64)	14 (64)
* 1 Early Death		

Ferrajoli et al; ASH 2009 Abstract 206: Lenalidomide and rituximab

High Dose Methylprednisolone (HDMP) & Rituximab – Fludarabine Refractory



ORR: 93%
CR: 36%
TTP 15 months
OS-median: Not reached after 40 months

29

Castro JE, et al. *Leukemia*. 2008; Nov 22(11):2048-53

UC San Diego Moores Cancer Center

High Dose Methylprednisolone (HDMP) & Rituximab – Fludarabine Refractory

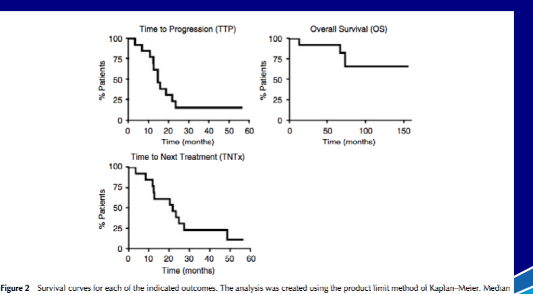


Figure 2 Survival curves for each of the indicated outcomes. The analysis was created using the product limit method of Kaplan-Meier. Median time-to-progression (TTP)-15 months. Median time-to-survival (OS) has not been reached (median follow up 40 months after treatment and 78 months after diagnosis). Median time to next treatment (TNTx) 22 months.

Castro JE, et al. *Leukemia*. 2008; Nov 22(11):2048-53

UC San Diego Moores Cancer Center

High Dose Methylprednisolone (HDMP) & Rituximab – Fludarabine Refractory

Table 2 Adverse events

Adverse event	*Grade I–II*	*Grade III–IV*	*Total no. of patients/(%)*
Fluid retention	6		6/43
BM suppression	1	4	5/36
Neutropenia		2	
Thrombocytopenia		2	
Anemia	1		
GERD/dyspepsia	3		3/21
Fatigue	3		3/21
Hyperglycemia	3		3/21
Cough	3		3/21
Fever	2		2/14
Mood changes	2		2/14
Sore throat	2		2/14
Nausea/vomiting	2		2/14
Myalgias	2		2/14
Flushing	1		1/7
Insomnia	1		1/7
Pneumonia		1	1/7
Electrolyte disorder	1		1/7
Leg pain	1		1/7
Photophobia	1		1/7
Anxiety	1		1/7
Rigors/chills	1		1/7
Hiccups	1		1/7
Visual hallucinations	1		1/7

Castro JE, et al. *Leukemia*. 2008; Nov 22(11):2048-53

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Relapsed CLL - Conclusions

FCR retreatment possible
- better results if first remission >3 years

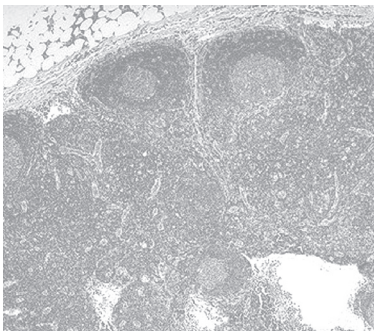
Alemtuzumab is an under-rated antibody
- less effective in bulky adenopathy

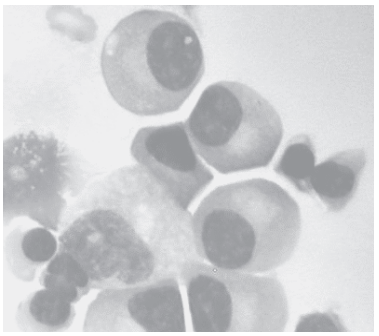
Ofatumumab in most refractory population
- very little myelosuppression

Lenalidomide ± R
- effective regimen, myelosuppressive

HDMP + Ritux
- impressive data, small N

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies

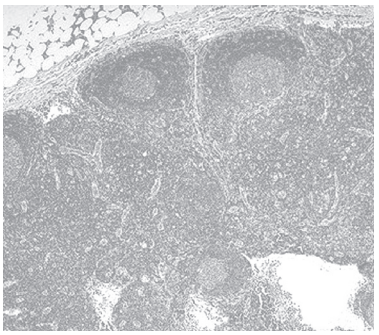


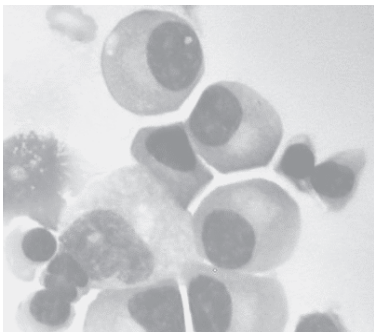


Novel approaches to CLL: Exciting new agents

Richard Furman, MD

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies

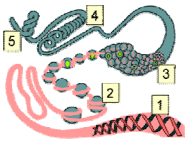




New molecular targets in large cell lymphoma

Lisa M. Rimsza, MD

New Molecular Targets in Large Cell Lymphoma



Lisa M. Rimsza, M.D.
University of Arizona, Tucson

Educational Objectives

- High through-put technologies
- Targets, diagnostics, & agents for:
  - Cell of origin: ABC-DLBCL vs. GCB-DLBCL
  - Survival strategies (ABC): BCR signalling, NF-kB
  - Epigenetics (GCB): DNA methyltransferases
  - Oncogenes: BCL2, MYC
  - Microenvironment:
    - Enhancing immune surveillance
    - Inhibiting angiogenesis

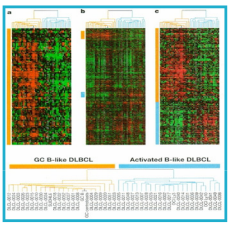
High Through-put Methods

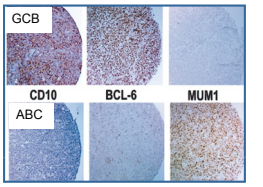
	Methods	Information
Chromatin: Epigenetics	Methylation profiling	Nucleotide methylation
DNA: Genomics	Automated sequencing and SNP array	DNA sequence
	Array Comparative Genomic Hybridization (aCGH)	Gains and losses of regions of DNA
	Chromatin Immunoprecipitation "ChiP on Chip" or "Chip-Seq"	Transcription Factor associations on DNA
RNA: Transcriptomics	Gene Expression Profiling (GEP)	mRNA expression levels
	RNA-sequencing	Changes in mRNA (DNA) sequences
	siRNA screening	Critical mRNAs for cell
Proteins: Proteomics	Mass spectroscopy	Expressed proteins

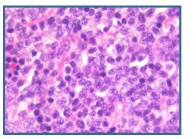
DLBCL Cell of Origin Subtypes

Germinal Center

Activated B- Cell







Alizadeh et al. Nature 2000

Hans et al, Blood 2004
80% agreement with GEP

Modified "Choi" added GCET1 and FOXP1, 93% agreement

Cell of Origin Significance: R-CHOP

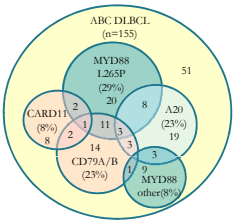
- Immunohistochemistry
  - "Choi" algorithm, Choi et al, Clin Can Res 2009
  - "Tally" algorithm, Meyer et al, JCO 2011
  - LM02, Natkunam et al, JCO 2008
- RT-PCR for BCL6 and LM02 as part of 6 gene model
  - Malumbres et al, Blood 2008
- Gene Expression Profiling
  - Lenz et al, NEJM 2008, Gascoyne et al, JMD 2010, Rimsza et al, JCO 2010, Gutierrez-Garcia et al. Blood 2011
- MicroRNA profiling
  - Alencar et al, Clin Cancer Res 2011

Comparison of COO Classification Methods

- Immunohistochemistry
  - Inexpensive
  - Better for cases with infrequent tumor cells
  - Limitations:
    - Need for additional antibodies that are specific for the ABC subtype
    - Qualitative and subjective data
    - Tissue quality issues
- Molecular assays
  - More quantitative
  - Can analyze many more genes
  - More objective
  - Limitations:
    - Need to work on FFPE tissues
    - Need to be easy to use, widely available, and billable

ABC-DLBCL: B-cell receptor signalling

- Mutations in:
  - CARD11
  - CD79A/B
  - MYD88 (gain of function)
  - A20
- Lead to activation of:
  - NF-kB (MYD88 or CARD11)
  - JAK kinase activation of STAT3 (MYD88)
    - Increases autocrine IL6, IL10, and beta-IFN
  - PI3K/AKT/mTOR pathway



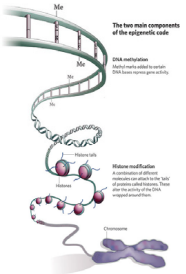
Lenz et al, Science 2008;
Compagno Nature 2009;
Ngo et al, Nature 2011;
Shipp et al, Nat Med 2002;
and others)

ABC-DLBCL: Targeting BCR signalling

- Tonic BCR signalling
  - SYK inhibitor
  - BTK inhibitor
  - PI3K inhibitor
  - mTOR inhibitors
  - NF-kB pathway inhibitors
    - CARD11
    - Proteosome
    - IkappaB kinase
    - PKC beta
  - JAK/STAT
- Agents
  - Fostamatinib
  - PCI32765
  - CA-101
  - rapalogs, small molecule
    - Fostamatinib
    - Bortezomib, carfilzomib
    - PS1145
    - Enzastaurin
  - SB1518, INCB018424

GCB-DLBCL & Epigenetics: disruptions of chromatin

- Histone methyltransferase mutations
  - MLL2 inactivated, disrupts H3K4 methylation that "marks" activated genes
  - MEF2b, cooperates with CREBBP and EP300 in acetylating histones
  - EZH2, methylates H3K27 to interfere with histone acetylation



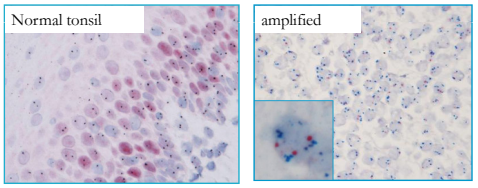
R. Morin et al, Nature Genetics 2010;
C. Steidl et al, Nature 2011;
Pasqualucci Nature Genetics 2011

GCB-DLBCL: Methyltransferases & BCL6

- Targeting strategies
  - Drugs to inhibit EZH2 activity
- BCL6
  - Retroinverso BCL6 peptide inhibitor (Melnick)
  - Class I and II histone deacetylase inhibitors
    - Vorinostat (SAHA), romidepsin, mocetinostat, panabinostat, belinostat
    - Hyperacetylate BCL6 and disrupt HSP90

Oncogenes: MYC

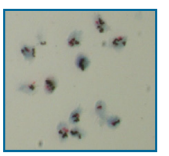
- 10% have translocations, up to 30% have amplifications
- Over-expression associated with poor outcome
- New colorimetric ISH and rabbit mAB IHC stains may help in identifying cases



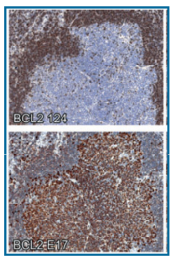
Savage, Blood 2009;
Stasik, Haematologica 2010;
& unpublished

Oncogenes: BCL2

- 20-30% of DLBCL have translocations (mainly GCB-DLBCL)
- ABC-DLBCL have even higher mRNA levels through unclear mechanisms
- New colorimetric ISH and rabbit mAB IHC to detect cases with increased expression



ABC cell line with amplified BCL2



Masir et al, Brit J Haematol, 2008:
& unpublished

Targeting MYC and BCL2

- MYC
  - Disruption of Myc/Max dimers
  - BET Bromodomain Inhibition, JQ1
  - G-quadruplex inhibitors of DNA secondary structure
- BCL2
  - BH3 mimetics
    - ABT263, Obatodax, AT101
  - Antisense
    - Oblimersen
  - G-quadruplex inhibitors of DNA secondary structure

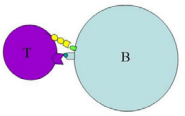
Microenvironment: Increased tumor infiltrating cells

- "Lymph Node" signature
- "Host-response" signature
- 2 gene model in DLBCL reflecting tumor and microenvironment
  - LM02: marker of GCB-DLBCL
  - Tumor Necrosis Factor Receptor Superfamily Member 9 (TNFRSF9), aka CD137
    - Marker of activated CD8+ T cells and NK cells

Rosenwald NEJM 2002;
Monti et al, Blood 2005;
Alizadeh et al, Blood 2011

Targeting T-cell subsets

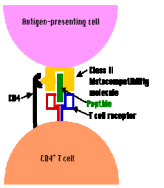
- Abnormal T-cell subsets
  - TNFRSF9:
    - Anti-CD137 agonistic antibodies
    - Other TNF receptor superfamily receptors
      - Anti-CD40 agonistic antibody (dacetuzumab or HCD122)
      - Anti-TNF-related apoptosis-inducing ligand death receptor (TRAIL receptor-1)
  - T-regulatory cells (anti-CD25)
    - Denileukin diftitoxin



- General immunomodulatory
  - Lenalidomide (thalidomide derivative)

Microenvironment: MHC & Immune Surveillance

- Major Histocompatibility Class II
  - Decreased expression poor prognostic feature in CHOP & R-CHOP patients
  - MHC II transactivator, CIITA, recurrently translocated in PMBCL
    - ↓MHC II expression and↑ ligands of Programmed cell death 1 and 2 (PDL1 & 2) on T-cells
- MHC Class I
  - Biallelic inactivation of beta-2-microglobulin in DLBCL



Rosenwald , NEJM 2002;
Rimsza , Blood 2004 & 2008;
Montes-Moreno , Haematologica 2010;
Steidl , Nature 2011;
Pasqualucci , Nature Genetics 2011

Targeting MHC II

- HDAC-inhibitors
  - Class I inhibitors: vorinostat, romidepsin, panobinostat
  - Class II inhibitors: mocetinostat, entinostat
- Resveratrol
  - Upregulates MHC II mRNA expression and recycling mechanism

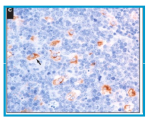


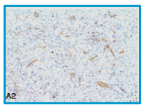


Radwan, Leuk Lymph 2011;
and unpublished

Microenvironment: Stromal gene signatures

- Prognostic signatures identified by GEP in R-CHOP treated DLBCL
- Stromal-1 (good outcome): genes related to monocytic/histiocytic and extra-cellular matrix components (fibronectin, osteonectin, collagen, laminin, matrix metalloproteinase, CTGF)
  - IHC for SPARC
- Stromal-2 (poor outcome): genes related to endothelial cells, angiogenesis
  - IHC for CD31

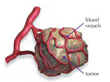




Lenz, NEJM 2008;
Meyer, AJCP 2011;
Cardesa-Salzmann, Haematologica 2011

Targeting the Stroma

- Stromal 1 signature
  - SPARC: paclitaxel
  - CTGF: anti-CTGF mAb

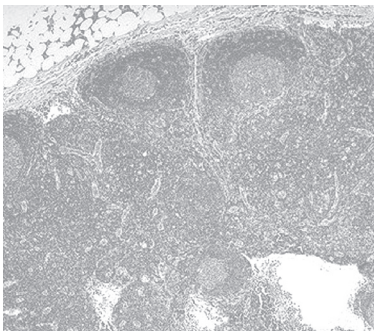


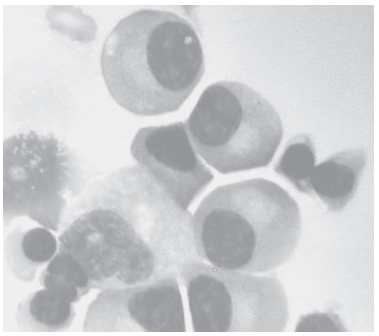
- Stromal 2 signature:
  - Anti-VEGF: bevacizimab, Tie-2 inhibitors, enzastaurin (inhibits pKCbeta)
  - CXCR4 small molecule inhibitors
  - Anti-PDGFR: vatalanib, pazopanib, ABT-869

Future

- Ultimate goal:
  - Tumor analysis will yield not only the diagnostic signature but also the "therapeutic signature"
  - Single platform to do all of the above
  - "SPECS II" funding mechanism by Lymphoma and Leukemia Molecular Profiling Project (LLMPP)
- Develop same level of detailed information for other lymphomas, MCL, T-NHL, HL.

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





BCL-6: a regulator of lymphomagenesis

Ari Melnick, MD

Epigenetic Programming in B-cell Malignancies

Ari Melnick, MD

Division of Hematology/Oncology
Weill College of Medicine
Cornell University

Weill Cornell Medical College

Genetics and Epigenetics

EPIgenetic information

.... A T C G ....

DNA - genetic information

Inherited across generations

Transmitted by mother to daughter cells

Required for life

Comparing genetic and epigenetic codes

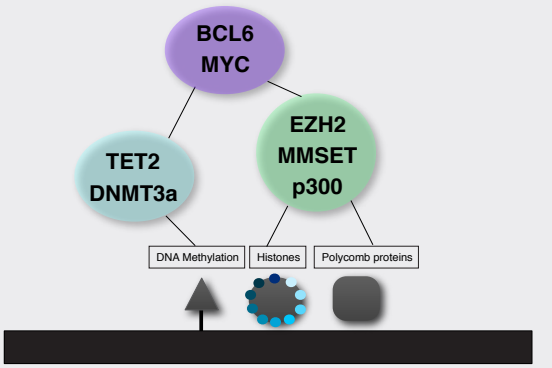
EPIgenetic code
Hundreds of proteins and chemical modifications

DNA Methylation Histones Polycomb proteins

.... A T C G ....

DNA - genetic code
4 nucleotides

Epigenomic regulators mutated in Heme Malignancies



Epigenetic vs Genetic information

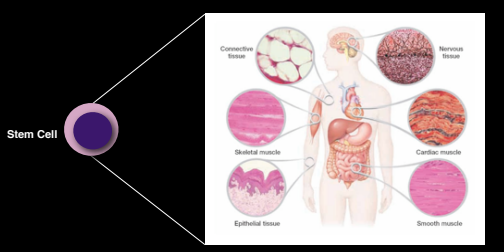
EPIgenetic information has plasticity

Genetic information is constant

Conception Death

Epigenetic plasticity is required for complexity

Genetic Content



Epigenetic Content

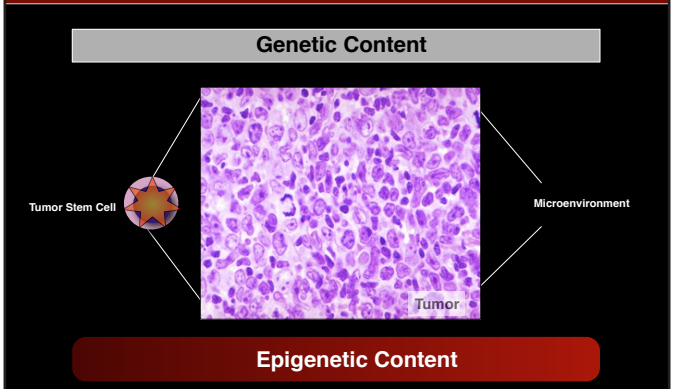
Genetic and epigenetic variation and cancer

EPIgenetic code - extreme plasticity (tens of thousands of abnormalities)

Genetic code - some plasticity (tens of abnormalities)

Initiation → Death

Epigenetic plasticity is required for malignancy



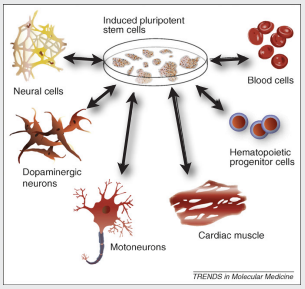
Epigenetic programming can be erased

EPIgenetic code - Can be reprogrammed

Genetic code - Cannot be reprogrammed

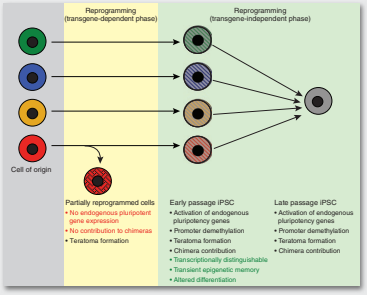
Initiation → Death

Terminally differentially cells can be reprogrammed into stem cells



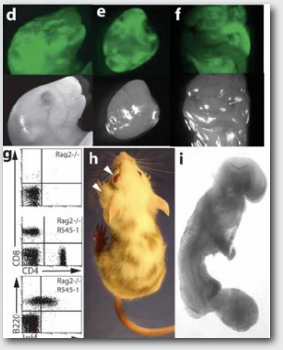
Amabile and Meissner et al, Trends in Molecular Medicine

Epigenetic memory transiently persists and restricts cell fate in iPS cells



Polo et al, Nature Biotechnology 2010

Cloned melanoma cells contribute to normal development



Horschlinger et al, Genes and Development

Comparing genetic and epigenetic codes

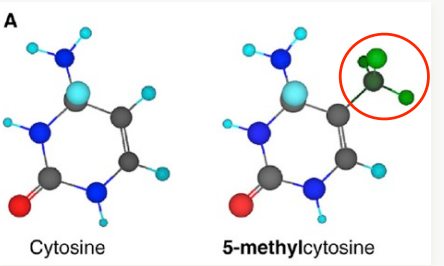
EPIgenetic code
Hundreds of proteins and chemical modifications

DNA Methylation Histones Polycomb proteins



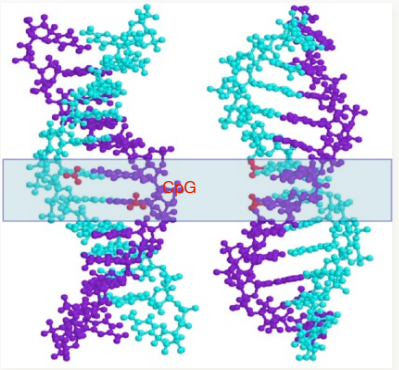
DNA - genetic code
4 nucleotides

Methyl-cytosine - the 5th base



DeFossez and Prokhortchouk, Biochim Bioph Acta, 2008

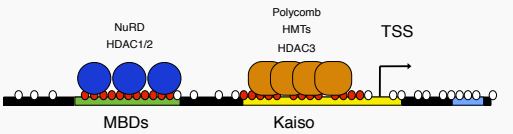
Methyl groups from Me-CpGs project into the major groove



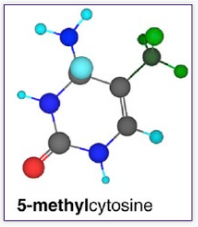
DeFossez and Prokhortchouk, Biochim Bioph Acta, 2008

The DNA methylation mark is read by methylation dependent transcriptional regulators

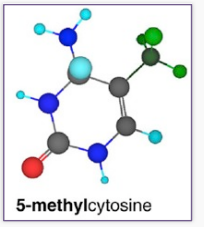
- Methylated
- Unmethylated



DNA methylation regulates critical biological processes

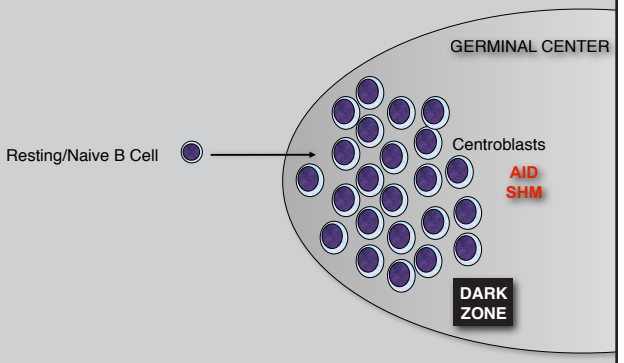


DNA methylation regulates critical biological processes



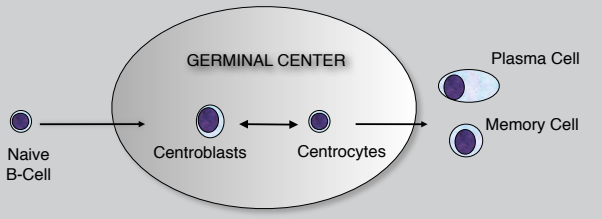
- Regulation of gene expression
- Silencing repetitive DNA elements
- Development
- Chromosomal stability
- Genomic imprinting
- X-chr inactivation
- Cellular differentiation

Germinal Center B-cell Differentiation



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Most lymphomas arise from GC B cells



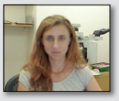
GCB-DLBCL ABC-DLBCL

Burkitt Lymphoma Follicular Lymphoma

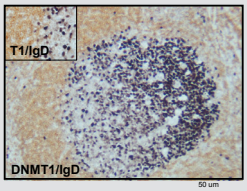
Thursday, September 29, 2011

DNMT1 is upregulated in germinal center B-cells

Rita Shaknovich, et al unpublished



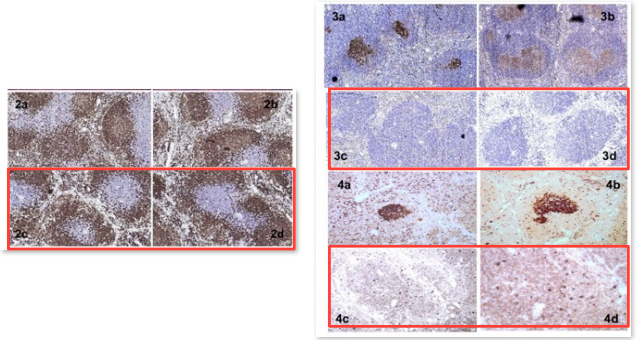
Rita Shaknovich, MD PhD
Assistant Professor
Department of Pathology,
Weill Cornell Medical College



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DAC Treatment abrogates germinal center formation in immunized mice

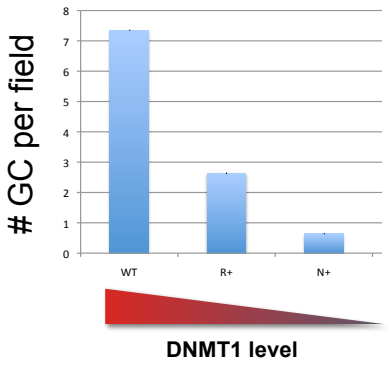
Rita Shaknovich, et al unpublished



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Genetic depletion of DNMT1 leads to progressive loss of germinal centers

Rita Shaknovich, et al unpublished

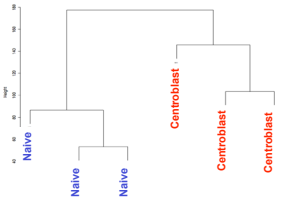


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Centroblasts display distinct patterns of methylation vs. NBC

Rita Shaknovich, et al unpublished

Hierarchical clustering dendrogram

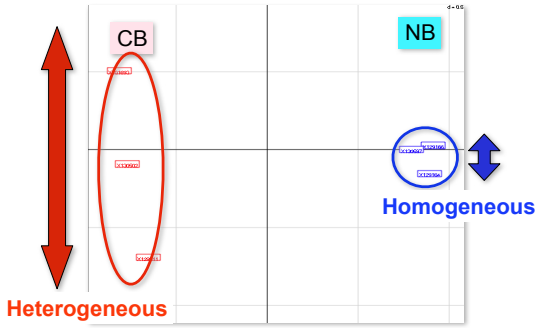


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Centroblasts display epigenetic heterogeneity

Rita Shaknovich, et al unpublished

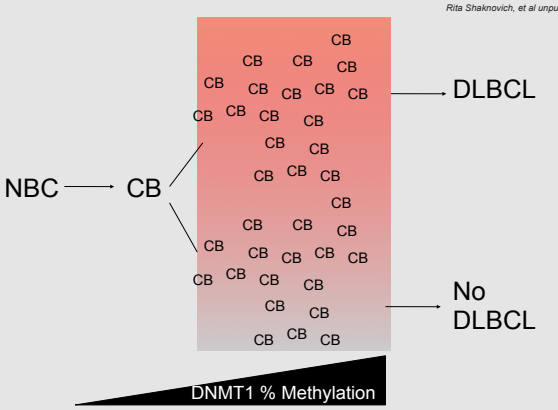
Principal component analysis



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Does epigenetic heterogeneity in GC B-cells contribute to DLBCL?

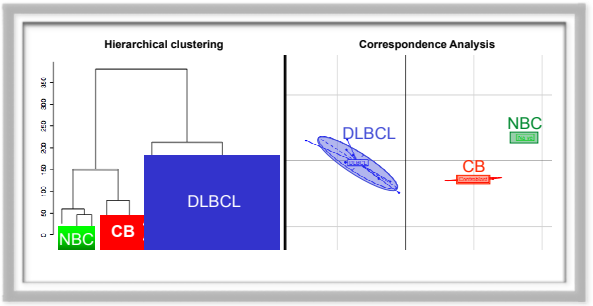
Rita Shaknovich, et al unpublished



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DNA methylation distribution is altered in DLBCL

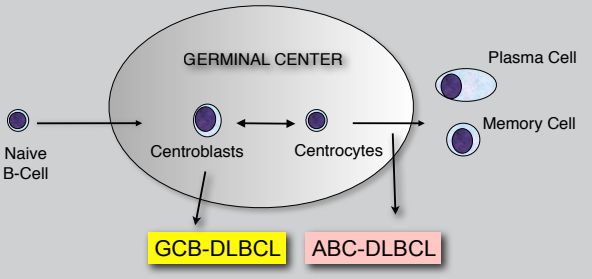
Rita Shaknovich, et al unpublished



Greater heterogeneity in DLBCL than in normal GC B-cells

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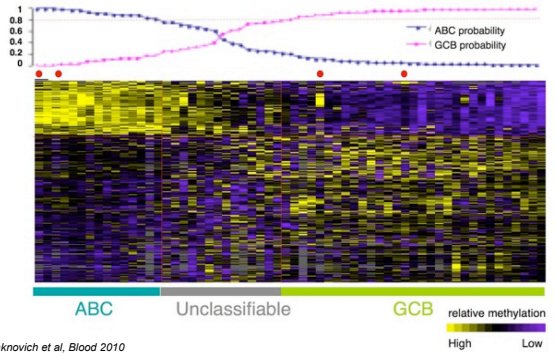
Most lymphomas arise from GC B cells



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Distinct epigenetic signatures underlie ABC and GCB DLBLCs

Shaknovich et al, Blood 2010

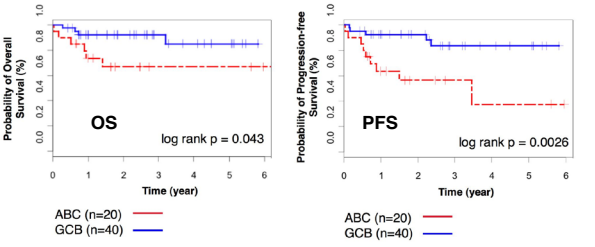


Shaknovich et al, Blood 2010

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Confirmation of clinical difference between epigenetically defined ABCs and GBCs in this patient cohort

Shaknovich et al, Blood 2010



Shaknovich et al, Blood 2010

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TNFa pathway is differentially methylated

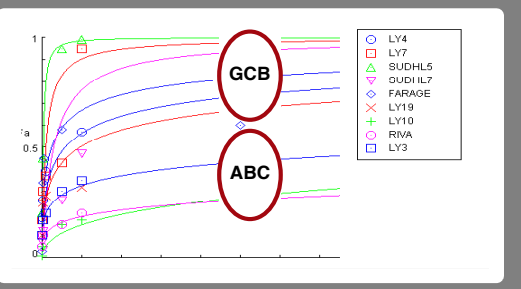
Shaknovich et al, Blood 2010



Shaknovich et al, Blood 2010

Thursday, September 29, 2011

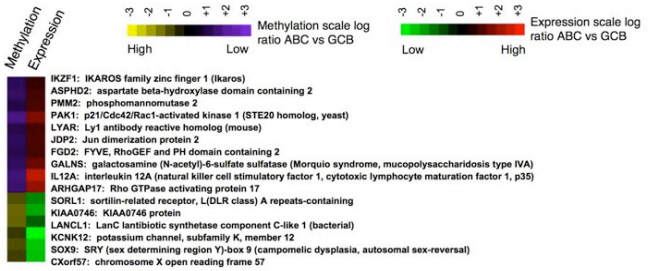
GCBs are generally more steroid responsive



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16 genes overlap between DNA methylation and GEP

Shaknovich et al, Blood 2010

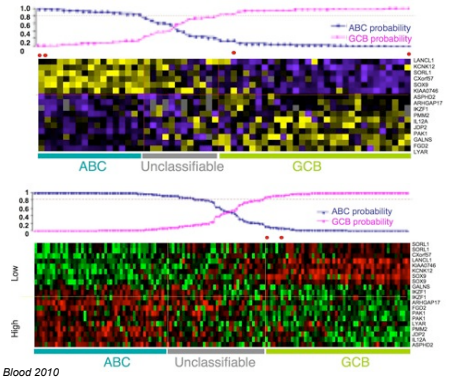


Shaknovich et al, Blood 2010

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16 gene overlap predicts class label for DLBCL

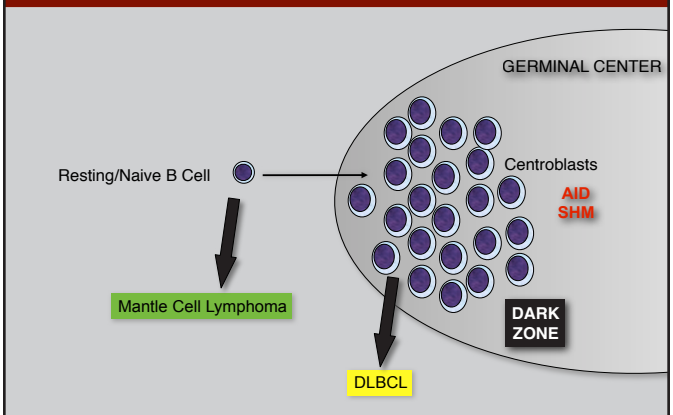
Shaknovich et al, Blood 2010



Shaknovich et al, Blood 2010

Thursday, September 29, 2011

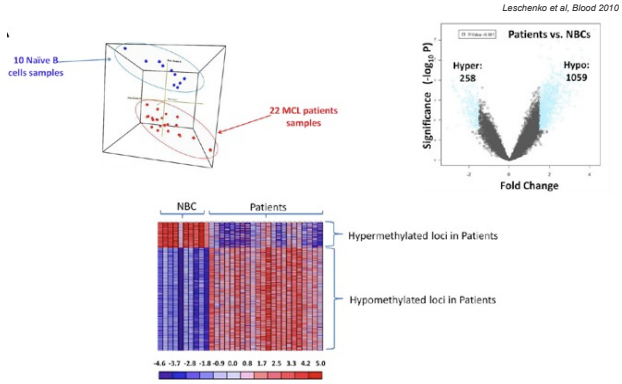
Mantle Cell Lymphomas arise from NBCs



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MCL patients display aberrant hypomethylation

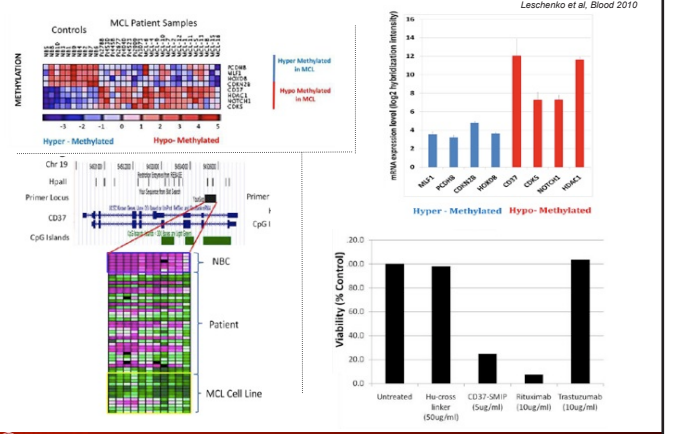
Leschenko et al, Blood 2010



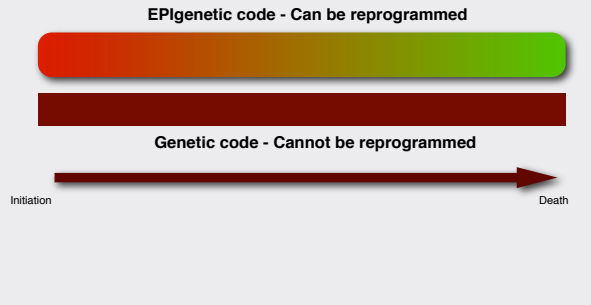
Samir Parekh MD, Albert Einstein College of Medicine

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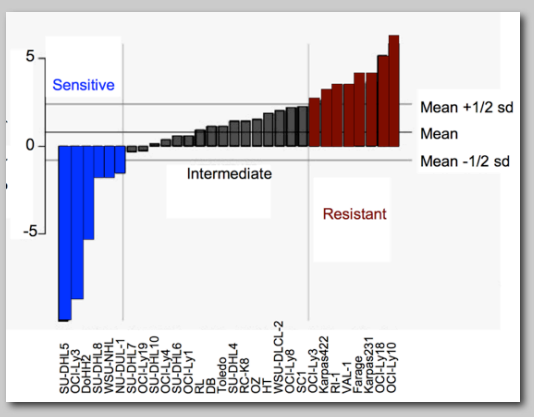
Targeting an overexpressed hypomethylated gene in MCL



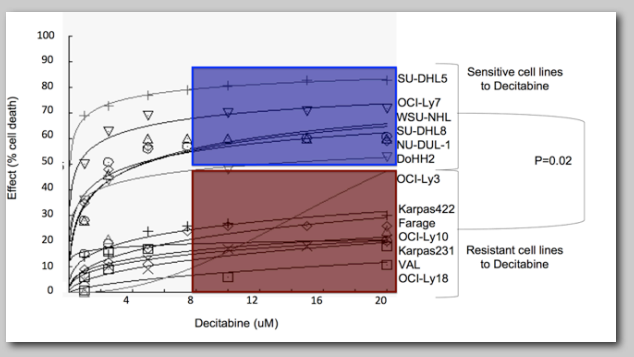
Epigenetic programming can be erased



A subset of DLBCLs are responsive to MTIs

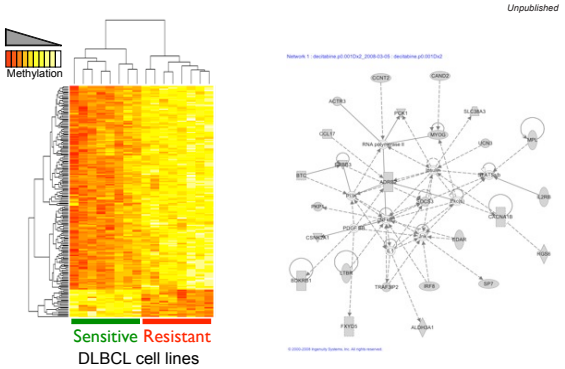


MTIs can potently kill a subset of DLBCLs



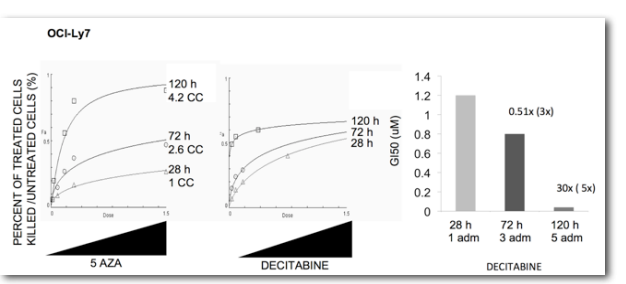
MTI responsive DLBCLs display a hypermethylated signature

Unpublished



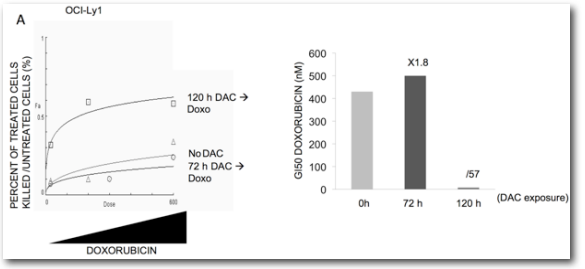
Longer administration of lower dose MTI has more potent anti-lymphoma activity

Unpublished



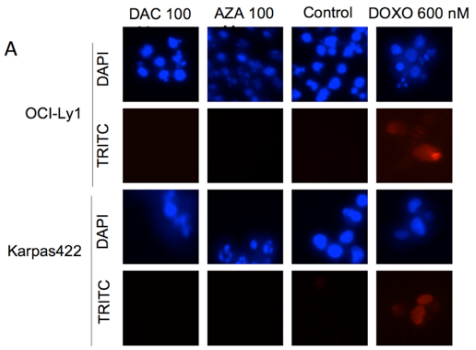
Low dose and longer exposure sensitizes cells to MTI anti lymphoma effects

Unpublished



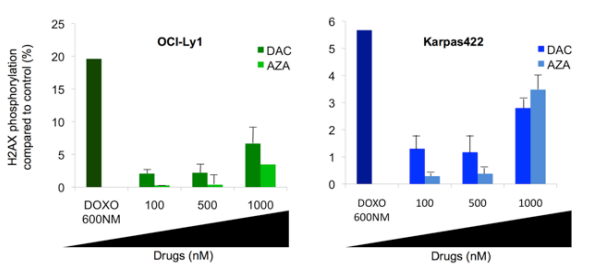
Low dose MTI does not induce DNA damage

Unpublished

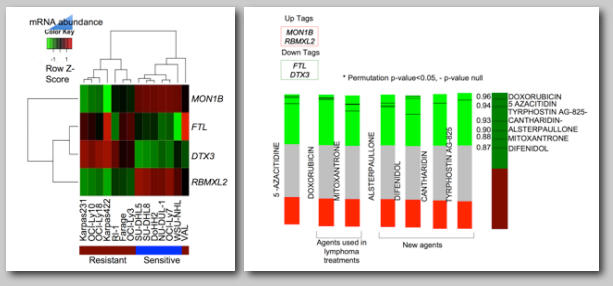


Low dose MTI does not induce DNA damage

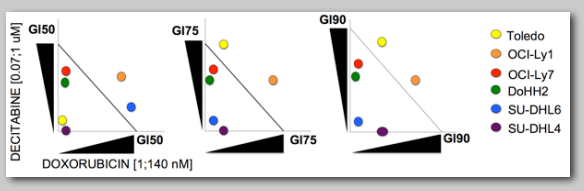
Unpublished



Using connectivity mapping to design combinatorial MTI therapy

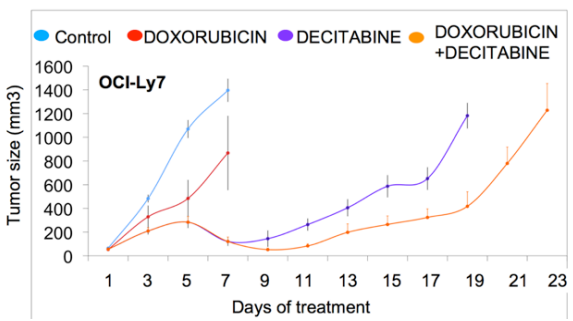


Doxorubicin synergizes with MTIs



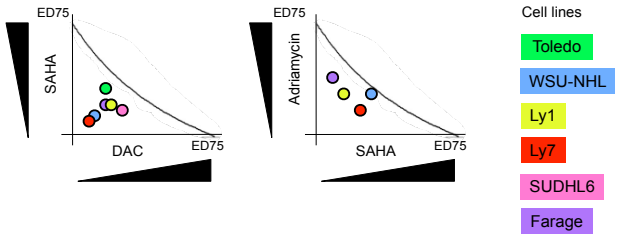
MTIs potently suppress DLBCLs in vivo

Unpublished



Synergy between MTI, HDI and Doxorubicin

Unpublished

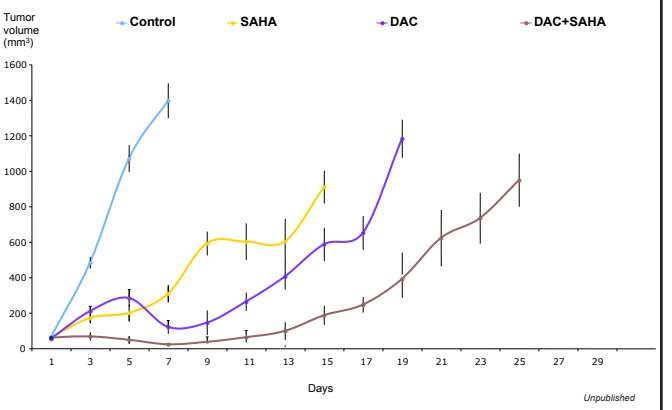


Cell lines

- Toledo
- WSU-NHL
- Ly1
- Ly7
- SUDHL6
- Farage

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SAHA enhances DAC activity in vivo

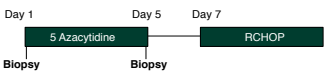


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Phase I/II clinical trials at WCMC

John Leonard
Rebecca Elstrom
Peter Martin

5 Aza + RCHOP



5 Aza + SAHA

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Summary

Variance of DNA methylation occurs naturally during immune response and may contribute to lymphomagenesis
DNMT1 is highly expressed in normal GC B-cells and DLBCL
DNMT activity is required for GC formation
DLBCL heterogeneity maybe partially explained by epigenetic patterning
ABC and GCB DLBCLs have distinct DNA methylation signatures, involving TNFa signaling pathways
A DNA methylation classifier can predict ABC vs GCB identity
A subset of DLBCLs may respond to DNMT inhibitors and these drugs synergize with HDAC inhibitors and chemotherapy
Aberrant hypomethylation predominates in MCL, and epigenetic therapy can synergize and sensitize MCL

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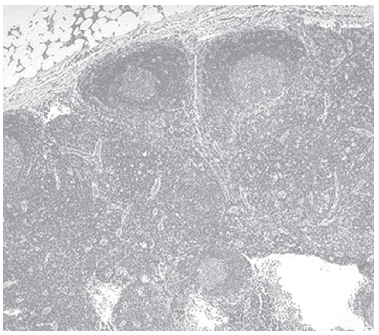
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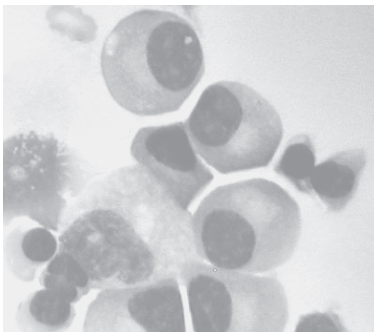
Rita Shaknovich

Olivier Elemento
Randy Gascoyne
Nathalie Johnson
Samir Parekh
Rebecca Elstrom
Peter Martin
John Leonard
Wayne Tam

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Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Limited treatment for limited disease?

Volker Diehl, MD

Hodgkin's disease
Limited treatment for limited disease?

Volker Diehl
For the German Hodgkin Study Group

New York,
October 22, 2011

Early stage Hodgkin Lymphoma
State of the Art and Future Perspectives

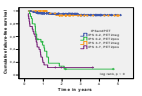
- **Background**
- **Early favorable**
- **Early unfavorable**
- **Ongoing studies (PET)**
- **IN-RT & Quality Assurance**
- **Future**
- **Summary**

How to personalize therapy?
..until we have the right targets...

Use:

1.Risk Factor Prediction (IPS, GHSG-EORTC- Criteria)

2.Response Adaptation (FDG-PET)



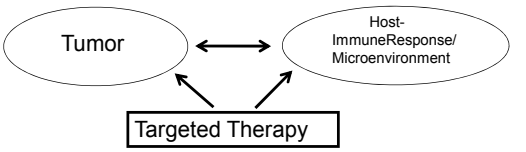
3. Molecular-Genetic Markers

f.e. CD68+ macrophages: Steidl et al, NEJM, 2010

The Road to „Personalized“ Therapy“!

1. Search for the molecular target
2. Specify the role of the microenvironment
3. Find molecular- genetic risk/prognostic markers

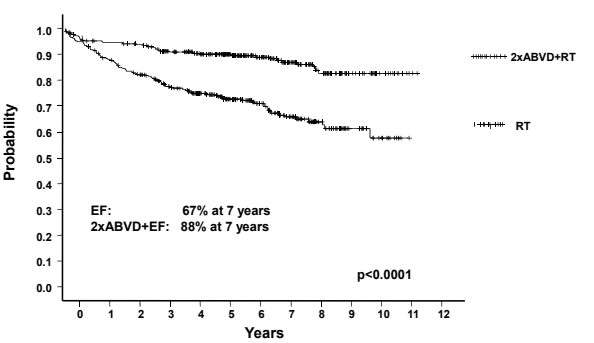
f.e. CD68+ macrophages (Steidl et al NEJM)



Hodgkin Lymphoma: Risk Adaptation in the GHSG

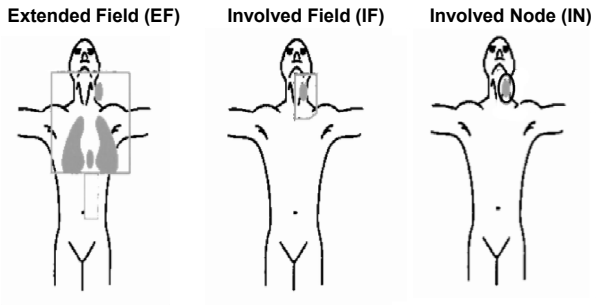
	Stage			
Risk factors	IA, IB, IIA	IIB	IIIA, IIIB	IVA, IVB
No	Early favourable		Advanced Stages	
≥ 3 LN- areas				
Elevated ESR	**Early unfavor-able**			
Large mediastinal mass				
Extranodal disease				

HD7 trial
For early favorable HL (FFTF)

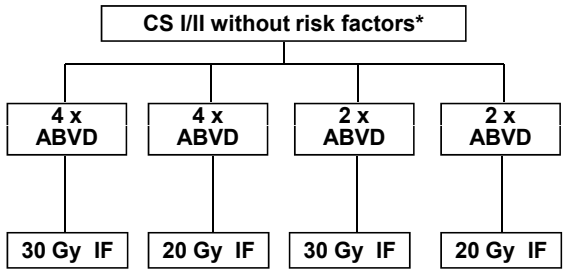


Engert et al JCO 2007

Radiation fields used
in Hodgkin Lymphoma

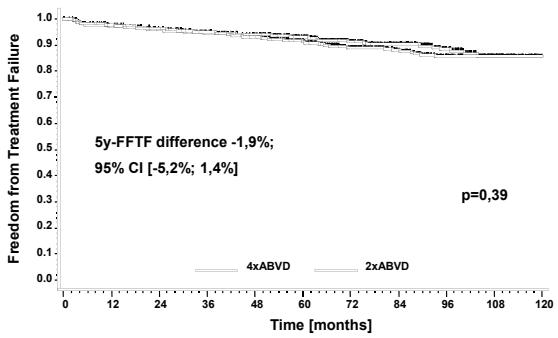


GHSG HD10 Study
Early favorable HL



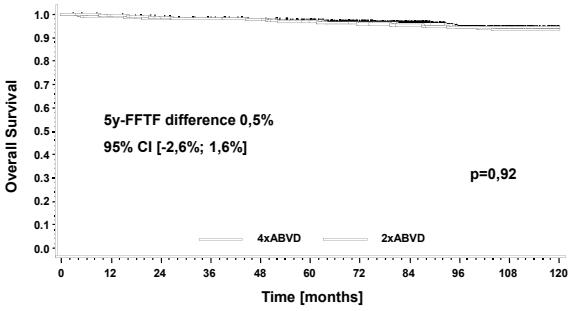
*Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved

GHSG HD10 Study
Chemotherapy (FFTF)



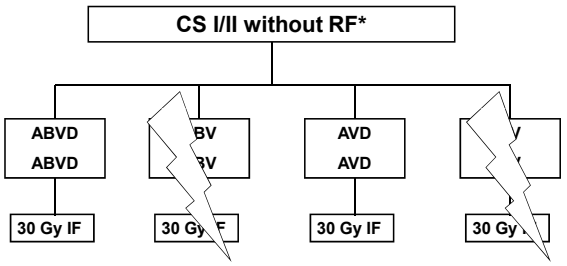
Engert et al NEJM 2010

GHSG HD10 Study
Overall Survival



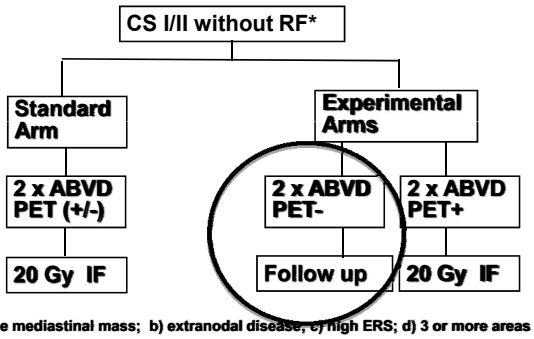
Engert et al NEJM 2010

HD13 Study
Early favorable HL



*Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved

Ongoing HD16 Trial:
GHSG-Study for Early favorable Stages



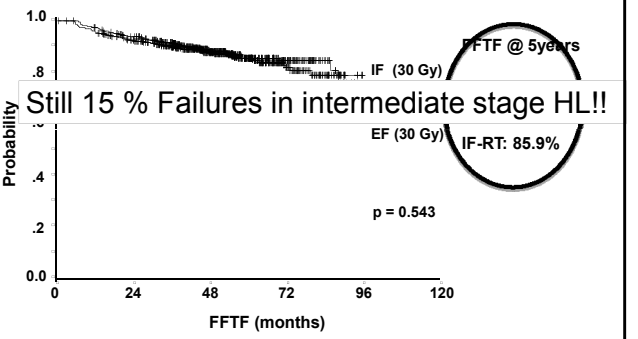
*a) large mediastinal mass; b) extranodal disease; c) high ERS; d) 3 or more areas

Advanced Stages of Hodgkin Lymphoma in the GHSG

	Stage			
Risk factor	IA, IB, IIA	IIB	IIIA, IIIB	IVA, IVB
No	Early favourable		Advanced Stages	
≥ 3 LN- areas				
Elevated ESR	Early unfavor-able			
Large mediastinal mass				
Extranodal disease				

11.10.2011 13

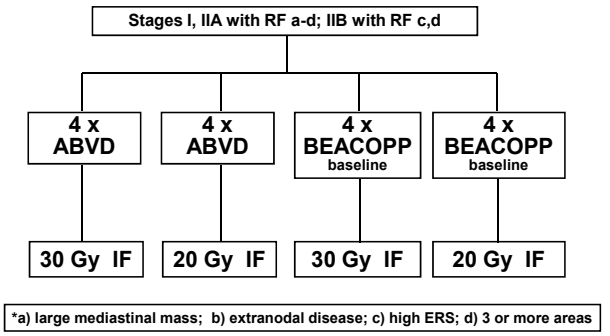
HD8 Study
for early unfavorable HL (FFTF)



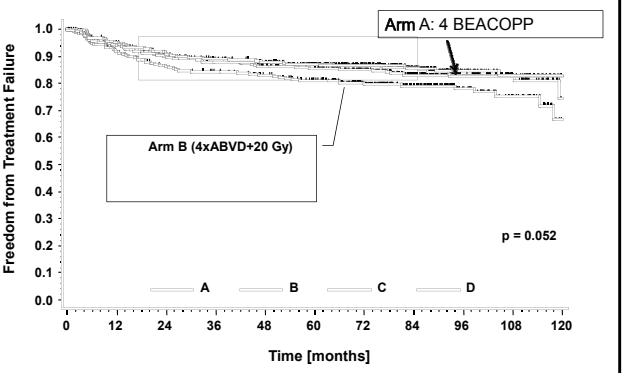
Still 15 % Failures in intermediate stage HL!!

Engert et al JCO 2003

HD11 trial
for early unfavorable HL

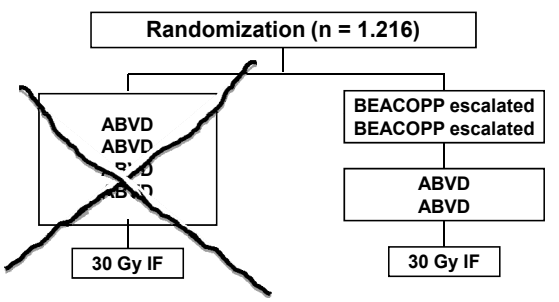


HD11 trial
FFTF – all 4 arms



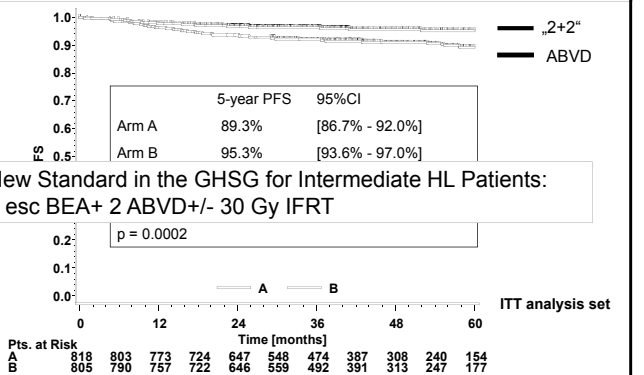
Eich et al JCO 2010

Increasing the intensity of chemotherapy: The GHSG HD14 trial



5.02.22

Improved lymphoma control by intensification of chemotherapy



New Standard in the GHSG for Intermediate HL Patients:
2 esc BEA+ 2 ABVD+/- 30 Gy IFRT

GHSG HD14 - Final Analysis July 2010 - V 2.0 (October 2010) 18

Progression and Relapse

Median observation time = 42 months

ITT analysis set	Arm A (ABVD) N=818		Arm B ("2+2") N=805	
Type of event	N	%	N	%
progression	**24**	**2.9**	**7**	**0.9**
Early relapse	**23**	**2.8**	**7**	**0.9**
Late relapse	**19**	**2.3**	**7**	**0.9**
Σ	**66**	**8,1**	**21**	**2,6**

GHSG HD14 – Final Analysis July 2010 + 2.5 (October 2010)

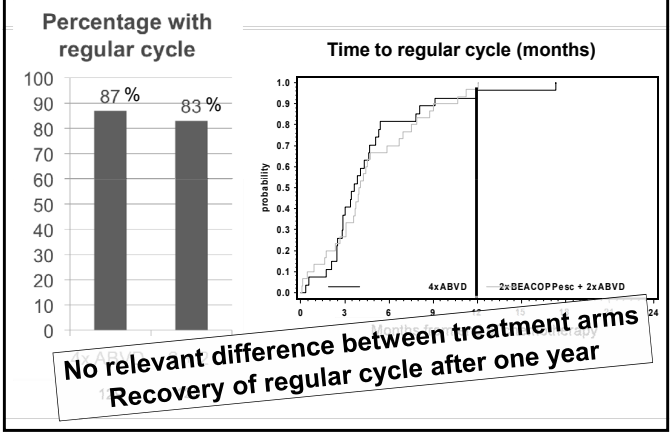
19

Pregnancy, offspring, or ammenorrhea after therapy

Only women up to 40 y from the ongoing HD14 fertility survey project

fertility status **> 1y AFTER** therapy	4x ABVD (arm A)		„2+2" (arm B)	
	N	**%**	**N**	**%**
pregnancy/child: **NO**	**114**	**89**	**93**	**82**
pregnancy/child: **YES**	**14**	**11**	**21**	**18**
amenorrhea: **NO**	**119**	**87.5**	**109**	**83.8**
amenorrhea: **YES**	**17**	**12,5**	**21**	**16,2**

Regular cycle and CTx-arm



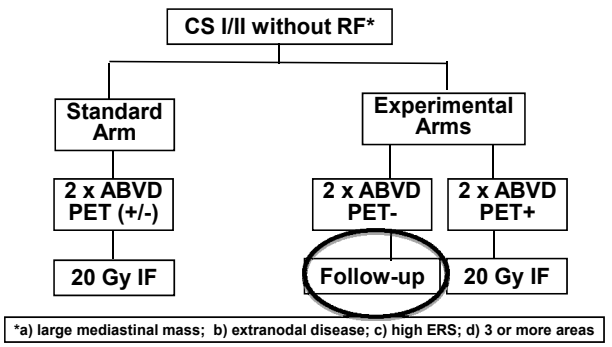
Progress in Intermediate stages GHSG data

Trial	**Chemotherapy**		**Failure Rate**
HD 8	**4 C/ABVD**		**18%**
HD11	**4 BEACOPP or 4 ABVD**		**15%**
HD14	**2 BEAesc + 2 ABVD**		**5%**

Early Favorable Stages
Ongoing Studies

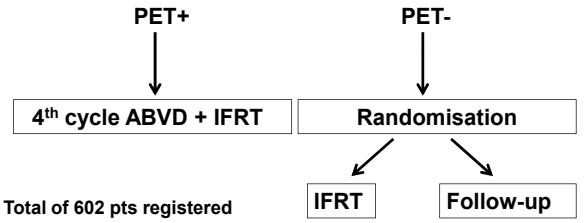
- GHSG HD16: 2 ABVD → PET neg Nil
- UK- RAPID Trial : 3 ABVD → PET neg Nil
- EORTC HD10: 4 ABVD → PET neg Nil
- USA-Intergroup: 4 ABVD → PET neg Nil

Ongoing GHSG trial (HD16)
for early favorable HL



UK RAPID trial
Stage IA/IIA; no bulk

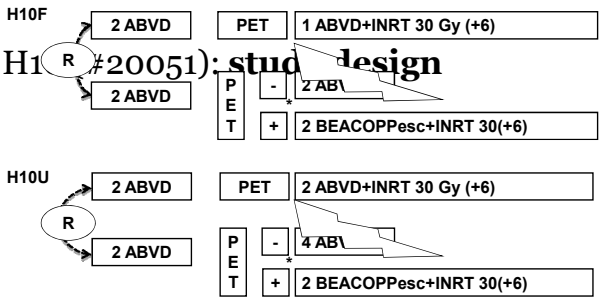
Initial treatment: 3xABVD
Re-assessment: NR/PD: off study
CR/PR: PET



Total of 602 pts registered
>400 PET- pts randomized
Closed 8-2010

Courtesy of John Radford

EORTC/GELA/IIL H10 Study
For early favorable and unfavorable HL

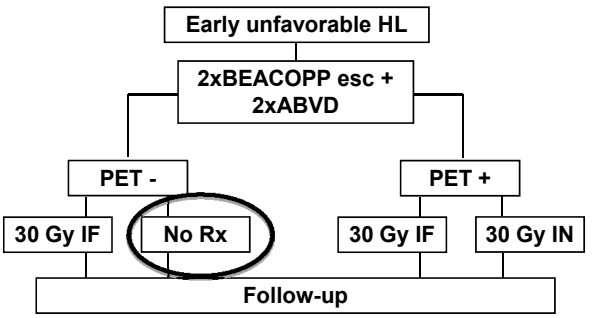


H1 #20051): stud design

*PET-/+ according to protocol criteria

Hodgkin - CS I/II – untreated - 15-70 yrs – supradiaphragmatic - no NLPHL

Next GHSG trial
for early unfavorable (HD17)

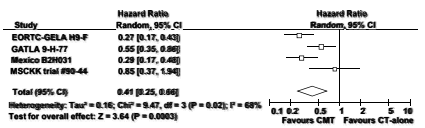


GHSG 2010

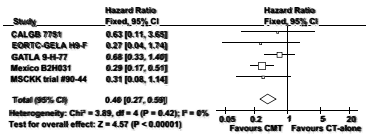
Early stage Hodgkin Lymphoma
State of the Art and Future Perspectives

- **CMT vs Chemo alone**

Hodgkin Lymphoma
Metaanalysis CMT vs. Chemo in early stages



Tumor control



Overall survival

Herbst et al Hematologica 2009

Early stage Hodgkin Lymphoma
State of the Art and Future Perspectives

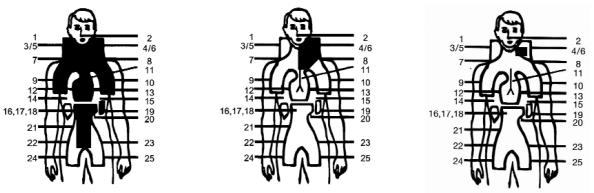
- **Background**
- **Early favorable**
- **Early unfavorable**
- **Ongoing studies (PET)**
- **IN-RT & Quality Assurance**
- **Future**
- **Summary**

Strahlentherapie und Onkologie — Original Article

Involved-Node Radiotherapy in Early-Stage Hodgkin's Lymphoma

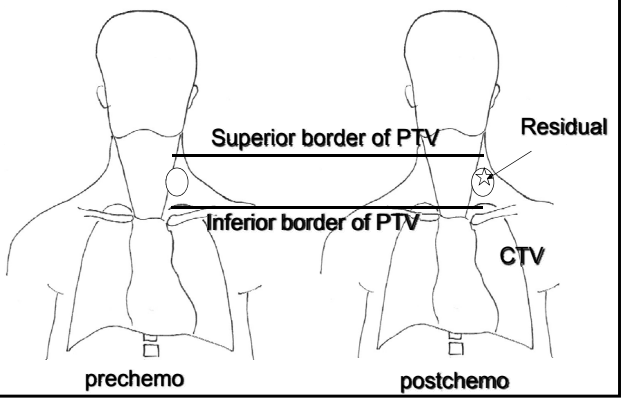
Definition and Guidelines of the German Hodgkin Study Group (GHSG)

Hans Theodor Eich[1], Rolf-Peter Müller[1] in Cooperation with Rita Engenhart-Cabillic[2], Peter Lukas[3], Heinz Schmidberger[4], Susanne Staar[5], Normann Willich[6]

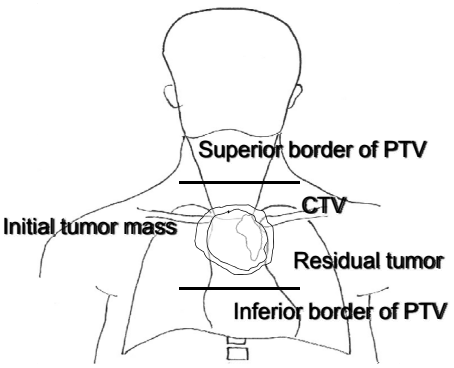


EF-RT IF-RT IN-RT

IN-RT – Target definition



IN-RT – Target definition Mediastinum



Main Focus at ASH 2010:
Future Perspectives

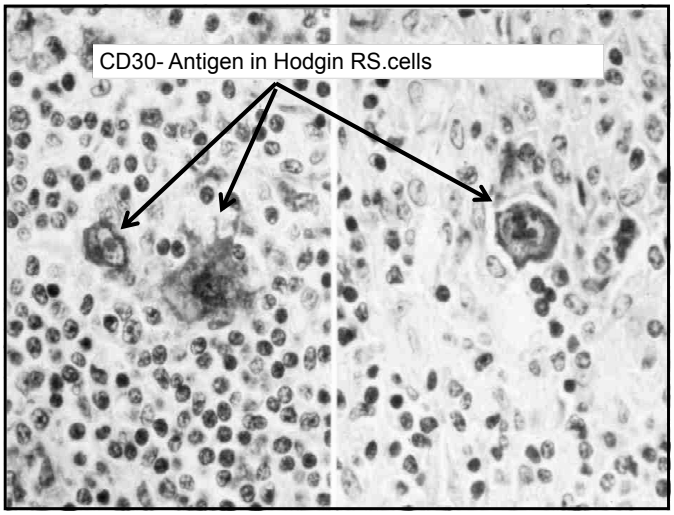
Comprehensive Aim:

Combine conventional with targeted therapy

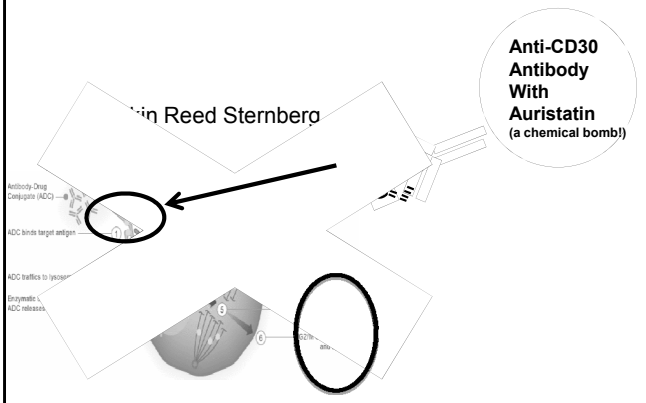
New Generation of Drugs other than Moabs
in Patients with refractory HL (Selection)

Drug	Type	Patients (n)	Response (%)
ZenaRX[1)]	RIT (anti-CD25)	23	67
SGN-35[2)]	IT (anti-CD30)	217	67
MGCD0103[3)]	HDAC-Inhibitor	20	40
RAD001[4)]	m-TOR-Inhibitor	14	42
Lenalidomide[5)]	IMID	7	56

[1)]Waldmann ISHL 2007; [2)] Younes et al ISHL 2007; [3)]Younes et al ISHL 2007; [4)]Johnston et al ISHL 2007; [5)]Borchmann et al unpubl 2007



„Targeted therapy“ with Antibodies in Hodgkin Lymphoma



Targeted (individualized) Therapy
Brentuximab Vedotin (SGN-35)

Phase 1, single-agent[1]
- Relapsed CD30-positive lymphomas (45 HL, 2 ALCL, 1 AITL)
- Well tolerated: Mostly grade 1 or 2 adverse events—fatigue, fever, diarrhea, nausea, neutropenia, peripheral neuropathy
- MTD: 1.8 mg/kg every 3 weeks
- Across all dose levels: 44 evaluable patients; 39% objective response (82% responded: 25% CR, 14% PR, 43% SD)
- At 1.2 mg/kg and higher: 15/28 patients (54%) objective response
  Median duration of response: 9.7 months

Phase 2, pivotal single-agent[2]
- 1.8 mg/kg every 3 weeks for up to 16 doses
- 75% objective response
- Median duration of response: >6 months
- Granted fast track designation by FDA for HL

1) Younes A et al, NEJM 2010;363:1812-1821
2) Chen R et al, ASH 2010

Targeted (individualized) Therapy
Lenalidomide

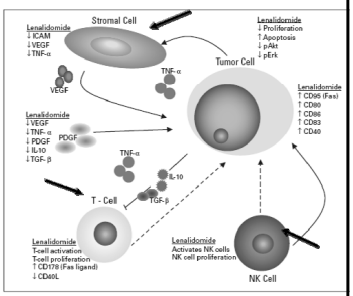
A new principle of targeted therapy in Hodgkin´s lymphoma

Interfering with the micro- enviroment

Mode of Action

-Thalidomide analogue

- Immune-modulatory properties
  - down-regulation of pro-survival cytokines (TNF-a, VEGF, Il-8, Il-6) and
  -interference with the micro-enviroment
  - stimulation of T-cells and NK-cells
- antiangionetic activity
- pro-apoptotic effect



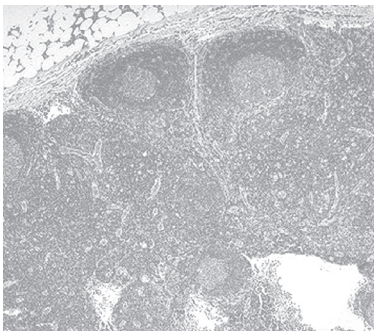
Early stage Hodgkin Lymphoma
Summary

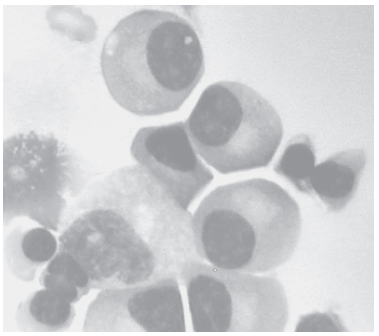
- **In early favorable HL, 2xABVD equal to 4xABVD, 20Gy equal to 30Gy IFRT (GHSG HD10); 3xABVD not needed**
- **2xABVD plus 20Gy IFRT new standard for early favorable HL?**
- **In early unfavorable HL, 2xBEACOPP*esc* + 2xABVD plus 20Gy IFRT new GHSG standard**
- **Outside GHSG trials, 4xABVD plus 30Gy IFRT**
- **Chemo alone should be restricted to clinical trials**
- **Ongoing trials aim at further reducing toxicity and better individualizing treatment by PET-guided strategies**

Early stage Hodgkin Lymphoma
Current most relevant open questions

- **Can we beat 2xABVD+20Gy IFRT?**
- **Will PET-guided strategies work?**
- **PET: Liver or mediastinal bloodpool as reference? Standardize set-up! Compare results between groups!**
- **Reevaluate current RFs; find new biological-genetic RFs!**
- **Reevaluate impact of treatment on fertility!**

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Emerging new agents in Hodgkin's and lymphoma

Jonathan Friedberg, MD

Emerging new agents in Hodgkin and non-Hodgkin lymphoma

Jonathan W. Friedberg MD MMSc

Chief, Hematology/Oncology Division

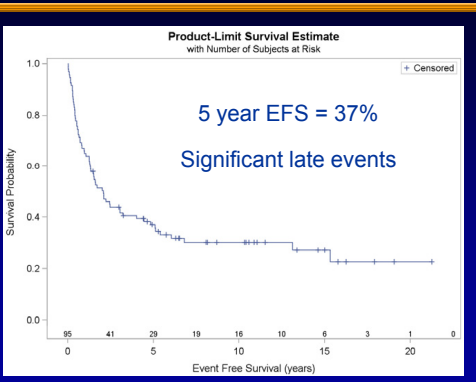
JAMES P. WILMOT CANCER CENTER

University of Rochester Medical Center

Focus on Hodgkin lymphoma

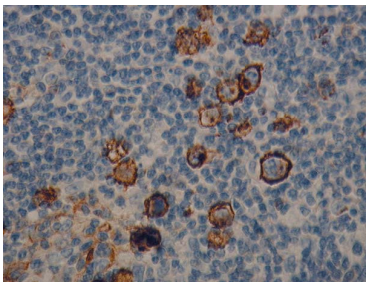
- Three novel agents with activity in both Hodgkin and non-Hodgkin lymphoma
  - Brentuximab vedotin
  - Lenalidomide
  - mTOR inhibitors

Hodgkin lymphoma: Outcome following ASCT in ABVD era



Keller et al, *BBMT* 2011

CD30 Surface Expression is a defining attribute of classical HL

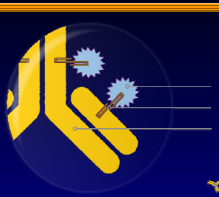


CD30 is present on virtually all HRS cells.

The near-ubiquitous expression of CD30 in HL makes it a defining attribute of this malignancy.

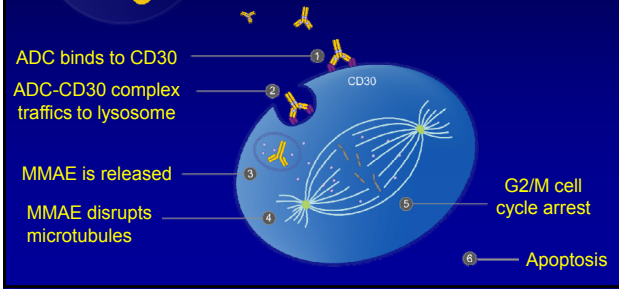
CD30 also expressed in other NHLs:
Anaplastic T cell
Other T cell NHLs
DLBCL

Brentuximab Vedotin: antiCD30 conjugate



monomethyl auristatin E (MMAE)

potent antimicrotubule agent



Pivotal trial of brentuximab vedotin in Hodgkin lymphoma relapse after ASCT

- 1.8 mg/kg (max 180 mg) q 3 weeks
  - 30 minute infusions; no premeds needed.
- N=102
  - Median age 31
  - 71% relapsed < 1 year post ASCT
  - Median time from ASCT to relapse: 6.7 mos
- KEY TOXICITIES
  - Neurological
  - Neutropenia

Younes et al, Lugano 2011

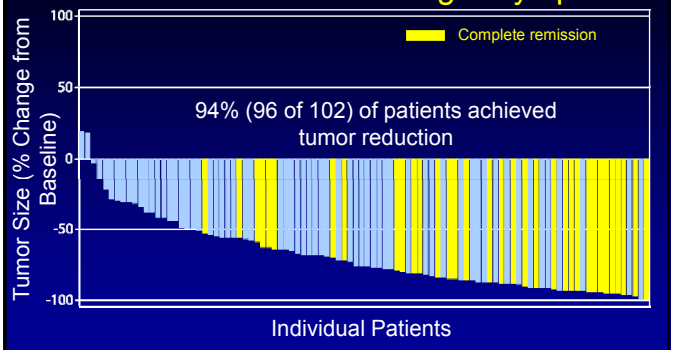
Response Results Summary: Brentuximab vedotin for Hodgkin lymphoma

	N=102
Objective response (OR) rate	75%
95% CI	65, 83
Median duration of OR	6.7 mo
95% CI	3.6, 14.8

Median (range) cycles of treatment = 9 (1–16)

Estimated 12-month overall survival = 89%

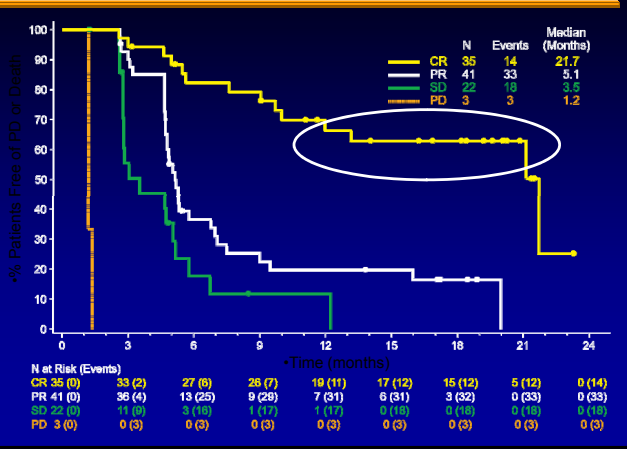
Maximum Tumor Reduction: Brentuximab vedotin for Hodgkin lymphoma



Complete Remissions: Brentuximab vedotin for Hodgkin lymphoma

	N=102
Complete remission (CR) rate	34%
95% CI	25, 44
Median duration of response in patients with CR	20.5 mo
95% CI	10.8, –

PFS by Best Response: Brentuximab vedotin



PFS in Patients with CR by Subsequent Transplant: Brentuximab vedotin for Hodgkin lymphoma

Patients who achieved a CR	N	Events	Median PFS (95% CI)	Median number of cycles received
Allogeneic transplant	5	1	21.1 (–,–)	14
No transplant	30	13	21.7 (9.7, –)	13

Should patients who receive brentuximab vedotin proceed to alloSCT?

CR vs. PR patients?

Future directions: Brentuximab vedotin for Hodgkin lymphoma

- Approved in US for relapsed Hodgkin lymphoma
  - New benchmark for this histology
- **Ongoing studies:**
  - BV vs. Placebo as maintenance post ASCT
  - AVD + BV for upfront Hodgkin lymphoma
- **Planned studies:**
  - ICE vs. ICE+BV vs. BV salvage pre ASCT
  - AVD + BV vs. ABVD for upfront therapy

Brentuximab vedotin: ALCL data

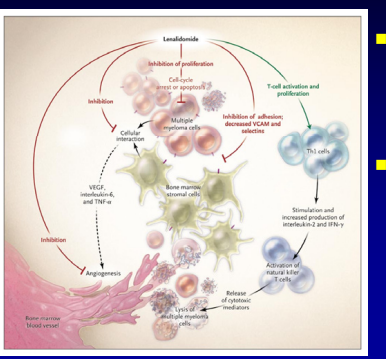
- Durable complete remissions achieved with brentuximab vedotin in highly refractory systemic ALCL patients

	CR	OR
Rate	57%	86%
Median Duration	13.2 mo	12.6 mo

- Adverse events were similar to Hodgkin lymphoma, including peripheral neuropathy
- BV is now approved for ALCL

Shustov et al, Lugano 2011

Lenalidomide: IMIDs



- Lenalidomide mechanism of action remains poorly understood
- Antiangiogenic, microenvironment, direct antiproliferative, NK, and T-regs

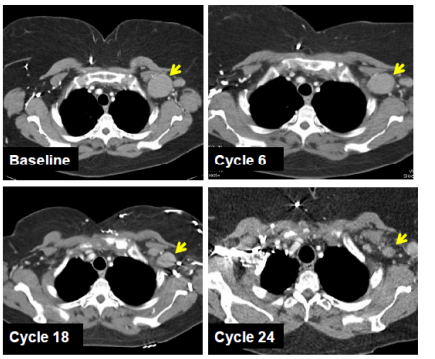
List AF. N Engl J Med. 2007;357:2183-2186.

Lenalidomide in classical Hodgkin lymphoma: Phase 2 study

- Lenalidomide 25 mg day 1-21 q 28 days
- N=38; 87% prior ASCT
- ORR 19%; stable disease 33%
- Late responses observed

Fehninger et al, *Blood* on line 2011

Classical Hodgkin lymphoma post ASCT: Late response after lenalidomide therapy



Fehninger et al, *Blood* on line 2011

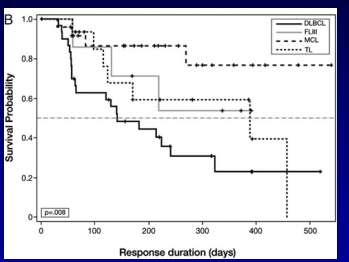
Lenalidomide in MCL: Single agent International Trial

N=217

MCL N=57

ORR MCL 42%

Median response duration not reached for MCL pts



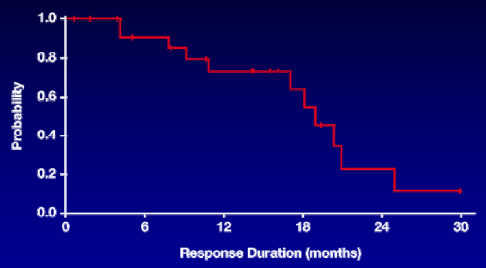
Witzig et al Ann Oncol 22:1622, 2011

Phase II study of lenalidomide (20mg) and rituximab in mantle cell lymphoma

Response	N=46 (%)
Overall response	26 (57)
Complete response	15 (33)
Partial response	11 (24)
Stable disease	10 (21.5)
Progressive disease	10 * (21.5)
Time to first response	2 (2-8)

Wang et al Ann Oncol 22: iv119, 2011

Response Duration:
Phase II study of lenalidomide (20mg) and rituximab in mantle cell lymphoma



- **Median response duration = 18.9 months (range 17–not reached)**

Wang et al Ann Oncol 22: iv119, 2011

ECOG 1409/SWOG/CALGB: Randomized Phase 2 Study

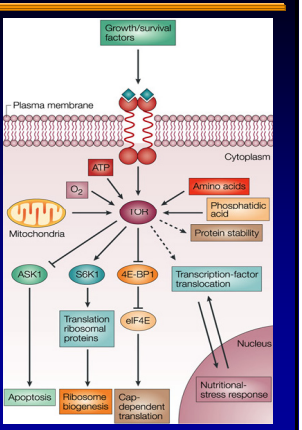
For previously untreated pts with MCL > 65 or 60-64 not ASCT candidates

- Arm A = R-B ⇒ lenalidomide/rituximab
- Arm B= R-B ⇒ rituximab
- Arm B = R-B-V ⇒ lenalidomide/rituximab
- Arm D = R-B-V ⇒ rituximab

mTOR Inhibitors

mTOR Inhibitors

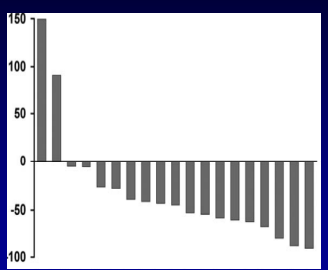
- mTOR regulates:
  - Cell-cycle progression
  - Translation initiation including cyclin D1
  - Stress responses
  - Protein stability
  - Survival
- mTOR pathways are activated in NHL and Hodgkin
- Analogs of rapamycin developed as antitumor agents
  - Temsirolimus
  - Everolimus (RAD001)



Bjornsti. *Nat Rev Cancer*. 2004;4:335.

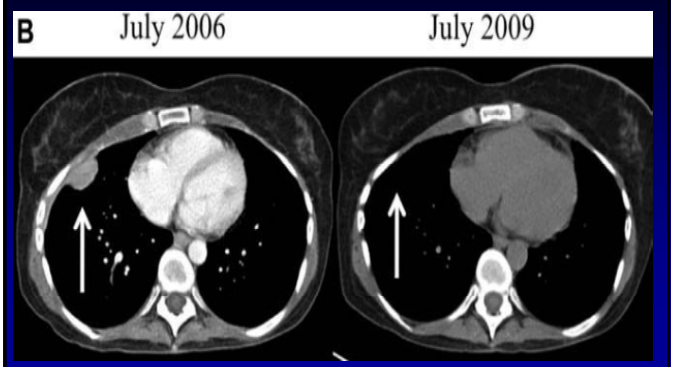
Everolimus in classical Hodgkin lymphoma: Phase 2 study

- Everolimus 10 mg daily; N=19 patients
- Median age 37; 84% prior ASCT
- ORR 47%; 1 CR
- Four patients experienced grade 3+ pulm tox



Johnston et al, *Am J Hematol* 85:320

Everolimus in classical Hodgkin lymphoma: Phase 2 study



Patients remained on treatment up to 3 years

Phase III Trial of Temsirolimus vs Investigator's Choice in Relapsed/Refractory MCL

Relapsed/refractory MCL

2-7 prior therapies with alkylating agent AND anthracycline AND rituximab

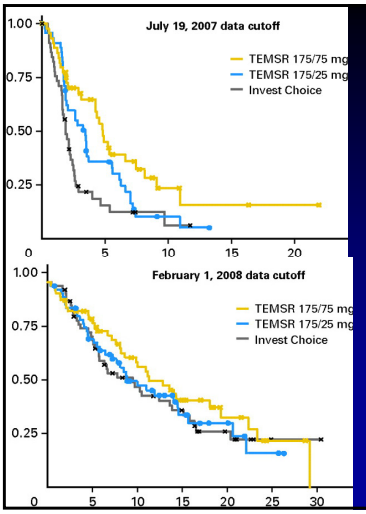
N=162

RANDOMIZED

- Temsirolimus 175 mg weekly x 3 Then 75 mg every week N=54
- Temsirolimus 175 mg weekly x 3 Then 25 mg every week N=54
- Investigator's choice, single agent N=54

Primary endpoint: PFS
Secondary endpoints: OS, ORR, safety

JCO 27:3822, 2009



Progression-free survival

Median 4.8 months vs. 3.4 and 1.9 months; p=0.0009.

Overall survival

Median 11.1 months vs. 8.8 and 9.5 months, p=NS

Temsirolimus vs Investigator's Choice in MCL

Grade 3/4 AE	Temsirolimus 175 mg/75 mg	Temsirolimus 175 mg/25 mg	Investigator's Choice
Asthenia	13%	19%	8%
Diarrhea	7%	11%	0
Fever	6%	2%	0
Hyperglycemia	7%	6%	6%
High lipid/cholesterol	0	2%	0
High creatinine	0	2%	0
Thrombocytopenia	63%	52%	40%
Neutropenia	24%	30%	45%
Anemia	17%	11%	17%
Infection	9%	4%	4%

Everolimus for aggressive NHL: Phase 2 study

10 mg po daily treatment

N=77; 32% prior ASCT

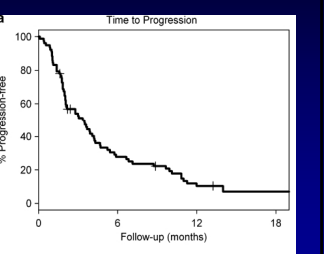
ORR=30%; 3 CRu's

DLBCL (N=47) ORR 30%

MCL (N=19) ORR 32%

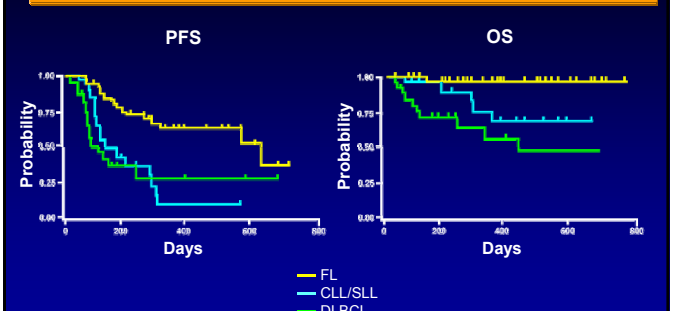
FL grade 3 (N=8) ORR 38%

Cytopenias major toxicity



Witzig et al, *Leukemia* 25:341

Temsirolimus in Relapsed/ Refractory Non-MCL NHL Phase 2 trial



Smith et al, *JCO* 28:4740

The future: m-TOR inhibition in NHL

- Phase III trial results were disappointing
  - High risk patient population with short survival
- Toxicity of class may preclude maintenance approaches, although studies are planned and ongoing
- Current studies continue with oral everolimus
- Opportunities for rational targeted combinations
- *Lesson: Understand optimal dose and schedule before moving to phase III study.*

Hodgkin lymphoma: Challenges in drug development

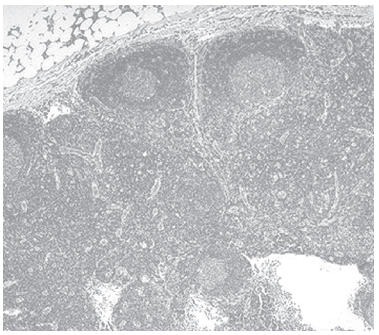
- Histone deacetylase inhibitors
  - Panobinostat
    - Phase 2; N=129: ORR 27%
    - FDA rejected application

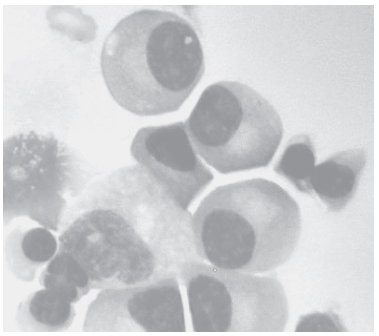
New agents for NHL: Challenges in drug development, 2011

- Diffuse large B-cell lymphoma
  - Overall reasonable cure rate
  - Salvage/ASCT standard of care
- Follicular lymphoma
  - PFS very long with R-Chemo + maintenance
    - No good surrogate; ? PET imaging ?
  - Bendamustine approval label
- Mantle cell lymphoma
- T-cell lymphoma



Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Is there a role for consolidation radiation in limited and advanced Hodgkin's disease in the era of PET scan?

Peter Johnson, MD

Is there a role for consolidation radiotherapy in Hodgkin Lymphoma in the era of the PET scan?

Peter Johnson
Cancer Research UK Centre
Southampton, UK

CANCER RESEARCH UK

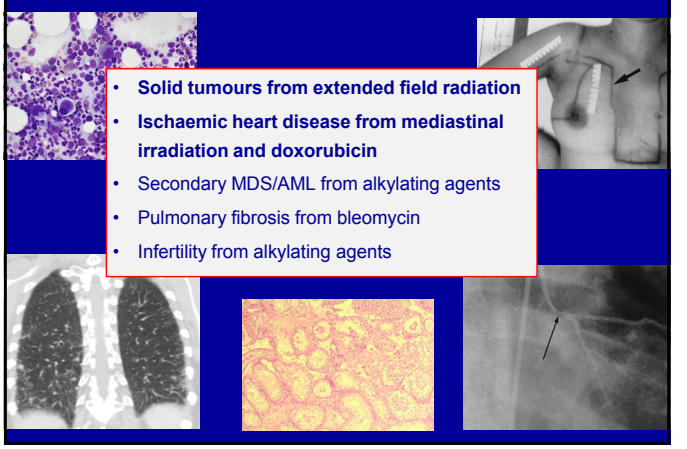
Introduction

- Lymphomas are extremely radiosensitive tumours which die from "interphase death" (apoptosis)
- High local complete response rates / clinical efficacy in all lymphoma subtypes
- RT was an important part of combined modality treatment (CMT) curative treatment : widely used for HL in last half century.
- Over the last decade enthusiasm for RT as part of CMT has waned : a result of late effects among survivors
- RT is increasingly replaced by additional cycles of systemic therapy. Local control rates will decrease : ? effect on overall survival

Reasons why RT is under-used

- Omitting RT may decrease radiation-related late mortality, thus raising overall survival
- Excellent outcomes with chemotherapy alone
- Chemotherapy alone, even if escalated or prolonged, is safe, thus unlikely to result in more toxicity ?
- Even if more failures occur without RT, salvage with high-dose chemotherapy and stem cell transplantation is well tolerated and safe ?

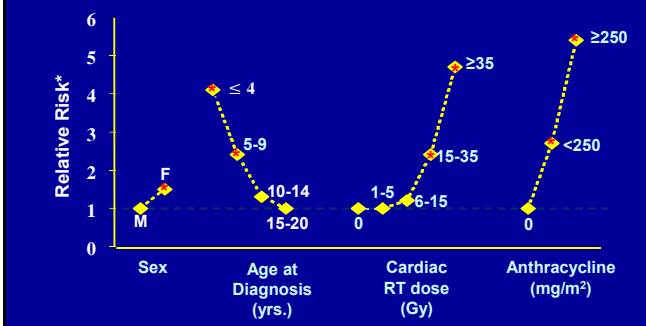
Late effects to avoid as cures increase



- **Solid tumours from extended field radiation**
- **Ischaemic heart disease from mediastinal irradiation and doxorubicin**
- Secondary MDS/AML from alkylating agents
- Pulmonary fibrosis from bleomycin
- Infertility from alkylating agents

Risk of Congestive Heart Failure

Multivariate Analysis Mulrooney BMJ 2009

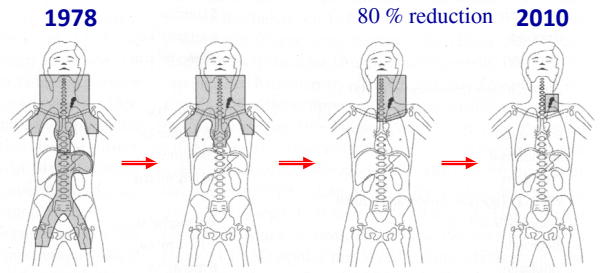


P <0.05 * Adjusted for race, BMI, income, education, smoking, treatment era

Overview

- When should modern RT be used to improve local control and outcome ?
- How to select patients who might benefit from RT ?
- Progress and pitfalls with risk adopted strategies.

Modern use of RT in Hodgkin Lymphoma
Transformation of Radiation Volumes / Doses



Total nodal	Regional nodal	Involved field	Involved node

Dose: 30-44 Gy → 20-30 Gy

Two thirds of women with early-stage HD do not require radiation of the axillae
Substantial reduction in breast, lung cancer risk, cardiac morbidity

Objectives in early stage HL

- Maximise number of cures and minimise late toxicity. Risk adjusted approach :
- Early stage favourable HD10 - 2 x ABVD + IFRT 20 Gy
  Engert A, et al NEJM. 2010 12:363 (7) : 640-52
- Early stage unfavorable HD11 trial : 4 x ABVD + IFRT 30 Gy
  Eich et al J Clin Oncol. 2010 Sep 20;28(27):4199-206
- Can late toxicity be further reduced by delivering RT only to selected patients with residual disease after chemotherapy ?
- Can a "negative" FDG-PET scan after initial therapy 2-3 x ABVD be a sufficiently sensitive/specific biomarker of disease elimination that RT can be avoided without unacceptable reduction in disease control

NCIC/ECOG study:
Omitting radiation completely may be detrimental

399 patients with early stage disease

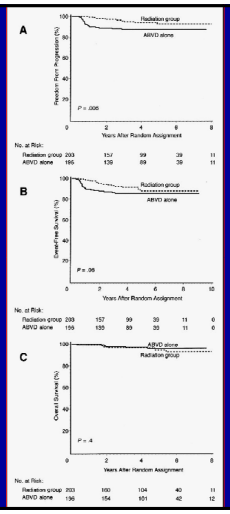
Favourable:
STNI vs ABVD 4-6 cycles

Unfavourable:
2 ABVD + STNI vs ABVD 4-6 cycles

Inferior EFS, FFP with ABVD alone

Overall survival the same
(95% at 5 yrs)

Meyer, R. M. et al. J Clin Oncol; 23:4634-4642 2005



German HD 11 Study:
Lower threshold of therapy
For early unfavourable disease

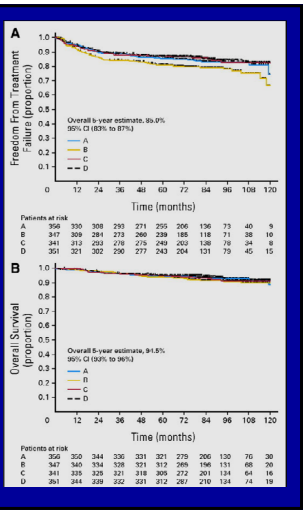
1395 pts 1998-2003
Early Unfavourable disease

Chemotherapy
→ 4 ABVD / 4 BEACOPP

Involved field RT
→ 20 Gy / 30 Gy

ABVD + 20Gy inferior on FFTF

Eich H T et al. J Clin Oncol 2010;28:4199-4206



Can we use FDG-PET to decide when to omit RT?
The UK RAPID study

Eligible Patient With Hodgkin Lymphoma stage I-IIA
→ 3 cycles ABVD
→ **PET scan: central review**

- Positive → 1 more ABVD Involved field RT (30Gy)
- Negative (score 1-2) → Randomised
  - Involved field RT (30Gy)
  - No further therapy

RAPID: Current Status

- 602 patients registered: median age 34 years
- Interim analysis reported at Menton 2011:
- 571 had a PET scan after 3 cycles ABVD
  - » Score 1, 53%
  - » Score 2, 22%
  - » Score 3, 16%
  - » Score 4, 6%
  - » Score 5, 4%
- Scores 1-2 "negative" 75%
- Scores 3-5 "positive" 25%
- 19 (5%) have progressed; 5 (1.5%) have died (HL 1, other 4), combined 3 year PFS 93% and OS 98.5%

EORTC H10 (#20051): study design

Hodgkin - CS I/II – supradiaphragmatic - untreated - 15-70 yrs

H10F

2 ABVD | PET | 1 ABVD+IN-RT 30 Gy (+6)

R

2 ABVD | PET | - 2 ABVD

2 ABVD | PET | + 2 eBEACOPP+IN-RT 30(+6)

H10U

2 ABVD | PET | 2 ABVD+IN-RT 30 Gy (+6)

R

2 ABVD | PET | - 4 ABVD

2 ABVD | PET | + 2 eBEACOPP+IN-RT 30(+6)

EORTC H10 IDMC conclusions Cologne 2010

PET2 negative

"…unlikely that the study will show that chemotherapy alone is non-inferior to combined modality treatment in PET2 negative patients; this holds for both F and U groups"

The IDMC/H10 team **rejects** the following conclusions that might be drawn based on the results of the H10 ***interim analysis***

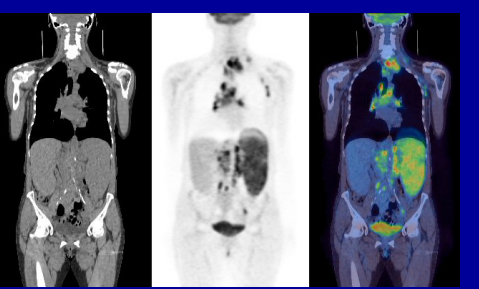
- All patients with CS I/II HL need IN-RT
- The PET2 scan has no prognostic impact
- The PET2 scan cannot be used to tailor Tx

Problem: non-blinded local PET reading used to determine therapy

Summary : Early Hodgkin lymphoma

- Outside clinical trials the current standard of care is :
  - 2 x ABVD + 20 Gy (F);
  - 4 x ABVD + 30 Gy (U)
  - Small RT Fields (ISRT or INRT) are effective (No marginal recurrences occurred after INRT < or = 5 cm; Campbell et al JCO 2008)
- RT is highly effective – Omission of RT leads to increased local failure
- Can PET be used to select patients where RT can be omitted ?
  - Trials illustrate : problematic and evolving
  - Dependent on definition and reproducibility of 'PET negative' in routine practice

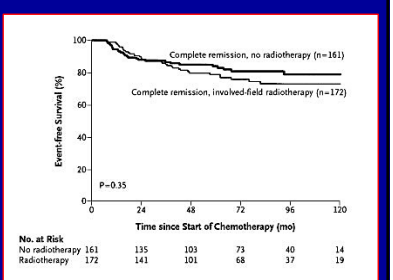
Advanced disease



EORTC study: Consolidation RT after MOPP/ABV chemotherapy

739 patients total
421 in CR
161 no further treatment
172 IFRT

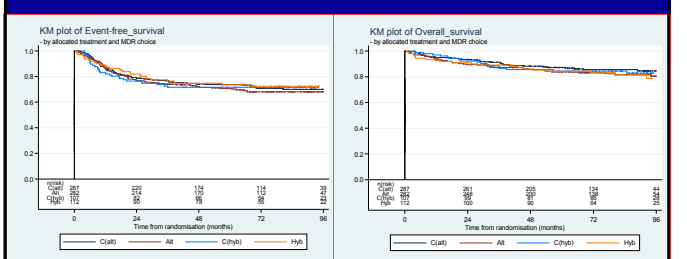
Among CR's:
5yr EFS 84 % if no RT
79 % with IFRT (P=0.35)
5 yr OS 91% and 85% (p=0.07).



Aleman BM et al. N Engl J Med 2003;348:2396-2406.

UK LY09: ABVD vs Alternating or Hybrid Regimens

Event-Free Survival | Overall Survival



807 patients stage II_{AX}-IV_B.
Median follow-up 79 months
Overall survival 90% at 5 yrs

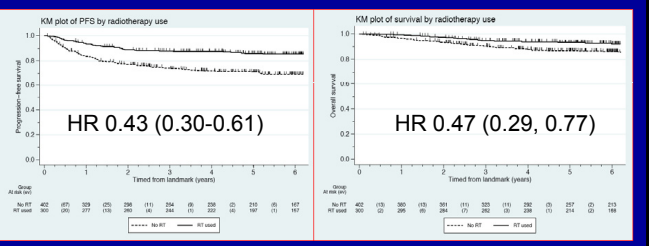
Johnson, P.W.M., et al. J Clin Oncol 23:9208-9218 2005

Characteristics of patients proceeding to Radiotherapy in UK LY09

		Non-RT N=402	RT patients N = 300
Median age at entry (quartiles)		36 (27, 48)	31 (24, 41)
WHO PS	0-1	90 %	87 %
	2-4	10 %	13 %
IPS score at entry	0-1	36 %	40 %
	2-3	43 %	46 %
	4-7	21 %	14 %
Stage	IB-IIB	46 %	66 %
	III	31 %	19 %
	IV	23 %	14 %
Bulk disease Mediastinal bulk		28 % 16 %	63 % 52 %
Response to chemotherapy	CR	62 %	20 %
	CRu	29 %	30 %
	PR	9 %	50 %

Comparison of outcomes in groups receiving/not receiving Radiotherapy

PFS & OS for both groups: radiated vs non-irradiated



Johnson, P.W.M., et al. J Clin Oncol 28:3352-9 2010

Forest plots of effect of radiotherapy (RT) in subgroups

IPS

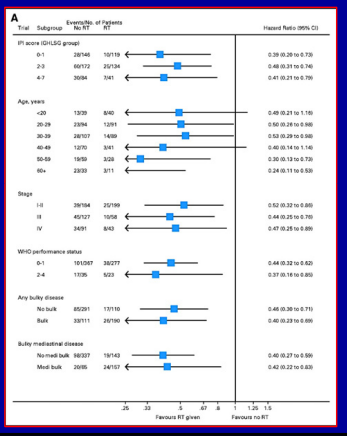
Age

Stage

PS

Bulk

Mediastinal bulk



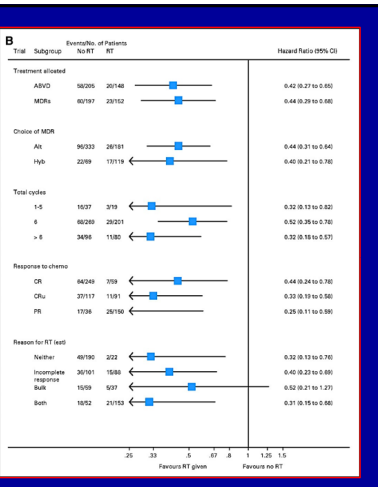
Chemotherapy

Choice of MDR

Total cycles

Response

Indication

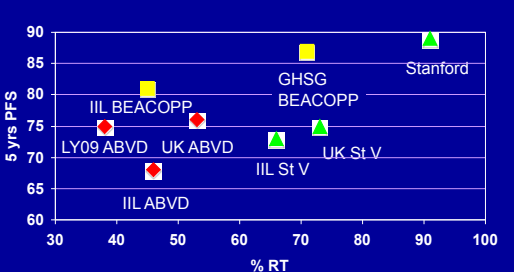


Comparison of results with ABVD and eBEACOPP: outcomes

	ABVD LY09	ABVD St V	ABVD GISL	BEACOPP GISL	eBEACOPP GHSG
Toxic death %	2	0.4	0	2	1.7
% irradiated	38	53	46	45	71
% 'treated more than once'	26	21	35	22	16
MDS/AML (cumulative 5 yr %)	0	0	0	1	2.5
Overall survival 5 years (CI)	87 (83-90)	90 (87-92)	84 (69-92)	92 (84-96)	92 (89-94)

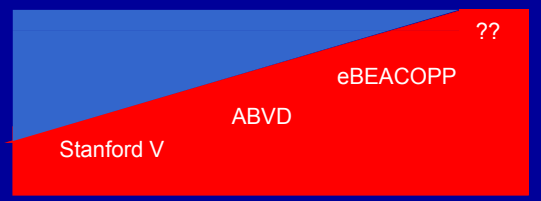
Do we know when to use Radiotherapy ?

- EORTC study showed no advantage to RT in CR after 8 MOPP/ABV
- Lower use of RT in Stanford V appears to reduce PFS
- Same may be true of ABVD/BEACOPP, but less obvious



The interaction of chemotherapy effect and radiation

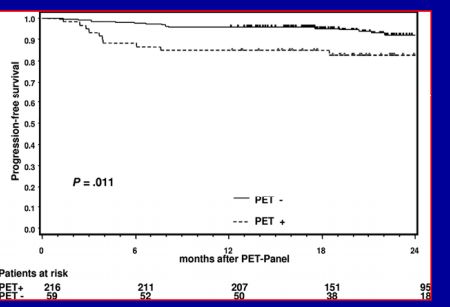
Increasing contribution of radiation to cure



Increasing chemotherapy effectiveness

GHSG HD 15

275 patients with residual masses after 6-8 BEACOPP
Underwent CT & PET: given RT if PET +ve



NPV 94%
PPV 15%

Kobe, C. et al. Blood 2008;112:3989-3994

Summary: advanced Hodgkin Lymphoma

- Recent evidence supports the use of RT to sites of previous bulk and/or residual mass
- Evidence for risk adjusted therapy on basis of completion FDG PET scan - strongest after BEACOPP
- Several trials currently testing the omission of RT in PET-negative cases

Acknowledgements

- Trial Collaborators
- Patients
- Trials Offices
- Funders

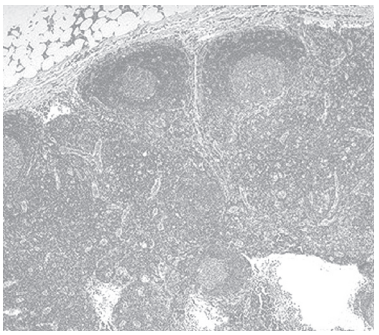


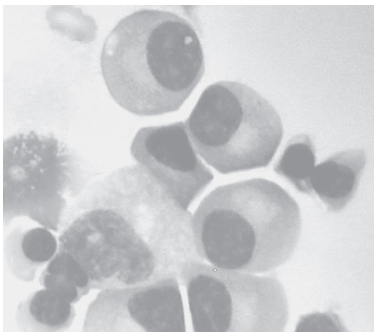
MRC Medical Research Council

NCRN National Cancer Research Network

CANCER RESEARCH UK

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Is R-CHOP-21 still the standard for all patients or is there a role for CHOP-14, ABVCP, EPOCH, etc?

Bertrand Coiffier, MD

Is R-CHOP-21 still the standard for all patients with DLBCL or is there a role for CHOP-14, ACVBP, EPOCH, etc?

Bertrand Coiffier

Hôpitaux de Lyon
Service d'Hématologie
Hospices Civils de Lyon

Equipe
« Pathologie des Cellules Lymphoïdes »
UMR 5239 CNRS – UCB – ENS - HCL

Gela
Groupe d'Étude
des Lymphomes de l'Adulte

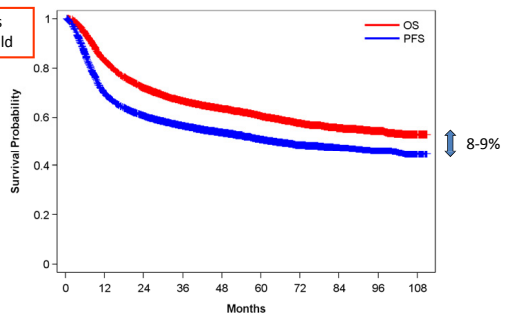
DLBCL = One Shot Cancer

- Only patients who reached a CR with the first line chemotherapy have a chance to be cured
  - Most true (with positive PET scan) PR progress
- A minority of patients who progressed responded to salvage chemotherapy and will be transplanted
  - Only 40% of transplanted patients did not relapse

Objective of treatment: Reach a CR and prevent a relapse

PFS and OS of 87/93/98 studies

7400 patients
18-80 years old



7 years: PFS = **47.5%** [46-49%]; OS = **56%** [54-57%]

Gela

What is important to know before treating a patient with DLBCL

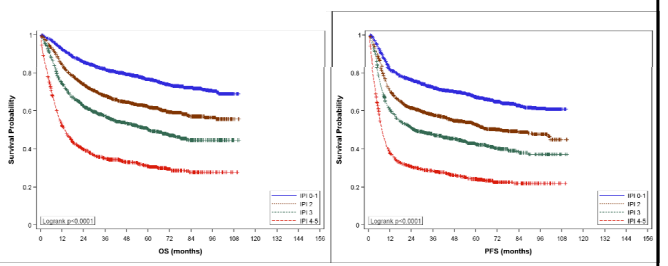
- Age
  - Young (<61 y)
  - Elderly (60-80 y)
  - Very old (>80 y)
- IPI – age-adjusted IPI
  - Score 0
  - Score 1
  - Score 2 or 3

Survival according to IPI score

6696 patients included in GELA randomized studies

Overall survival

Progression-free survival



Gela

B Coiffier unpublished data

New prognostic indicators

- New prognostic indicators
  - Cell of origin: GC, ABC, PML…
  - Important pathways
- Important prognostic value on retrospective analysis
  - Less for patients treated with R-CT
  - Less good for immunohistochemistry
  - Better for gene expression analysis
- Never tested in prospective way, in a randomized study

How to chose the good treatment?

- Patient
  - Age, concomitant diseases
  - Expectations
- Lymphoma
  - Prognostic factors
    - IPI, biological parameters …
  - Cell of origin

➡ No single solution for all DLBCL patients

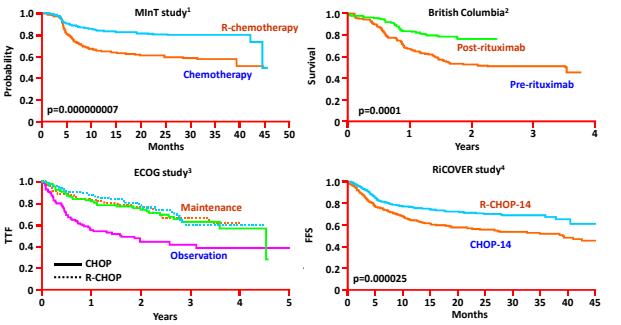
How to split and lump DLBCL patients?

- Young (<60 or 65 y)
  - Localized: stage I or aaIPI=0
  - Standard risk: aaIPI=1
  - Poor risk: aaIPI=2 or 3
- Elderly (65 – 80 y)
  - Localized: stage I or aaIPI=0
  - aaIPI=1 to 3
- Very old (>80 y)

Results with R-CHOP-21

- Randomized studies
  - GELA
  - German High-Grade NHL Study Group
  - US Intergroup Study
- Registry data
  - British Columbia CA registry
  - Czech Republic registry

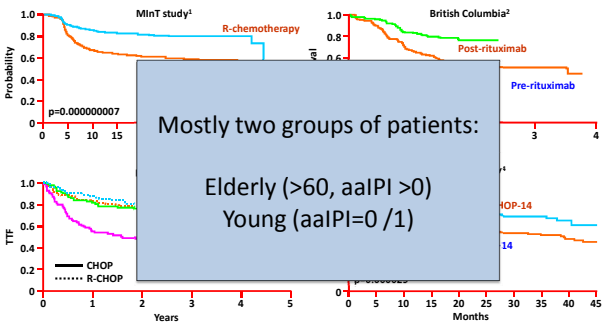
R-CHOP: a consistent clinical benefit



MInT = MabThera International Trial
ECOG = Eastern Cooperative Oncology Group
TTF = time-to-treatment failure
FFS = failure-free survival

¹Pfreundschuh M, et al. Lancet Oncol 2006;7:379–91
²Sehn LH, et al. J Clin Oncol 2005;23:5027–33
³Habermann T, et al. J Clin Oncol 2006;24:3121–7
⁴Pfreundschuh M, et al. Lancet Oncol 2008;Jan 14:Epub ahead of print

R-CHOP: a consistent clinical benefit



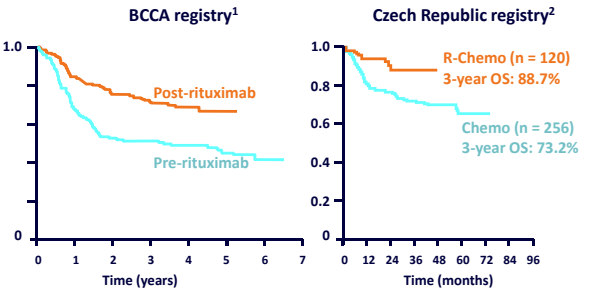
Mostly two groups of patients:

Elderly (>60, aaIPI >0)
Young (aaIPI=0 /1)

MInT = MabThera International Trial
ECOG = Eastern Cooperative Oncology Group
TTF = time-to-treatment failure
FFS = failure-free survival

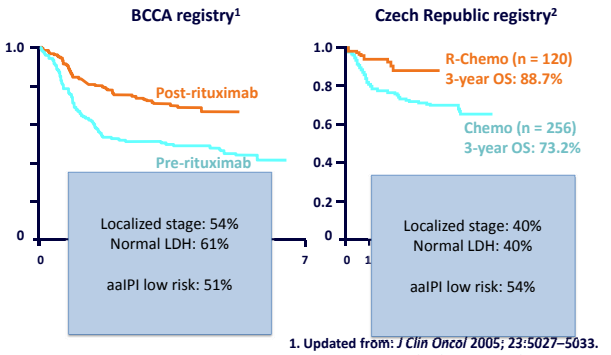
¹Pfreundschuh M, et al. Lancet Oncol 2006;7:379–91
²Sehn LH, et al. J Clin Oncol 2005;23:5027–33
³Habermann T, et al. J Clin Oncol 2006;24:3121–7
⁴Pfreundschuh M, et al. Lancet Oncol 2008;Jan 14:Epub ahead of print

Registry data show that these improvements in survival extend to the clinic



1. Updated from: *J Clin Oncol* 2005; 23:5027–5033.
2. *Blood* 2005; 106:Abstract 2444.

Registry data show that these improvements in survival extend to the clinic



1. Updated from: *J Clin Oncol* 2005; 23:5027–5033.
2. *Blood* 2005; 106:Abstract 2444.

Conclusion R-CHOP21

- Randomized studies and registry data addressed mainly
  - young patients with good risk profile
  - Elderly non-localized patients
- No randomized study for young patients with poor risk DLBCL
- They were underrepresented in registry studies

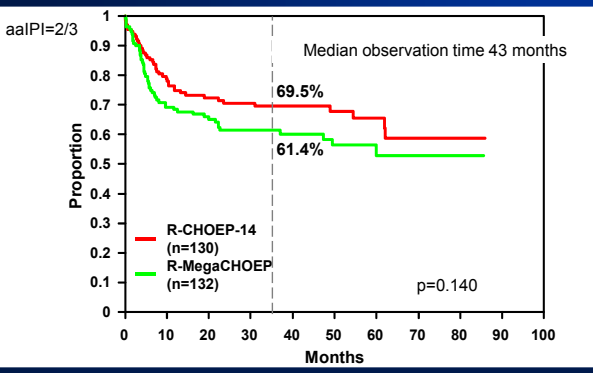
R-CHOP21 in high-risk young patients

- A few randomized study comparing R-CHOP to another regimen
- A few retrospective analyses
- Usually with short follow-up
- Difficult to conclude: results seemed different from one study to another

R-MegaCHOEP Study

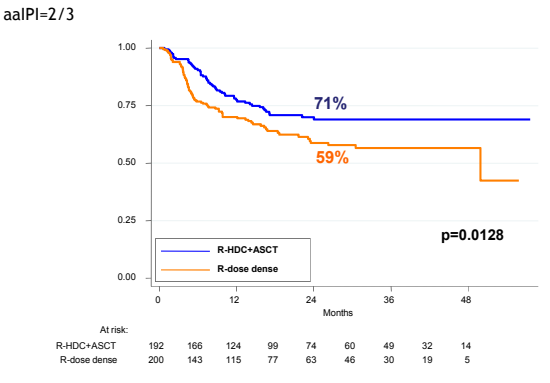
EFS ACCORDING TO TREATMENT ARM

GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)
www.lymphome.de/en/Groups/DSHNHL



N Schmitz et al. ICML 2011

2-year PFS: R-HDC+ASCT vs R-CHOP/R-MegaCHOP median follow-up 24 months



11-ICML

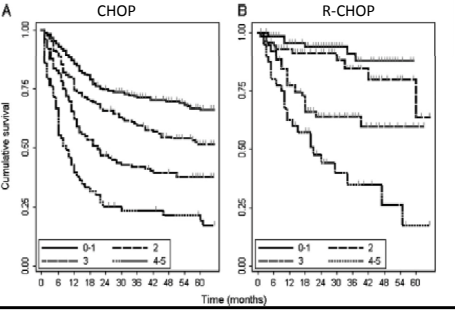
FONDAZIONE ITALIANA LINFOMI — *Umberto Vitolo*

original article

Annals of Oncology 21: 1486–1491, 2010
doi:10.1093/annonc/mdp531
Published online 17 November 2009

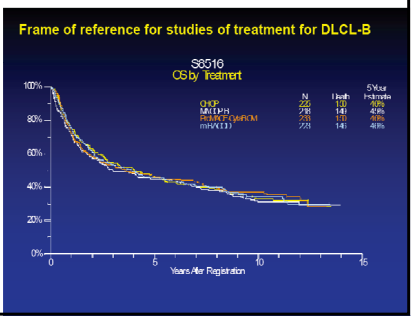
Prognostic models for diffuse large B-cell lymphoma in the rituximab era: a never-ending story

A. Bari[1], L. Marcheselli[1], S. Sacchi[1]*, R. Marcheselli[1], S. Pozzi[1], P. Ferri[2], E. Balleari[3], P. Musto[4], S. Neri[5], M. A. Aloe Spiriti[6] & M. C. Cox[6]



Other regimens

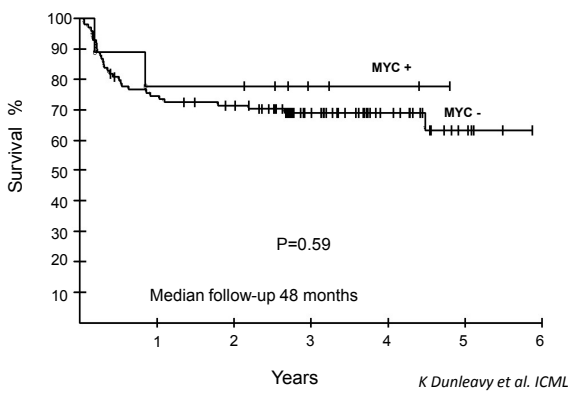
- R-CHOP14
- DA-EPOCH-R
- R-MACOP-B
- R-Mega-CHOEP
- R-ACVBP



DA-EPOCH-R

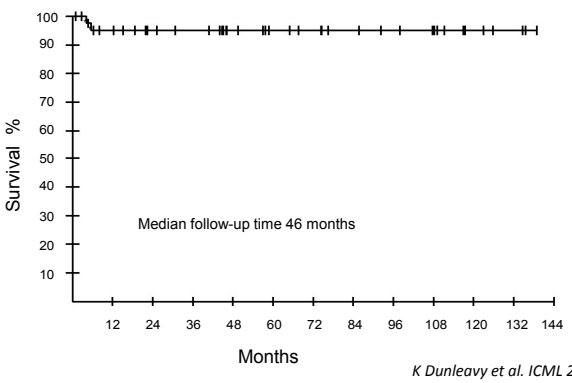
- Mostly used in NCI
- No randomized comparison
- Only phase II or retrospective analyses
- Most of them is more aggressive subgroups
- Currently tested in a phase III against R-CHOP

Event-Free Survival: DA-EPOCH-R in DLBCL



K Dunleavy et al. ICML 2011

Event-Free Survival : DA-EPOCH-R - PMBL

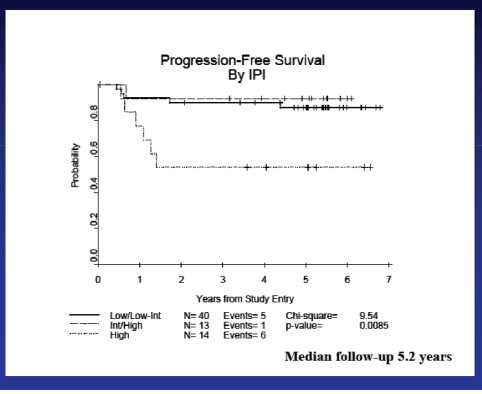


K Dunleavy et al. ICML 2011

CALGB Phase II

DA-EPOCH-R

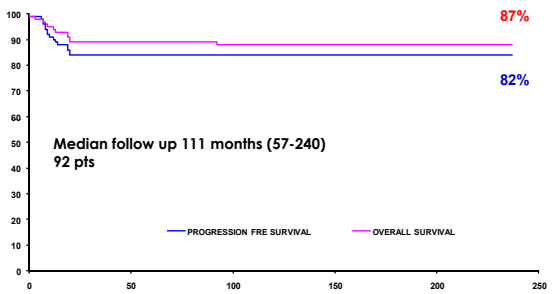
R Fisher Bologna 2010



R-MACOP-B

- Mostly used in Italy
- In patients with primary mediastinal lymphoma
- No randomized study

10 years PFS and OS



M Martelli et al. ICML 2011

M Martelli et al. ICML 2011

10 years PFS and OS

MACOP-B+ IFRT
June1991- May 2004
78 pts

R-MACOP-B+ IFRT
June 2004-Dec 2006
14 pts

Patients	92
Age (mean age)	45 (15-61)
Females	66 (72%)
Stage	
II	71(78%)
IIE-IV	21 (22%)
B symptoms	44 (41%)
Increased LDH values	52 (56%)
Bulky mass at presentation	89 (88%)
Superior V.Cava Syndrome	47 (51%)
Low risk patients (aaIPI=0-1)	55 (60%)
High risk patients (aaIPI=2-3)	42 (40%)

M Martelli et al. ICML 2011

M Martelli et al. ICML 2011

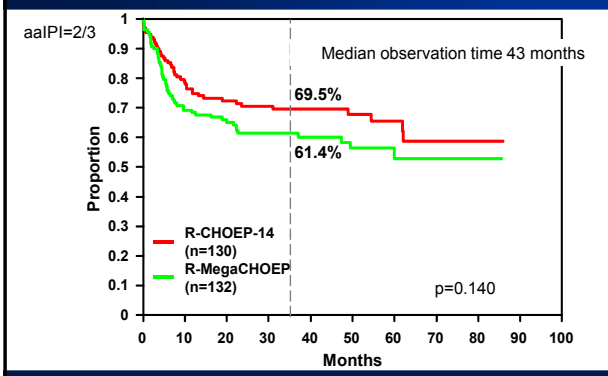
R-MegaCHOEP

- Mostly used in Germany
- For poor risk young patients
- Compared to R-CHOP-14

R-MegaCHOEP Study

EFS ACCORDING TO TREATMENT ARM

GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)
www.lymphome.de/en/Groups/DSHNHL



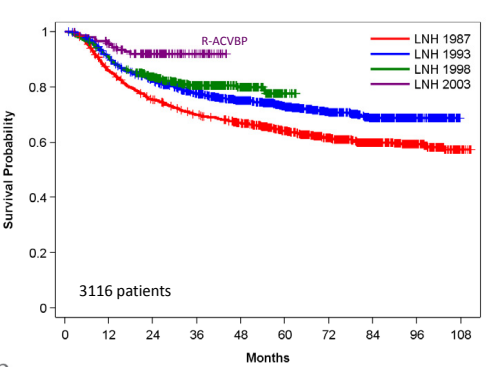
N Schmitz et al. ICML 2011

R-ACVBP + sequential consolidation

- Fist study with ACVBP done in 1984
- Mostly use d by GELA members
- Gave repeatedly identical results
- Allowed longer PDS and OS than R-CHOP

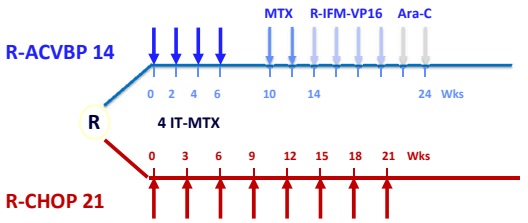
Survival with ACVB in LNH Regimens

(in randomized studies)



Gela

LNH 03-2B study

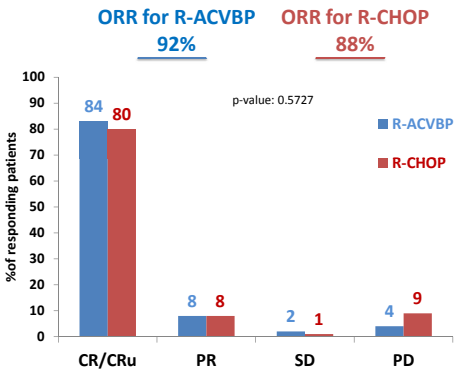


*No radiotherapy in both arms

Gela

ClinicalTrials.gov: NCT00140595

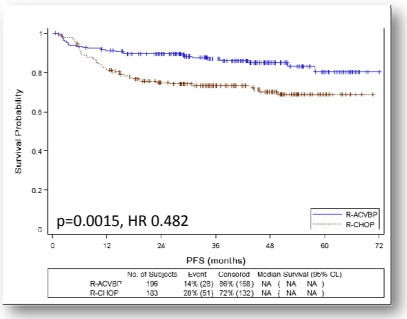
Response at the end of treatment



Gela

C Recher et al. ASH 2010

Progression-Free Survival

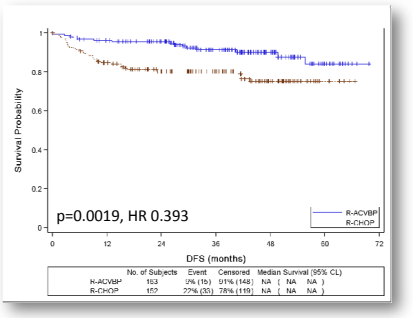


The 3-y PFS was 87% (95% CI, 81-91) in the R-ACVBP arm and 73% (95% CI, 66-79) in the R-CHOP arm

Gela

C Recher et al. ASH 2010

Disease-Free Survival

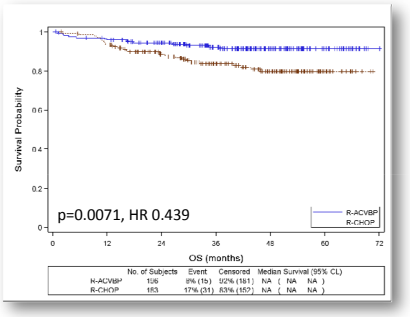


The 3-y DFS was 91% (95% CI, 85-95) in the R-ACVBP arm and 80% (95% CI, 73-86) in the R-CHOP arm

Gela

C Recher et al. ASH 2010

Overall Survival



The 3-y OS was 92% (95% CI, 87-95) in the R-ACVBP arm and 84% (95% CI, 77-89) in the R-CHOP arm

Gela

C Recher et al. ASH 2010

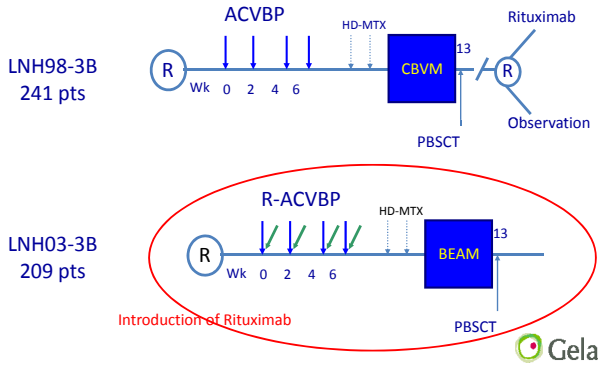
R-ACVBP or R-CHOP?

- R-CHOP is easier for patients and physicians
- R-CHOP is a good but significantly inferior to R-ACVBP + sequential consolidation
- Solution:
  - Find prognostic parameters before treatment
  - R-CHOP for good risk patients
  - R-ACVBP for poor risk patients

goals:
- increase the complete remission rate
- decrease the relapse rate

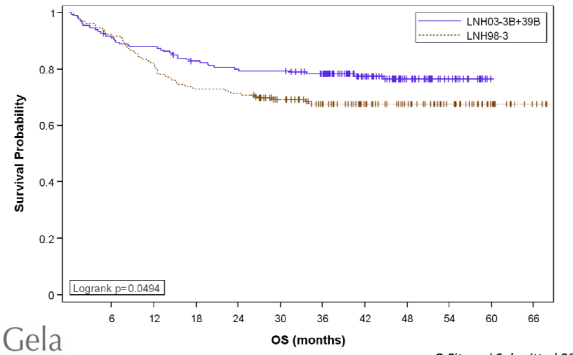
GELA Trials

In DLBCL with ASCT
< 60 yrs, 2-3 aa-IPI factors



Gela

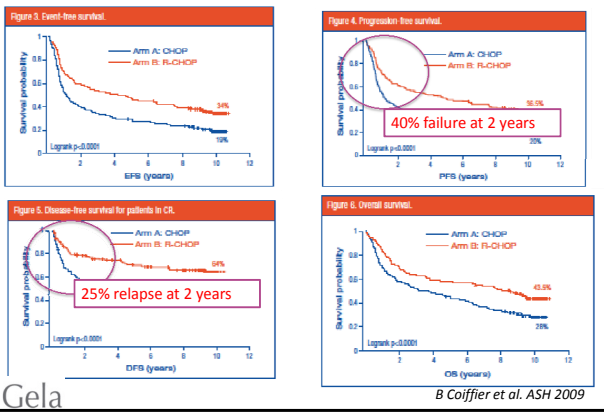
Overall survival in ACVBP and R-ACVBP plus HDT-autologous transplant in First CR



Gela

O Fitoussi Submitted 2010

GELA study: 10 years follow-up



Gela

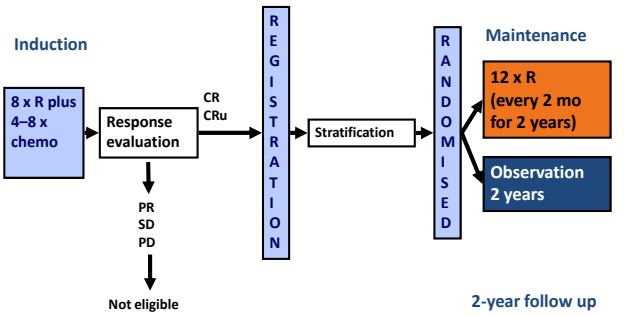
B Coiffier et al. ASH 2009

R2(Lenalidomide)-CHOP

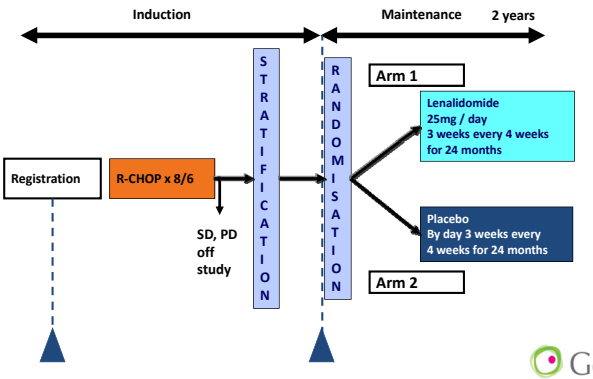
R2- CHOP		Dose (mg/m²)	Days
Cyclophosphamide	IV	750	1
Doxorubicine	IV	50	1
Vincristine	IV	1,4 (max 2 mg)	1
Prednisone	PO	40	1 to 5
Rituximab	CI	375	1
Lenalidomide	PO	See dose levels	1 to 14

Dose level	Days of treatment	Lenalidomide Dose	Number of patients
1	D1 to D14	2.5 mg	3-6
2	D1 to D14	5 mg	3-6
3	D1 to D14	10 mg	3-6
4	D1 to D14	15 mg	3-6
5	D1 to D14	20 mg	2-6
Expansion group	D1 to D14	Recommended dose	Up to 12 patients

Rituximab maintenance therapy in DLBCL or follicular NHL grade 3b: NHL-13 trial



ReMaRC study: Design

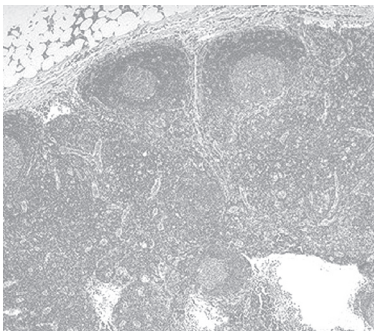


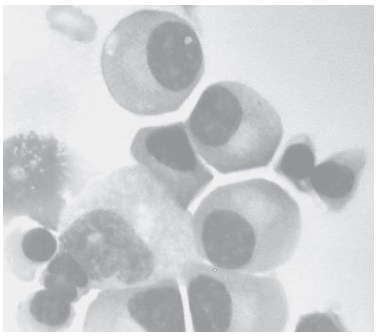
Gela

Conclusion

- Only R-ACVBP + sequential consolidation was superior to R-CHOP in randomized studies
- This is only for young patients with adverse prognostic parameters
  - To be refined
- In other setting R-CHOP is the standard
- But it is insufficient in half of stage III/IV patients

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Treatment approaches for untreated and relapsed disease

Stephen M. Ansell, MD, PhD

Waldenström macroglobulinemia

Treatment approaches for newly diagnosed and relapsed disease

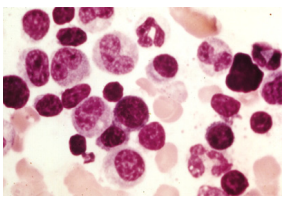
Stephen Ansell, MD, PhD
Mayo Clinic

Topics to be covered -

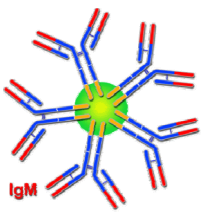
- What is Waldenström macroglobulinemia?
- Who needs treatment?
- Choice of therapy –
  - Newly diagnosed patients
  - Relapsed patients
- Questions

What is Waldenström macroglobulinemia?

Waldenström macroglobulinemia "A disease with two problems"



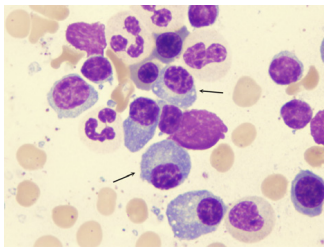
Lymphoplasmacytic infiltrate



Monoclonal IgM protein

Gertz et al. The Oncologist 2000;5:63-67

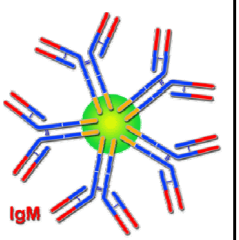
Waldenström macroglobulinemia Morphology and Immunophenotype



- Lymphoplasmacytic infiltrate (usually intertrabecular)
- Immunophenotype - surface IgM+, CD19+, CD20+, CD79a+ and PAX5+. CD5–, CD10–, CD23–.
- exclude CLL and mantle cell lymphoma
- del(6)(q21) is the most common genetic abnormality seen

Waldenström macroglobulinemia Monoclonal IgM

- Symptoms related to the monoclonal IgM protein are attributable to -
  - its characteristics in the circulation,
  - its interaction with various body tissues when deposited,
  - and its autoantibody activity.

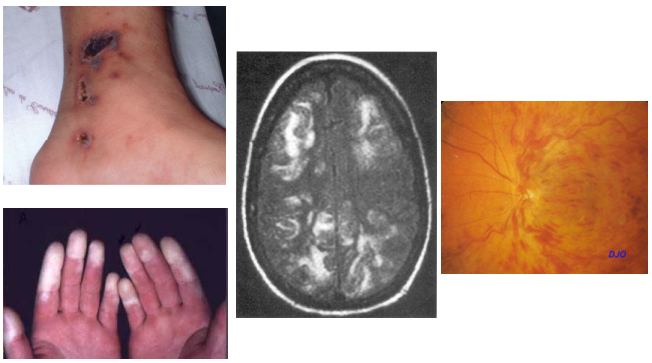


Waldenström macroglobulinemia – presenting symptoms

- 217 patients with serum monoclonal IgM protein ≥ 3 g/dl and > 20% bone marrow involvement -
  - Asymptomatic (27%)
  - Anemia (38%),
  - Hyperviscosity (31%),
  - B symptoms (23%),
  - Bleeding (23%)
  - Neurological symptoms (22%)

García-Sanz et al. Brit J Haematol. 115: 575-582, 2001

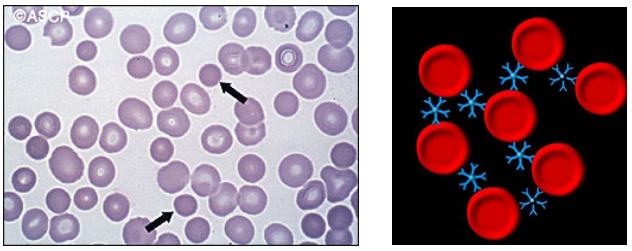
Hyperviscosity due to Waldenström macroglobulinemia



IgM deposition due to Waldenström macroglobulinemia



Autoimmune hemolysis secondary to Waldenström macroglobulinemia



Diagnostic Criteria for Waldenström macroglobulinemia

Waldenström macroglobulinemia
IgM monoclonal gammopathy (regardless of the size of the M protein) with >10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (surface IgM^+, $CD5^-$, $CD10^-$, $CD19^+$, $CD20^+$, $CD23^-$) that satisfactorily excludes other lymphoproliferative disorders, including chronic lymphocytic leukemia and mantle cell lymphoma

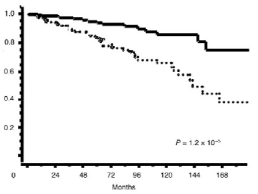
IgM MGUS
Serum IgM monoclonal protein level <3 g/dL, bone marrow lymphoplasmacytic infiltration <10%, and no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly

Smoldering Waldenström macroglobulinemia (also referred to as indolent or asymptomatic Waldenström macroglobulinemia)
Serum IgM monoclonal protein level ≥3 g/dL and/or bone marrow lymphoplasmacytic infiltration ≥10% and no evidence of end-organ damage, such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly, that can be attributed to a lymphoplasmacytic proliferative disorder

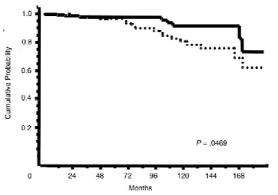
Kyle et al. Leukemia. 2009 Jan;23(1):3-9.

Time to developing WM and Survival in patients with Indolent WM or IgM MGUS

Time to evolution



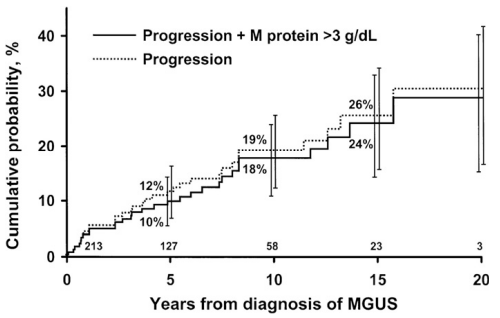
Overall survival



(— **MGUS; · · ·IWM)**
MGUS (217 patients) and indolent Waldenström's macroglobulinemia (201 patients) groups

Baldini L et al. JCO 2005;23:4662-4668

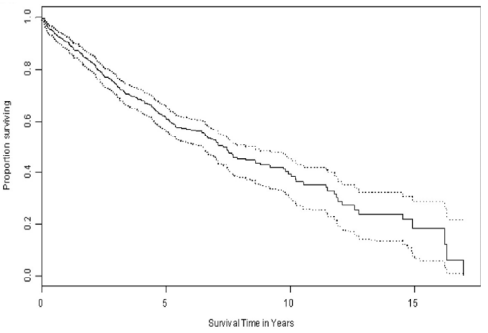
Risk of progression from IgM MGUS to WM or another B-cell malignancy



The overall average risk for progression is approximately 1.5% per year.

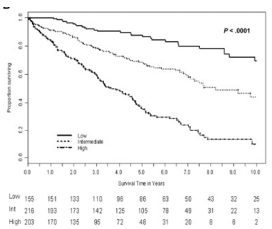
Kyle R A et al. Blood 2003;102:3759-3764

Survival of 587 symptomatic patients with Waldenström macroglobulinemia



Morel P et al. Blood 2009;113:4163-4170

International Prognostic Staging System for Waldenström's macroglobulinemia.



Age >65 years
Hemoglobin ≤11.5g/dL
Platelet count ≤100,000/mcL
β_2-Microglobulin >3mg/L
Monoclonal IgM >7g/dL

Low-	0 or 1 (except age)	142.5
Intermediate-	2 or age >65 yr	98.6
High	>2	43.5

Morel P et al. Blood 2009;113:4163-4170

Who needs treatment?

Patient 1

- 66 year old man
- Went for an executive physical – in good health with no symptoms
- Found to be mildly anemic (Hgb 12.8g/dl). Other blood counts – normal
- Also noted to have increased total protein with an increased gammaglobulin level.
- Monoclonal IgM – 1.4 g/dl
- Bone marrow biopsy – 20% involvement by lymphoplasmacytic lymphoma
- CT scan – no lymph nodes

Patient 2

- 67 year old man
- Severe fatigue, nausea, visual difficulties, increasing confusion and sleepiness, gums bleed easily.
- Anemic (Hgb 8.8g/dl). Platelets decreased to 96,000.
- Ulcers have developed on his ankles
- Monoclonal IgM – 6.6 g/dl. Viscosity – 5.8
- Bone marrow biopsy – 85% involvement by lymphoplasmacytic lymphoma
- CT scan – enlarged liver and spleen and multiple bulky lymph nodes in the abdomen

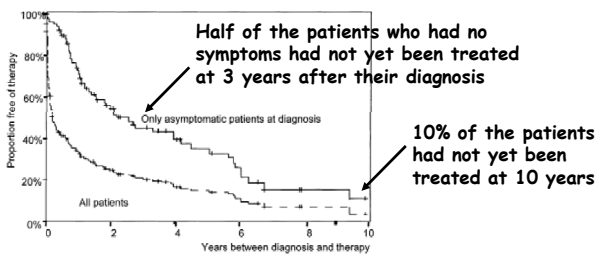
Many treatment options

- Watch and wait
- Single agent rituximab
- Chemoimmunotherapy combinations
- Plasmapheresis
- Clinical trials with new agents
- Stem cell transplantation

- **Which approach is best?**

Does everyone need treatment at diagnosis?

Watch and wait in Patients with Waldenström's macroglobulinemia



García-Sanz et al. Brit J Haematol. 115: 575-582, 2001

What clinical findings suggest that treatment should be started?

- Fever, night sweats, or weight loss.
- Lymphadenopathy or splenomegaly.
- Hemoglobin ≤ 10 g/dL or a platelet count < 100 x 10(9)/L due to marrow infiltration.
- Complications such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia.

Kyle et al. Semin Oncol. 2003 Apr;30(2):116-20

Before starting therapy –

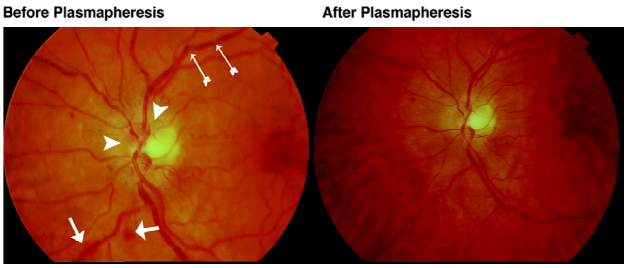
Does the patient have hyperviscosity and do they need plasmapheresis?

Plasmapheresis for Waldenström's patients with hyperviscosity

- Symptoms of hyperviscosity –
  - Visual deterioration
  - Neurological symptoms
  - Bleeding

- Rarely seen with IgM <4g/dL

Efficacy of Plasmapheresis for Waldenström's patients with hyperviscosity



Before plasmapheresis - optic disc edema (arrowheads), central retinal hemorrhages (bold arrows), and venous "sausaging" (thin arrows).

Menke et al. Invest Ophthalmol Vis Sci. 2008Mar;49(3):1157-60.

Initial treatment for untreated symptomatic WM patients

Common Treatments used as initial therapy for WM

- Purine analogue based combinations –
  - FCR/FR
- Alkylating agent based combinations –
  - R-CHOP
  - DRC
  - R-Bendamustine
- Bortezomib based combinations –
  - BDR
- Rituximab alone

Purine analogue based combinations – FCR/FR

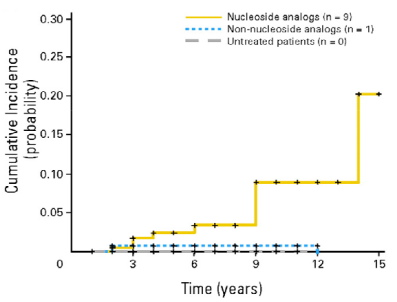
Fludarabine, cyclophosphamide, rituximab (FCR) –
43 untreated, symptomatic WM patients
ORR 79% - 12% CRs, 21% PRs
EFS – 50.1 months
44% had prolonged neutropenia

Tedeschi et al, Cancer. 2011 Jul 5.

Fludarabine, rituximab (FR) –
43 symptomatic WM patients
ORR- 95% - 5% CRs, 81% PRs
PFS – 51.2 months
63% had ≥ grade 3 neutropenia, thrombocytopenia or infection.

Treon et al. Blood. 2009 Apr 16;113(16):3673-8.

Increased incidence of transformation and myelodysplasia in WM patients treated with nucleoside analogs.



193 – nucleoside analogue therapy
136 – other therapy
110 – no therapy

5% transformation and 2% MDS in NA group
0.4% transformation in other groups

Leleu X et al. JCO 2009;27:250-255

Alkylating agent based combinations – R-CHOP

Prospective randomized trial of CHOP compared to R-CHOP in WM patients.
64 patients with untreated LPL/WM
R-CHOP – 34 patients, CHOP – 30 patients

Higher ORR for R-CHOP (94 vs 67%, p=0.0085)
Longer TTF - median of 63 months for R-CHOP vs 22 months for CHOP (p=0.0033)
No major differences in treatment-associated toxicity

Buske et al. Leukemia. 2009 Jan;23(1):153-61.

Alkylating agent based combinations – DRC

72 patients with untreated symptomatic WM received Dex 20 mg IV, rituximab 375 mg/m^2 IV on day 1 and cyclophosphamide 100 mg/m^2 orally bid on days 1 to 5 (total dose, 1,000 mg/m2). Repeated every 21 days for 6 months.

ORR – 83% (95% CI, 73%-91%), including 7% CR, 67% PR, and 9% minor responses.
2-year PFS for all patients was 67%
9% of patients - grade 3 or 4 neutropenia

Dimopoulos et al. J Clin Oncol. 2007 Aug 1;25(22):3344-9.

Comparative outcomes following CP-R, CVP-R, and CHOP-R in Waldenström's macroglobulinemia.

Retrospective single institution study – CHOP-R (n = 23), CVP-R (n = 16), or CP-R (n = 19)

ORR and CR rates : CHOP-R (ORR, 96%; CR, 17%); CVP-R (ORR 88%; CR 12%); CP-R (ORR, 95%; CR, 0%); p= NS.

More treatment-related neuropathy and febrile neutropenia in patients treated with CVP-R and CHOP-R versus CP-R.

Ioakimidis et al. Clin Lymphoma Myeloma. 2009 Mar;9(1):62-6.

Alkylating agent based combinations – R-Bendamustine

30 patients with WM – bendamustine 90 mg/m2 I.V. on days 1, 2 and rituximab 375 mg/m2 I.V. on day 1.
6 patients received bendamustine with ofatumumab 1000 mg I.V. on day 1. Median number of treatment cycles was 5.
ORR - 83.3%, with 5 VGPR and 20 PR.
Median PFS was 13.2 months.
Prolonged myelosuppression was more common in patients who received prior nucleoside analogues

Treon et al. Clin Lymphoma Myeloma Leuk. 2011 Feb 1;11(1):133-5.

Bendamustine plus rituximab compared with R-CHOP in WM patients

- A subset analysis in the prospective randomized STIL trial - bendamustine plus rituximab (BR) compared with R-CHOP
- 41 patients with WM, 22 received BR and 19 received R-CHOP.
- In both groups, the response rate was 95%
- The median PFS for R-CHOP was 36 months in contrast to not being reached with BR ($p < 0.0001$).
- 4 relapses (18%) in the BR group and 11 relapses (58%) in the R-CHOP group.
- BR was better tolerated.

Rummel MJ, et al. The Sixth International Workshop on Waldenström's Macroglobulinemia. 2010 Oct 6-10, Venice, Italy.

Bortezomib based combinations – BDR/BR

Bortezomib, dexamethasone, rituximab (BDR) –
23 untreated, symptomatic WM patients
ORR 96% - 3 CRs, 5 VGPRs, 11 PRs
Short follow up - PFS – not reached
61% had peripheral neuropathy

Treon et al, J Clin Oncol. 2009 Aug 10;27(23):3830-5.

Bortezomib, rituximab (BR) –
26 untreated, symptomatic WM patients
ORR- 88% - 1 CR, 1 VGPR, 15 PRs
PFS – not reached
12% had ≥ grade 3 neutropenia, no grade 3 or 4 neuropathy.

Ghobrial et al. Am J Hematol. 2010 Sep;85(9):670-4.

Rituximab alone for Waldenström's macroglobulinemia

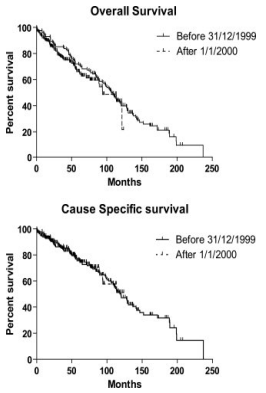
69 symptomatic WM patients – rituximab x 4 doses
ORR 52% - 27% PR, 25% MR
Median duration of response – 27 months

Gertz et al, Leuk Lymphoma. 2004 Oct;45(10):2047-55.

Same study – evaluated IgM levels for "flare"
54% had an increase in IgM
27% still elevated at 4 months
No factors predicting an increase in IgM levels could be identified.

Ghobrial et al. Cancer. 2004 Dec 1;101(11):2593-8.

No significant improvement in the outcome of patients with Waldenström's macroglobulinemia treated over the last 25 years

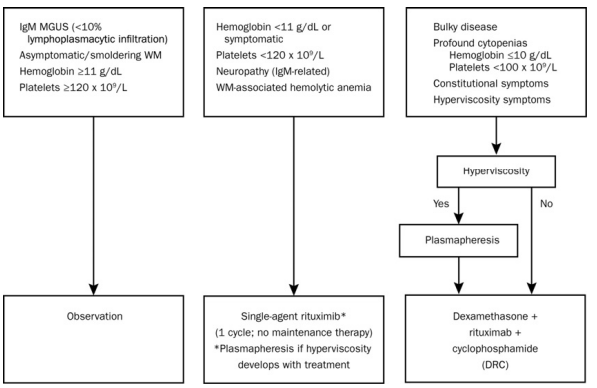


345 symptomatic patients with WM –

- 130 who initiated treatment before January 1, 2000 – alkylating agent based
- 215 who started treatment after January 1, 2000 – rituximab based

Kastritis et al. Am J Hematol. 2011 Jun;86(6):479-83.

Mayo Clinic (mSMART) consensus for management of newly diagnosed Waldenström macroglobulinemia



Ansell et al. Mayo Clin Proc. 2010;85:824-833

Subsequent treatment in relapsed WM patients

Which new drugs look promising?

- Bendamustine
- mTOR inhibitors - RAD001 (Everolimus)
- New anti-CD20 antibodies
  - Ofatumumab
  - Veltuzumab
- Anti-bcl2 agents - Obatoclax
- New HDAC inhibitors - LBH589
- New proteosome inhibitors – MLN9708
- New Imids - Pomalidomide (CC-4047)
- Other agents – Enzastaurin, Perifosine, Imatinib, Simvastatin, sildenafil citrate

Imids – Thalidomide and lenalidomide

Thalidomide and rituximab –

- 25 WM patients
- ORR 72% - 1 CR, 15 PRs
- Median TTP – 38 months
- 44% had peripheral neuropathy

Treon et al, Blood. 2008 Dec 1;112(12):4452-7.

Lenalidomide and rituximab –

- 16 WM patients
- ORR- 50% - 25% PRs
- Median TTP – 19 months
- Trial closed early due to significant anemia in 13/16 patients.

Treon et al. Clin Cancer Res. 2009 Jan 1;15(1):355-60.

RAD001 (Everolimus) in WM

50 WM patients
RAD001 10mg daily po
ORR 70% - 42% PRs
12 month PFS – 62%
56% grade 3 or higher toxicity – Most common were hematologic toxicities
Pulmonary toxicity occurred in 10% of patients.

Ghobrial et al, J Clin Oncol. 2010 Mar 10;28(8):1408-14.

Ofatumumab in WM patients

15 WM patients
Ofatumumab 300mg week 1, 1000mg weeks 2-4
ORR 43%
PFS – not yet reached
9 patients developed infections
2 patients required plasmapheresis

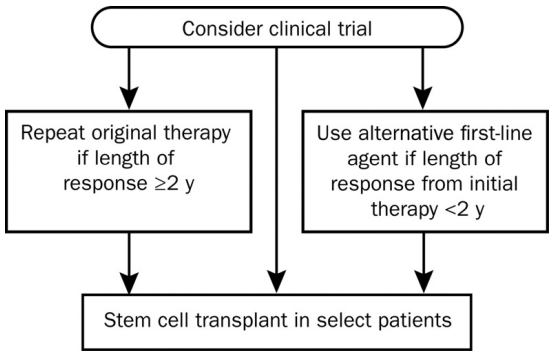
Furman et al, ASH 2010 , abstract #1795.

LBH589 (panobinostat) in WM patients

27 WM patients
Panobinostat 30mg 3x per week po
ORR 60% - 24% PRs
PFS – not yet reached
Grade 3 and 4 toxicities were predominantly hematological.

Ghobrial et al, ASH 2010 , abstract #3952.

Mayo Clinic (mSMART) consensus for management of relapsed Waldenström macroglobulinemia.



Ansell et al. Mayo Clin Proc. 2010;85:824-833

Transplantation in relapsed Waldenström macroglobulinemia.

Autologous transplant –
- 158 WM patients
- Non-relapse mortality – 3.8%
- 5-year PFS – 40%
- 5-year OS – 68%

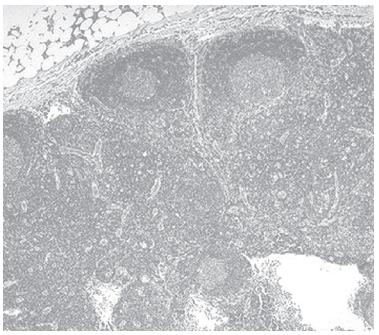
Kyriakou et al, J Clin Oncol. 2010 May 1;28(13):2227-32.

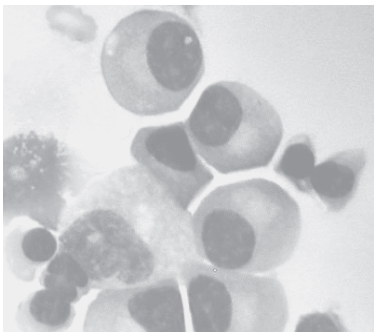
Allogeneic transplant –
- 86 WM patients (37 MAC and 49 RIC)
- Non-relapse mortality – 33%(MAC), 23% (RIC)
- 5-year PFS – 56%
- 5-year OS – 62%

Kyriakou et al. J Clin Oncol. 2010 Nov 20;28(33):4926-34.

Questions?

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies

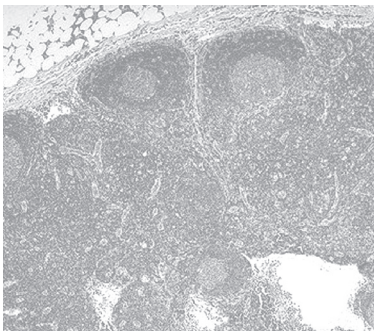


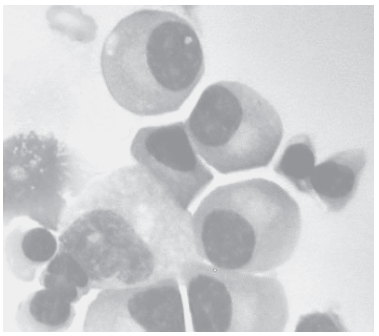


Debate: Should everyone receive maintenance rituximab?

Yes: David Maloney, MD, PhD

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Debate: Should everyone receive maintenance rituximab?

No: Bruce E. Cheson, MD

Should Everyone Receive Maintenance Rituximab? *NO!!*

Bruce D. Cheson, M.D.
Georgetown University Hospital
Lombardi Comprehensive Cancer Center
Washington, D.C.
Chair, CALGB/ACTION Lymphoma Committee

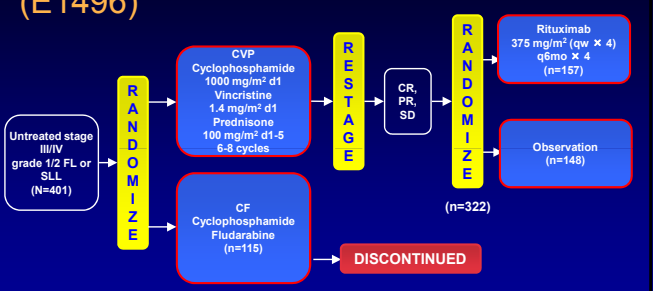
What We Need to Know Before We Accept Rituximab Maintenance

- Optimal maintenance regimen/duration
- Effect on overall survival
- Impact on subsequent therapies
- Role relative to retreatment
- Long-term toxicities

Maintenance Schedules

- 4 doses q 6 mo x 2 years
- Q 3 months
- Q 2 months x 4
- Q 2 months x 2 years (5 years or until progression?)
- Based on drug levels

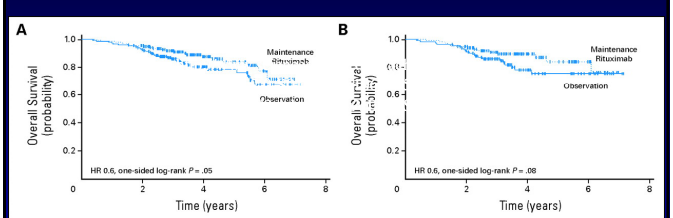
Phase III Trial of CVP ± Maintenance Rituximab in Advanced Indolent NHL (E1496)



- Primary end point: PFS from time of randomization post-CVP

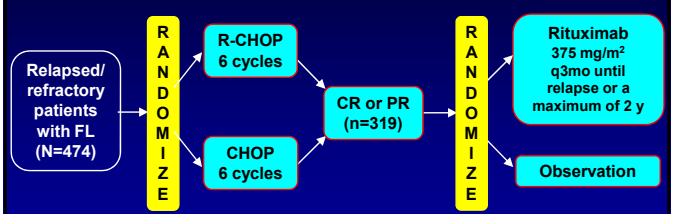
Hochster et al. *J Clin Oncol, 27:1549, 2009*

Overall survival for 311 evaluable indolent lymphoma patients randomized to maintenance rituximab (n = 158) or observation (n = 153)



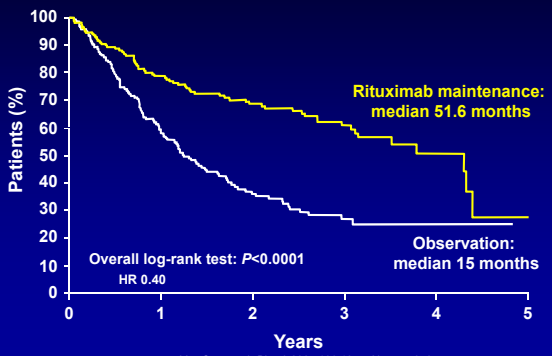
Hochster, H. et al. J Clin Oncol; 27:1607-1614 2009

Induction R-CHOP vs CHOP and Maintenance Rituximab vs Observation in Relapsed FL (Intergroup EORTC 20981)



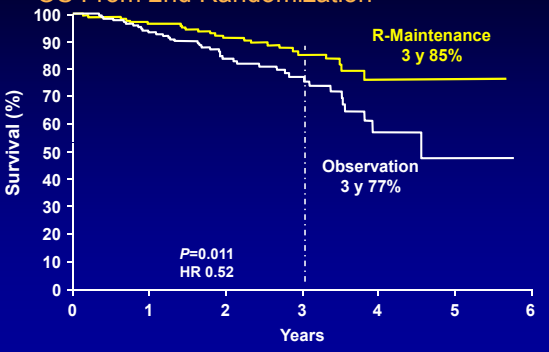
Van Oers et al. *Blood*. 2005;106:107a. Abstract 353.

Induction R-CHOP vs CHOP and Maintenance Rituximab vs Observation in Relapsed FL: PFS From 2nd Randomization



Van Oers et al. *Blood*. 2005;106:107a. Abstract 353.

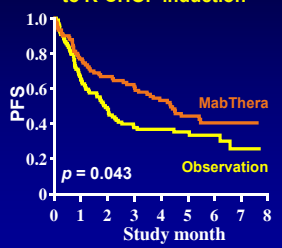
Induction R-CHOP vs CHOP and Maintenance Rituximab vs Observation in Relapsed FL: OS From 2nd Randomization



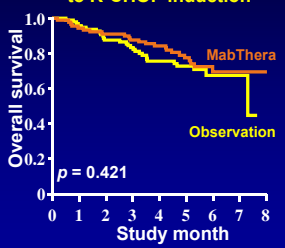
Van Oers et al. *Blood*. 2005;106:107a. Abstract 353.

Rituximab Maintenance in Relapsed Follicular NHL

PFS after response to R-CHOP induction

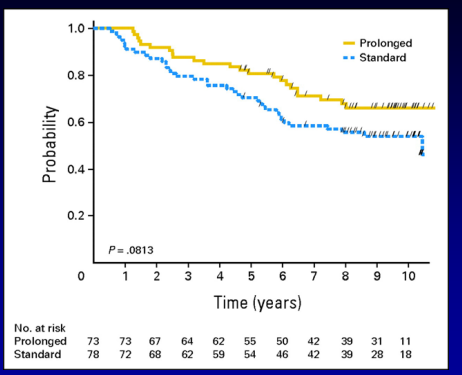


Overall survival after response to R-CHOP induction



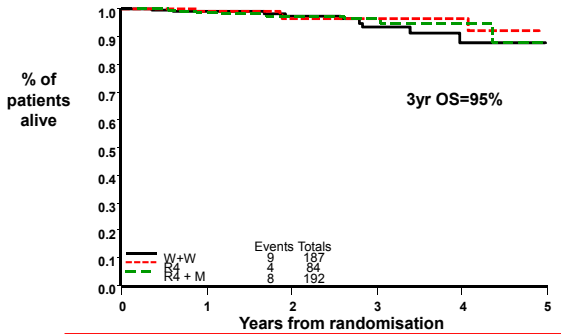
van Oers M, *et al. Blood* 2008; 112:Abstract 836.

Overall survival by treatment arm



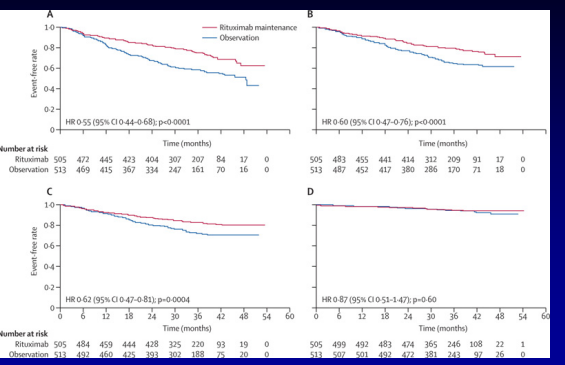
Martinelli G et al. JCO 2010;28:4480-4484

Overall survival



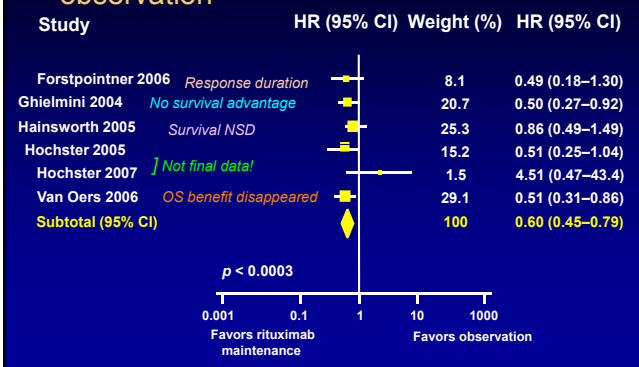
HR (Rituximab vs W+W) = 0.63, 95%CI = 0.21, 1.92, p=0.42
HR (Rituximab + M vs W+W) = 0.84, 95%CI = 0.32, 2.18, p=0.72
HR (Rituximab + M vs Rituximab) = 1.21, 95%CI = 0.37, 3.97, p=0.75

PRIMA Study

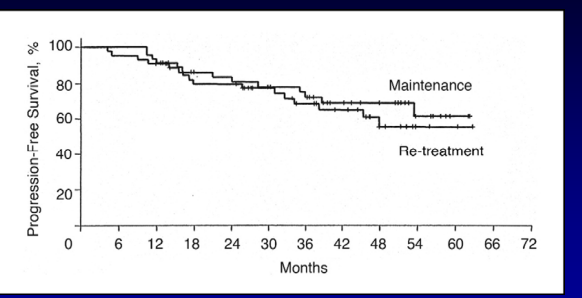


Salles et al, Lancet 377:42, 2011

Rituximab maintenance therapy consistently improves overall survival vs observation

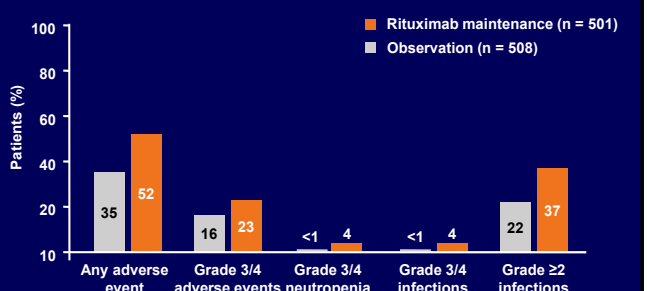


Vidal L, *et al. J Natl Cancer Inst* 2009; 101:248–255.



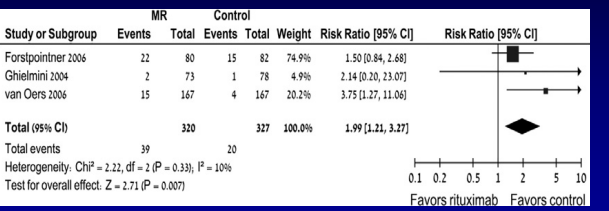
Hainsworth J D et al. JCO 2005;23:1088-1095

Rituximab maintenance: safety (1)

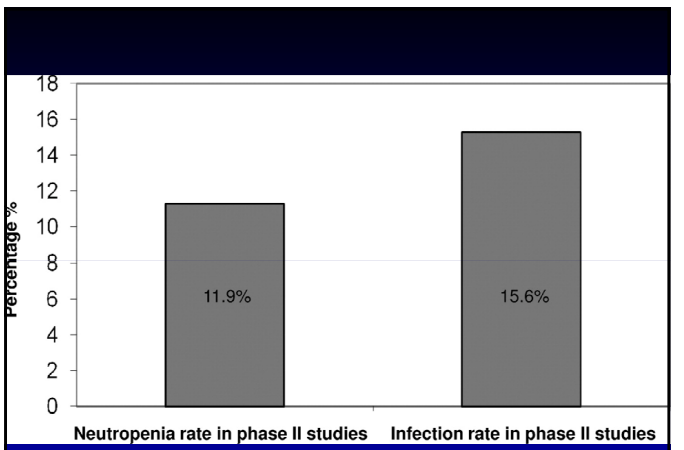


Infection-related adverse events in patients with follicular lymphoma treated with rituximab maintenance compared with observation

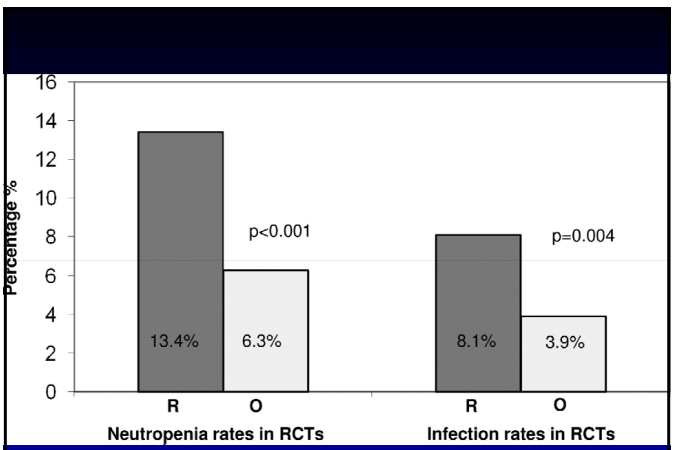
Increased Infections with RM



Vidal L et al. JNCI J Natl Cancer Inst 2009;101:248-255



Aksoy et al, Leuk Lymph 50:357, 2009

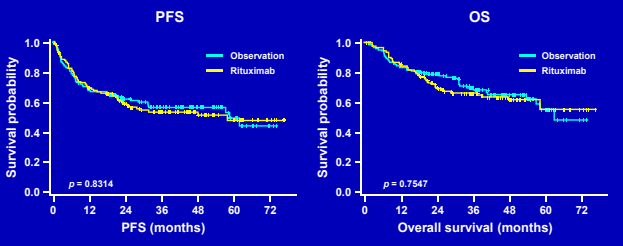


Aksoy et al, Leuk Lymph 50:357, 2009

Delayed Complications of RM

- Late cytopenias
- Prolonged reduction in serum Igs
- Infections
- Reactivation of HepB, HepC
- Interstitial pneumonitis

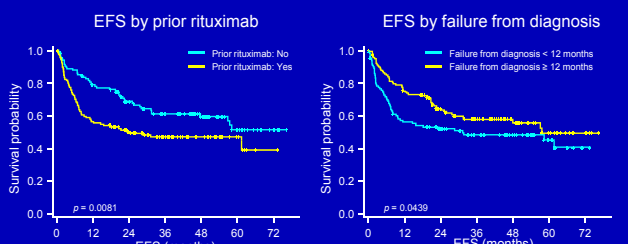
CORAL maintenance: PFS/OS by treatment arm



	n	Event	Censored	Median
Observation	120	43% (52)	57% (68)	58.22
Rituximab	122	45% (55)	55% (67)	57.59

	n	Event	Censored	Median
Observation	120	33% (40)	67% (80)	62.92
Rituximab	122	36% (44)	64% (78)	NA

CORAL maintenance: EFS by prognostic factors



	n	Event	Censored	Median
Prior rituximab: No	117	39% (46)	61% (71)	NA
Prior rituximab: Yes	125	52% (65)	48% (60)	24.51

	n	Event	Censored	Median
Failure from diagnosis < 12 months	105	51% (54)	49% (51)	31.44
Failure from diagnosis ≥ 12 months	137	42% (57)	58% (80)	57.59

Rituximab Maintenance: Summary

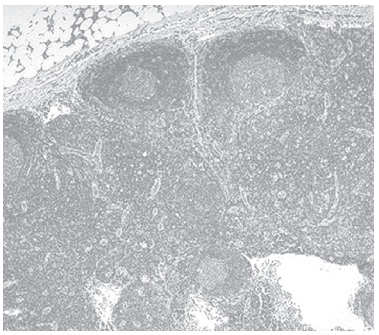
- Expensive
- Cumbersome
- Increased toxicities
- No survival benefit
- Retreatment comparable
- Impairs response to subsequent tx (?)
- Consider alternate agent

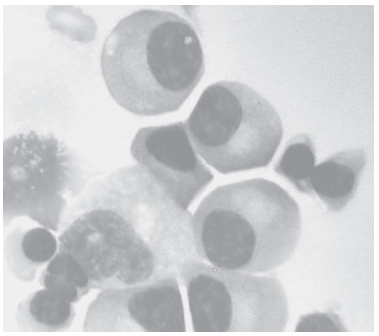
Conclusion ~

If we had better induction – we wouldn't need maintenance!

Thus, Maintenance is for losers!

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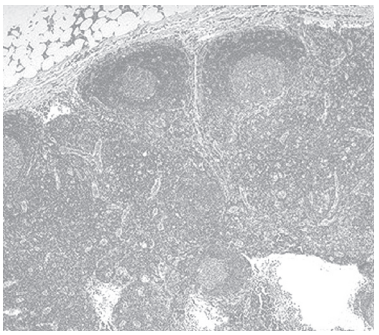


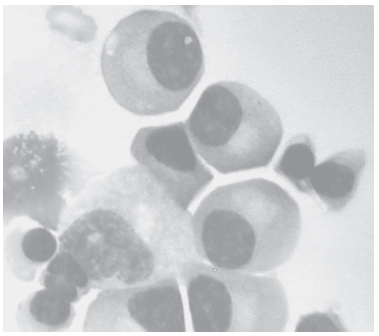


Debate: Is "watch and wait" passé in asymptomatic follicular lymphoma?

Yes: John P. Leonard, MD

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Debate: Is "watch and wait" passé in asymptomatic follicular lymphoma?

No: Myron Czuczman, MD

DEBATE: IS WATCH-AND-WAIT PASSÉ IN ASYMPTOMATIC FOLLICULAR LYMPHOMA?

ANSWER: NO!

Lymphoma and Myeloma 2011
October 22, 2100

Myron S. Czuczman, MD
Chief, Lymphoma/Myeloma Service
Head, Lymphoma Translational Research Laboratory
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Buffalo, NY

Disclosures for Myron S. Czuczman, MD

In compliance with ACCME policy, the ASH requires the following disclosures to the activity audience:

Research Support/P.I.	Genentech, GSK
Employee	N/A
Consultant	Genentech, GSK, Spectrum
Major Stockholder	N/A
Speakers' Bureau	N/A
Scientific Advisory Board	N/A

Presentation includes discussion of the following off-label use of a drug or medical device:
Rituximab in front-line Rx of asymptomatic FL

49th ASH Annual Meeting ♦ Orlando, Florida

Outline

- Definition of passé
- Background
- Asymptomatic FL (Clinical/Research data)
  - Early intervention in the "pre-rituximab" era
  - Early intervention in the "rituximab" era
- Conclusions
- Future directions?

Passé

- Adjective
  - "past one's prime"
  - "outmoded"
  - "behind the times"
- Origin
  - French

(The Merriam-Webster Unabridged Dictionary)

Approach to Advanced-Stage FL: Accepted Facts in 2011

- FL is incurable
- Often seen in older patients with co-morbid conditions
- Initiation of Rx soon after diagnosis in asymptomatic FL patients does not change "outcome"
- Rx with "sequentially" intensive therapy once intervention necessary (i.e. save more aggressive Rx)
- Palliation of symptoms is acceptable
- Transformation: independent of type or timing of Rx
- Median overall survival for FL improving in R era

Characteristics of Follicular Lymphoma

Clinical Pattern:
- Indolent clinical course (typical)
- Highly responsive to therapy but relapse is likely

Treatment decisions based on:
- Stage and Bulk
- FL IPI
- Transformation
- Sites of involvement
- Prior therapy
- Time from prior therapy

Current Treatment Approach (symptomatic pts):
- Frontline: Rituximab +/- chemotherapy (R-CHOP, R-Benda, R-CVP, etc)
- Consolidation: Rituximab, Radioimmunotherapy (RIT)
- Salvage: Clinical trial, chemoimmunotherapy; HDT/SCT; RIT

Indolent Lymphoma: Considerations in Choosing a Therapy

- Patient Characteristics
  - Age
  - Symptoms
  - Short & long term goals
  - Co-morbidity
  - Preserve future options
- Disease Characteristics
  - Stage
  - Grade*
  - Transformation
  - Sites of involvement
  - Prior therapy
  - Time from prior therapy
  - Prognostic factors

**FL, grade 3 is an area of controversy; commonly treated as DLBCL (i.e. "anthracycline-based" Rx if eligible – especially, FL, grade 3b!)*

FL, grades1,2: Indications for Rx of Advanced Disease (NCCN 2011)

- Candidate for clinical trial
- Cytopenias secondary to BM infiltration
- Threatened end-organ function
- Symptoms attributable to disease (e.g. pleural effusion, ascites)
- Bulky disease
- "Steady" progression
- Histologic transformation
- Massive splenomegaly

GELF Criteria* for Initiation of Rx in FL

- One of the following:
  - Maximum diameter of disease > 7 cm
  - ≥ 3 nodal sites, each with diameter of ≥ 3 cm
  - Systemic symptoms
  - Spleen > 16 cm on CT scan
  - Significant effusions
  - Risk of local compressive symptoms
  - Leukemia phase (> 5.0 x 10^9/L malignant cells)
  - Marrow compromise (Hgb < 10; WBC < 1.5; PLT C < 100k)

*Brice P et al. J Clin Oncol 1997; 15:1110

BNLI Criteria* for Initiation of Rx in FL

- One of the following:
  - B symptoms or pruritis
  - Rapid generalized disease progression
  - Marrow compromise
  - Life-threatening organ involvement
  - Renal infiltration
  - Bone lesions

*Ardeshana KM et al. Lancet 2003; 362:516

The Natural History of Initially Untreated Low-Grade NHL: The Stanford Experience[1]

- n=83 advanced-stage indolent (75% follicular) NHL initially managed without therapy
- Actuarial survival:
  - 82% at 5 years
  - 73% at 10 years
- Median time until initiation of Rx: 3 years
- Spontaneous regressions occurred in 30% of FL patients*
- Neither time to transformation nor incidence of transformation was influenced by when treatment was initiated

* Review of other databases: A small portion of FL patients (possibly in the 10%-20% range) may achieve 10+ years without requiring Rx; We need to be able to accurately identify these patients at time of diagnosis!

[1]Horning SJ and Rosenberg SA. NEJM 1984; 311:1471-1475

Who and When to Treat?

- Majority of FL patients present with asymptomatic, advanced-stage disease
  - Accepted and long-honored practice is "watchful-waiting": Why?
    - Standard chemotherapy (single- vs. multi-agent) did not change the relapsing nature or the OS of FL
    - Delayed initiation of "toxic" therapy until "needed"
  - Recently revisited in the "rituximab" era: To follow

Who and When to Treat?

- Pre-rituximab era:
  - Critical re-review of 2 historically important clinical trials which contributed to our current Rx approach of advanced-stage FL:
    - US NCI Watchful Waiting vs. Upfront Aggressive Combined Modality Treatment
    - BNLI Study of Immediate vs. Delayed Chlorambucil

"Early" Clinical Trials of Immediate vs. Delayed Therapy

1. US NCI Study in 104 advanced indolent NHL pts
- Randomized between:
  - Watchful waiting (n=44), then aggressive Rx @ POD: "A"
  - vs.
  - Aggressive upfront ProMACE-MOPP, then TNI (n=45): "B"
- Initial Results[1]: OS @ 5 years > 75% in both arms
  - 4-yr DFS of 51% (Arm B) vs. 12% (Arm A)
- Mature Data[2]: (13-yr median F/U):
  - 75% of patients alive in Arm B
  - 75% of patients alive in Arm A

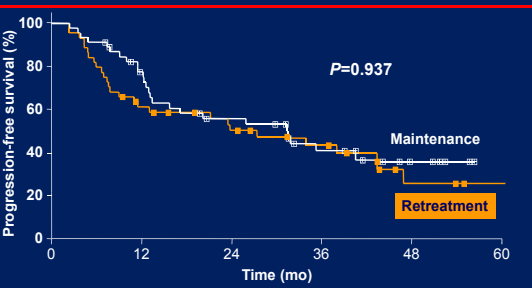
1. Young RC, Longo DL, Glatstein E, et al. Semin Hematol 1988; 25:11
2. D. Longo commentary on FL review article: Oncology 2005; 19:213 and personal communication

"Early" Clinical Trials of Immediate vs. Delayed Therapy

2. BNLI Study[1]: n=309 asymptomatic advanced-stage indolent (204 FL) NHL pts
- Randomized between:
  - (A): Immediate Chlorambucil (up to 10 mg po qd) to CR (vs)
  - (B): Delayed Chlorambucil (clinical progression)
  - Note: Both arms permitted palliative localized IFRT
- Median of 16 years:
  - Similar OS: 5.9 yrs in Arm A and 6.7 yrs in Arm B

[1]Ardeshna KM, Smith P, Norton A, et al. Lancet 2003; 362:516

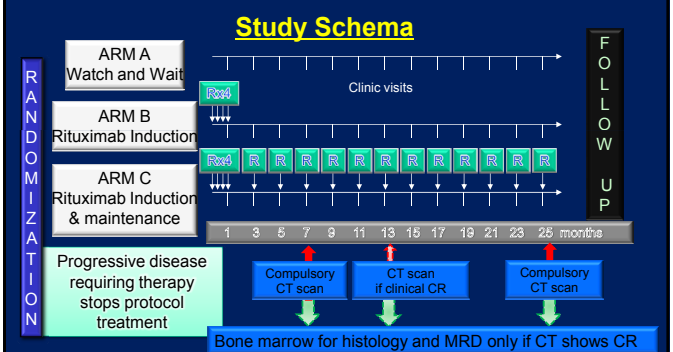
Rituximab era: Duration of rituximab benefit is limited



- Within 3 yrs, the majority of patients become refractory to rituximab
- New treatments are still needed for follicular NHL
- Unlikely that R maintenance will be utilized with each course of Rx

Hainsworth JD, *et al. J Clin Oncol* 2005;23:1088–1095

An Intergroup Randomized Trial of Rituximab vs. a Watch & Wait Approach in Patients with Advanced Stage, Asymptomatic, non-Bulky FL



Ardeshna et al. Blood 116: Abstract 6, 2010

Primary Endpoint: Time to initiation of next therapy

- Symptomatic enlarged LN or spleen
- 'B' symptoms or severe pruritus
- Lymphomatous mass > 7cm provided size increased by 25%
- >3 nodal sites with nodes >5cm
- Significant effusions
- Lymphoma-related cytopenias
- Near-critical organ involvement/compression
- Histological transformation

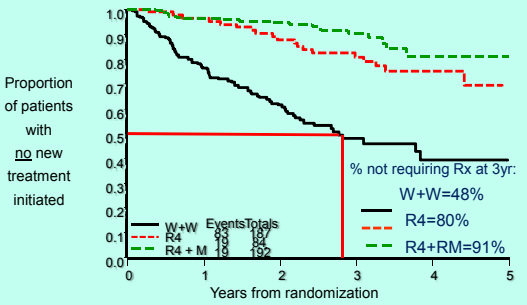
Limitation of Study:

"At the time of progression, rituximab monotherapy was not an option!"

Ardeshna et al. Blood 116: Abstract 6, 2010

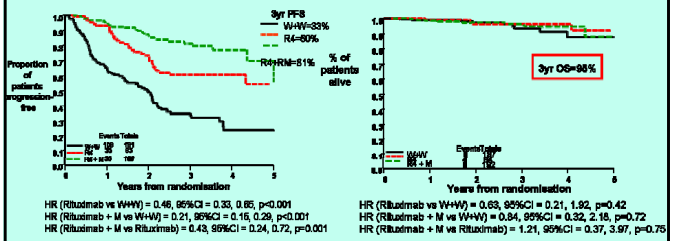
Results

Time to Initiation of New Therapy (TTNT)



Ardeshna et al. Blood 116: Abstract 6, 2010

PFS and OS



Conclusion: Rituximab significantly improves TTNT and PFS in patients with asymptomatic FL when compared with watchful waiting…

- **Is this clinically meaningful?**
- **Is TTNT the best clinical endpoint? / "subjective?"**
- **Additional Considerations: Next slide**

Ardeshna et al. Blood 116: Abstract 6, 2010

Additional Considerations: Problems Associated with Ardeshna Rituximab Early Intervention Trial*

- No data supporting an overall survival advantage
- No "optimal" rituximab schedule has been identified
- Associated costs and time requirements
- Infectious risks (notably small, but real)
- Responsiveness to second-line therapy? (unknown)
- Is R maintenance schedule used better than R "re-treatment" at relapse?

*Ardeshna et al. ASH 2010, Abst #6

Advantages Associated with Watch-and-Wait

- Improved quality-of-life for prolonged period of time
  - Delay toxicity associated with chemotherapy
    - Includes possible infertility/early menopause in younger pts
  - Decreased costs and inconvenience (associated with early Rx)
- Early intervention and/or excessive therapy
  - Increased risk for development of "resistance"

Conclusions

- **Is watch-and-wait passé in asymptomatic FL?**
  - **Answer: No!** Based on historic and current data
- **Watch-and-wait approach is the standard-of-care approach for asymptomatic FL around the world** (e.g. NCCN, GELF, BNLI, GSLG, etc.)
- **Potential impact from a palliative early intervention:**
  - **Resistance?** Responsiveness to subsequent therapies?
  - **Adverse events** (e.g. hypogammaglobulinemia, neutropenia, infections)
  - **Medical costs** cannot be justified in respect to no demonstrable improvement in OS

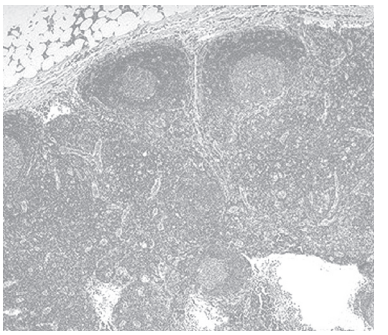
Future Directions

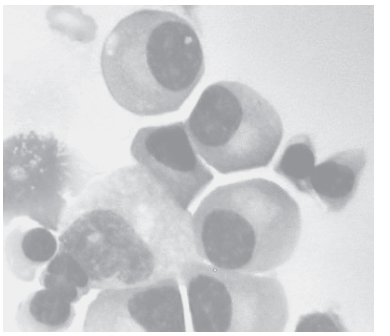
1. Need biomarkers which can reproducibly predict indolent versus aggressive FL subgroups at diagnosis
2. Improvement of induction regimens and/or use of consolidative agents not utilized in the induction therapy
3. Clinical trials of "curative" potential (e.g. combination immunochemotherapy) in asymptomatic follicular lymphoma! …but, for now:
4. **"WATCH-AND-WAIT"!**

Roswell Park Cancer Institute
Buffalo, NY



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Relapsed aggressive lymphoma: what approaches are applicable for transplant eligible and ineligible patients? What has the CORAL study taught us?

Craig Moskowitz, MD

Why do we cure less patients with relapsed and refractory DLBCL?

Craig Moskowitz, MD

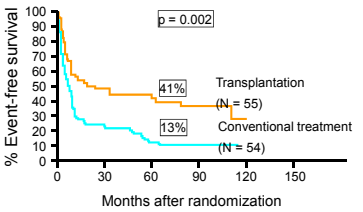
Clinical Director, Division of Hematologic Oncology
Attending Physician, Lymphoma and ABMT Services, Memorial Hospital
Member, Memorial Sloan-Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University

Disclosures

Research Support/P.I.	Seattle Genetics, Genentech Cephalon, Plexicon, Calistoga
Employee	None
Consultant	None
Major Stockholder	None
Speakers Bureau	None
Honoraria	none
Scientific Advisory Board	Seattle Genetics, Glaxo-Smith Kline. Genentech

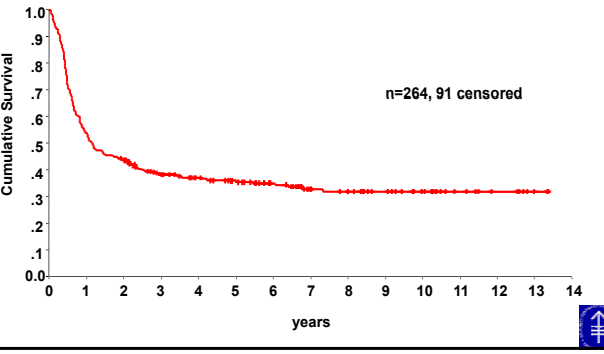
Salvage Regimens in Relapsed DLBCL in the Rituximab Era

- **Salvage is the standard of care in DLBCL patients failing first-line chemotherapy treatment, followed by autologous stem cell transplantation (ASCT) in chemo-sensitive patients**
- **In the Parma study, the 7 year event-free survival rate was 41% for ASCT vs 13% in the conventional arm**
- **Before rituximab: Different salvage regimens provided a 50-68% response rate with adequate mobilisation of hematopoetic peripheral stem cells for ASCT**

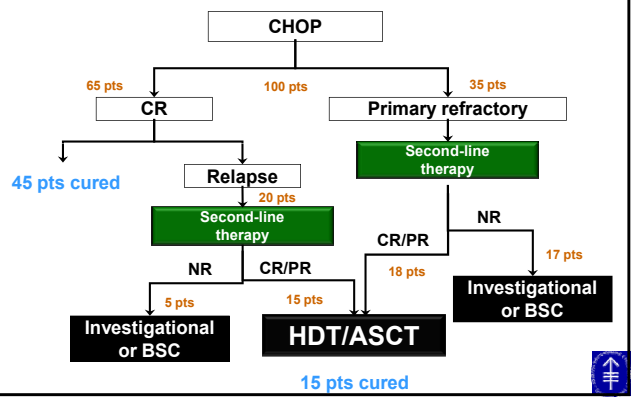


EFS: ICE followed by HDT-ASCT

intent to treat



Management of transplant-eligible pts with DLBCL-pre-rituximab era



ICE → HDT/ASCT for relapsed / refractory NHL

- **Pretreatment evaluation**
  - **Biopsy-proven refractory or relapsed disease**
  - **EF > 50, DLCO > 50, CrCl > 60; no active Hepatitis B or C**
- **All patients receive ICE-based second-line chemotherapy**
- **PBPCs are collected following cycle 3**
- **For chemosensitive patients (PR or CR):**
  - **in selected patients (≤ 2 fields), prior to HDT, involved-field accelerated fractionation radiation therapy is administered to a dose up to 36 Gy**
  - **HDT/ASCT**
- **Patients are analyzed from initiation of ICE-based therapy**

Moskowitz CH, *et al. J Clin Oncol* 1999; **17**:3776–3

Relapsed / primary refractory DLBCL

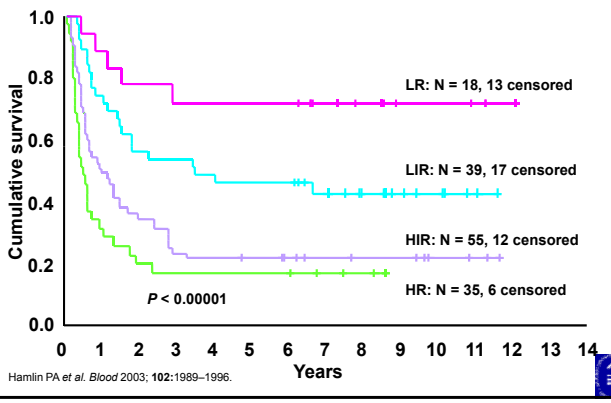
- 5 year event-free-survival (EFS) is 25–30% but, 40–45% for patients transplanted
- Chemosensitive disease is required for transplant eligibility in the USA and the addition of rituximab increases the number of a patients in CR pre-ASCT
  - Kewalramani et al Blood. 2004, 103: 3684-8
- Pre-treatment clinical prognostic factors predict outcome
  - Second-line age adjusted IPI
    - Hamlin et al Blood 2003, 102: 1989-1996
  - Relapse vs. primary refractory
    - Kewalramani et al Blood 2000, 96: 2399-2404
- the cell of origin as defined by IHC does not predict outcome in the relapse / refractory setting
  - Moskowitz et al Blood 2005,: 106: 3383-3386

Intent to Treat Outcome stratified by sAAIPI (MSKCC)

sAAIPI risk group		PFS at 4 yrs	OS at 4 yrs	Response to ICE chemotherapy		
				CR	PR	FAIL
	N	%	%	%	%	%
Low (0)	20	70	74	60	30	10
Int. (1)	40	39	49	28	58	15
High (2,3)	90	16	18	12	41	38

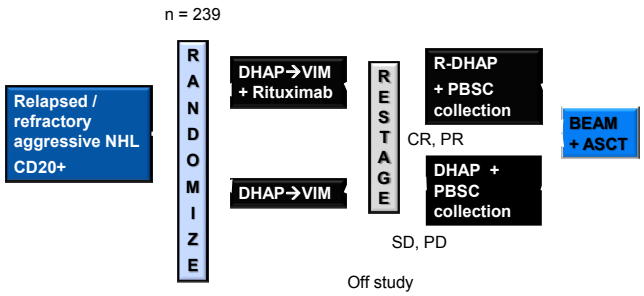
High Risk Patients can be identified PRIOR to second-line therapy

Overall survival: second-line age adjusted IPI



Hamlin PA *et al. Blood* 2003; **102**:1989–1996.

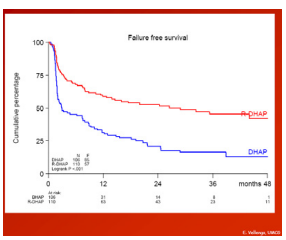
HOVON 44 randomized trial: salvage chemotherapy with or without rituximab

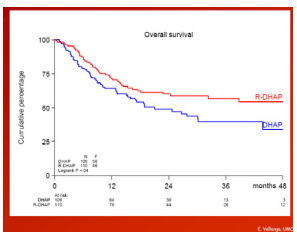


Primary endpoint: 2-year EFS

Vellenga E, *et al. Blood* 2006; 106:Abstract 328.

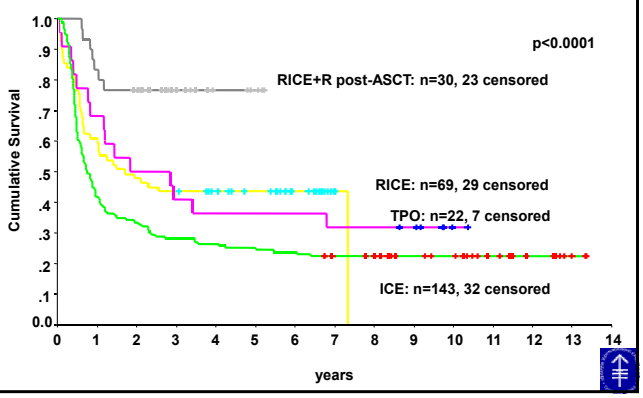
Rituximab improves treatment results of DHAP-VIM-DHAP and ASCT in Relapsed/Progressive Aggressive CD20(+) NHL. Prospective Rituximab HOVON Trial





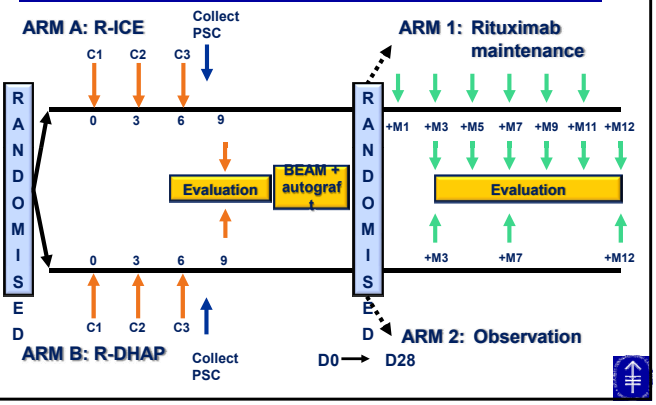
2 yr est.	DHAP	R-DHAP	Hazard Ratio	P value
FFS	21%	52%	0.4	<0.001
DFS	46%	82%	0.32	0.003
OS	48%	62%	0.61	0.03

EFS: Sequential ICE Programs, pre-CORAL (1993-2004)

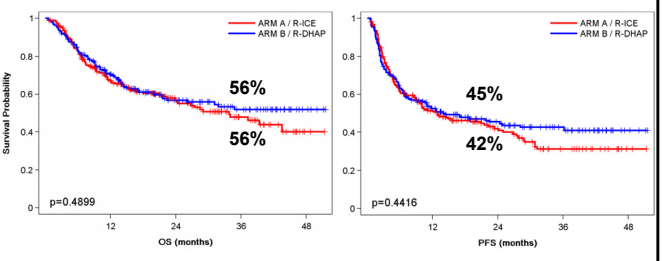


What happens if R-CHOP therapy does not work

CORAL trial (GELA and others): R-ICE vs R-DHAP



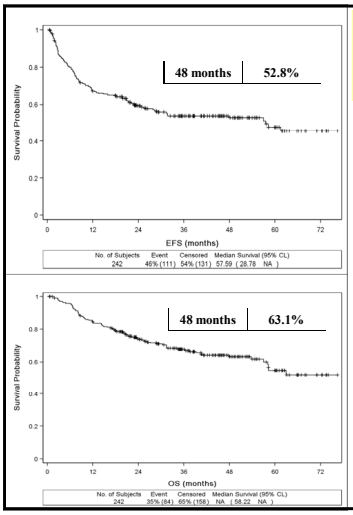
Coral Study: Outcomes RICE vs. RDHAP by ITT



Orlando ASCO May 2009 / Coral study C. Gisselbrecht

Results: Cox Regression Model for Event Free Survival

Prior rituximab	p < .01 3-year EFS 21% vs 47%
Relapse <12 months	p < .001 3-year EFS 20% vs 45%
Second-line aaIPI LR-LIR vs HIR-HR	p < .001 3-year EFS 18% vs 40%

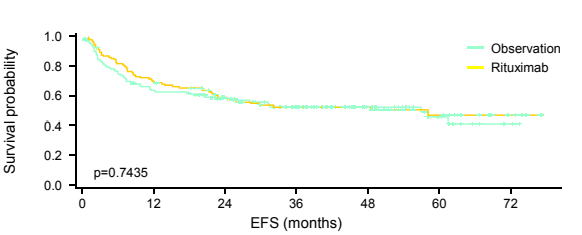


140 events were required to conclude.
Nowadays: 111 events
Final analysis of maintenance arm
ASCO 2011

Randomized in maintenance
N = 245
PR/CR →
RANDOMIZE
R x 6
N = 122
Obs
N = 120

Overall Survival of maintenance ITT population from date of 2nd randomization

CORAL Maintenance: Event-free Survival According to Treatment Arm (MITT)

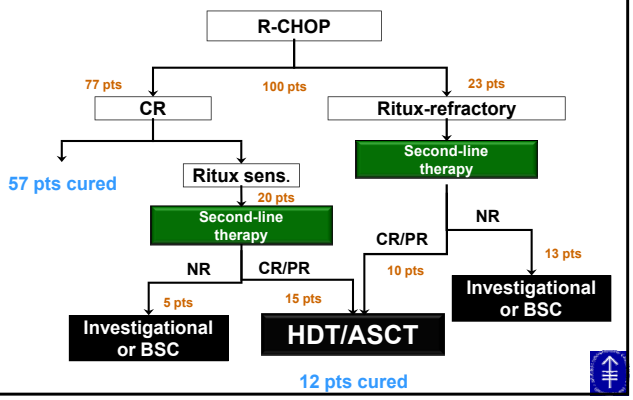


	No. of subjects	Event	Censored	Median	Survival (95% CL)
Observation	120	47% (56)	53% (64)	58.22	(25.89 NA)
Rituximab	122	45% (55)	55% (67)	57.59	(24.51 NA)

	Arm of 2nd randomization	N	Median	95% CI lower	95% CI Upper	Min	Max
EFS (months)	Rituximab	122	58	25	–	1	76
EFS (months)	Observation	120	58	26	–	1	74

Confidential Gisselbrecht

Management of transplant-eligible pts with DLBCL-2011

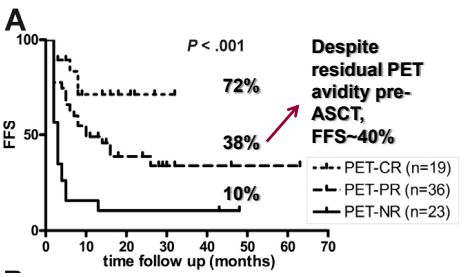


Relapsed / primary refractory DLBCL

- 5 year event-free-survival (EFS) in the rituximab era is <25% because:
  - No one is rituximab naiive
  - The majority of relapses occur within 12 months
  - The majority of patients have HIR/HR disease
- Chemosensitive disease is required for transplant eligibility in the USA
  - In the rituximab era, should a negative pre-ASCT FDG-PET scan be required
  - Patients with all 3 of the above risk factors should not get a RICE/RDHAP-based autotransplant program
  - What should oncologists do?

Can PET add prognostic information ?

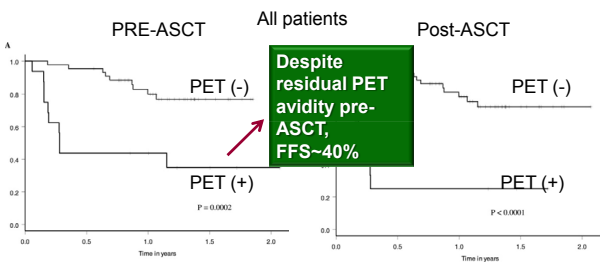
2 yr FFS: PET response



PR = minimal residual uptake

Schot, B. W. et al. Blood 2007;109:486-491

EFS according to pre and post ASCT PET results



1 yr EFS for aNHL: 79% vs. 42%

1 yr EFS for aNHL: 78% vs. 42%

Filmont, Gisselbrecht, Cuenca, et. Al. Cancer, Volume 110, Issue 6, 2007, Pages: 1361-1369

Priority of research in curable patients with relapsed/refractory DLBCL/HL should be to achieve a negative FDG-PET scan after salvage therapy

How is this going to be achieved?

What new agents can be incorporated?

The St. Thomas Hospital criteria

PET reporting

NEGATIVE SCAN
Score 1 no uptake
Score 2 uptake ≤ mediastinum
Score 3 uptake > mediastinum but ≤ liver

POSITIVE SCAN
Score 4: moderately ↑uptake > liver
Score 5 markedly ↑uptake > liver

Score X:
new areas of uptake unlikely to be related to lymphoma

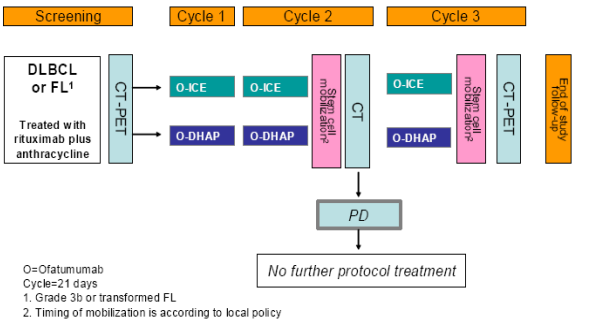
Courtesy of S. Barrinhton, Modena, 2009

DLBCL PET project at MSKCC

O-ICE/O-DHAP: Rationale

- **Ofatumumab (fully humanized IgG1κ anti-CD20) active in B-cell lymphoma**
  - **In vitro killing of rituximab-resistant Raji cell lines (low CD20 expression, high expression of CD55, CD59); similar ADCC to rituximab**
  - **Active and well tolerated as single-agent in relapsed CLL (6% gr3/4 infxn, 3% gr5 interstitial pna), 50% ORR**
  - **In FL, 2 patients had gr3 infxn, no gr4/5 toxicities; 43% ORR; 64% in rituximab-treated, and 3 of 4 rituximab-refractory patients responded**
- **Ofatumumab substitution in relapsed/refractory large cell lymphoma could potentially improve response rates**

O-ICE/O-DHAP: Study schema



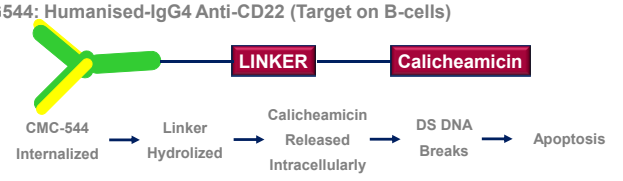
Safety, Pharmacokinetics, and Preliminary Clinical Activity of Inotuzumab Ozogamicin, a Novel Immunoconjugate for the Treatment of B-Cell Non-Hodgkin's Lymphoma: Results of a Phase I Study

Advani, et. Al.

Published online before print March 22, 2010, doi: 10.1200/JCO.2009.25.1900 *JCO April 20, 2010 vol. 28 no. 12 2085-2093*

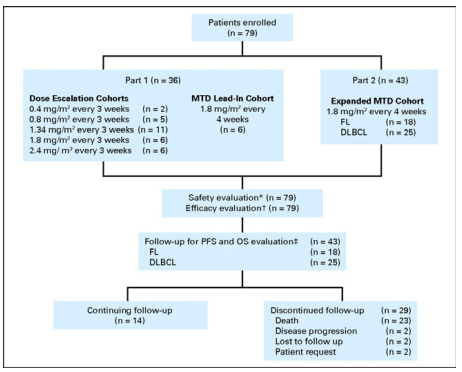
Inotuzumab ozogamicin

G544: Humanised-IgG4 Anti-CD22 (Target on B-cells)



- **Preferential delivery of a cytotoxin to tumor cells**
  - Specificity of target: CD22
  - Efficient internalization of immunotoxin
  - Linker: Stable in plasma, acid-labile
  - Potent cytotoxic component: calicheamicin
- **Reduction of non-specific toxicity (off-target effects)**

CONSORT diagram.

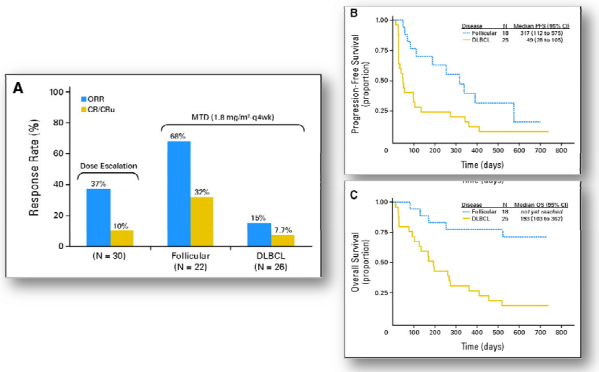


Advani A et al. JCO 2010;28:2085-2093

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JOURNAL OF CLINICAL ONCOLOGY

(A) Tumor response at end of treatment for all patients in dose-escalation cohorts and for all patients with follicular lymphoma and diffuse large B-cell lymphoma (DLBCL) receiving maximum-tolerated dose (MTD) treatment (lead-in cohort, n = 5; expanded MTD cohort, n = 43).



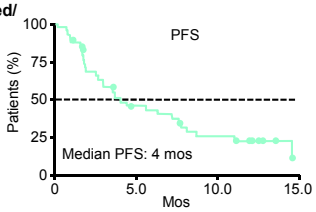
Advani A et al. JCO 2010;28:2085-2093

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Lenalidomide

- Lenalidomide: oral immunomodulatory agent
  - Antiangiogenic, less-toxic derivative of thalidomide
  - Recommended by NCCN as second-line regimen for MCL[1]
- Phase II study (N = 49) in relapsed/ refractory aggressive NHL[2]
  - ORR: 35%, including 12% CR/CRu
  - Responses seen in DLBCL, FL, MCL, transformed lymphomas
  - Primary grade 3/4 toxicity: myelosuppression

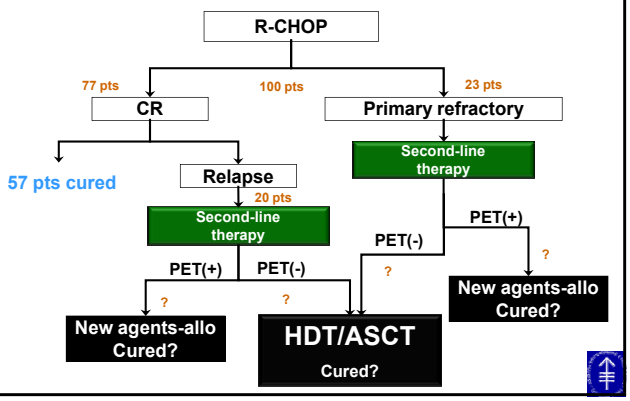


- Phase I/II trial of first-line lenalidomide plus R-CHOP in DLBCL or FL[3]

1. NCCN practice guidelines in oncology: non-Hodgkin's lymphomas. Available at: http:// www.nccn.org. 2. Wiernik PH, et al. J Clin Oncol. 2008;26:4952-4957. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved. 3. ClinicalTrials.gov. NCT00670358.

Add BTK trial

Management of transplant-eligible pts 2011



Lymphoma Service-MSKCC

- John Gerecitano
- Paul Hamlin
- Steve Horwitz
- Matt Matasar
- Alison Moskowitz
- Craig Moskowitz
- Ariela Noy
- Lia Palomba
- Carol Portlock
- David Straus
- Joachim Yahalom
- Andrew Zelenetz

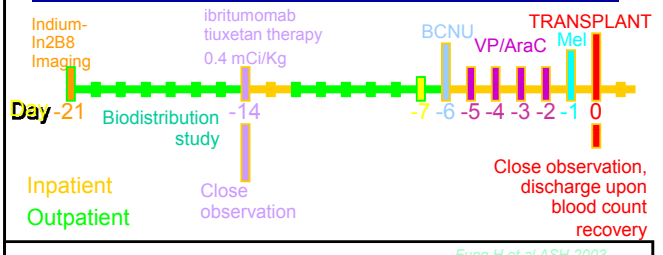
Improving conditioning regimen before ASCT

HIGH DOSE CONDITIONING REGIMEN

- **Conditioning regimens are designed to overcome drug resistance and stem cell autologous transplant to overcome toxicity**
- **Combination of drugs without TBI:**
  - **BEAM and others……**
- **Combination of drugs with TBI:**
  - **Cyc + Etoposide, Cytarabine+melphalan.**
- **Combination of drugs with involved field radiotherapy:**
  - **Pre transplant Parma study, MSKCC**
  - **Post transplant residual mass, routine practice**

TRIALS COMBINING CONVENTIONAL-DOSE RIT AND BEAM AS A CONDITIONING REGIMEN

(Z-BEAM)

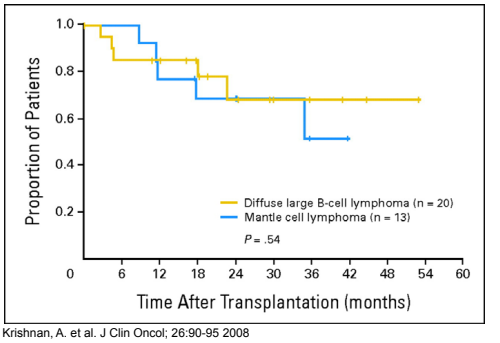


Fung H et al ASH 2003

Patients: 12 age: Median 61yr. 20-78 yr.
Histology: DLCL, MCL

- ^{90}Y ibritumomab tiuxetan 32 mCi (20.7-40) BEAM
- Time to recovery: WBC 11 days, platelets 11 jours

Phase II Trial of a Transplantation Regimen of Yttrium-90 Ibritumomab Tiuxetan and High-Dose Chemotherapy in Patients With Non-Hodgkin's Lymphoma



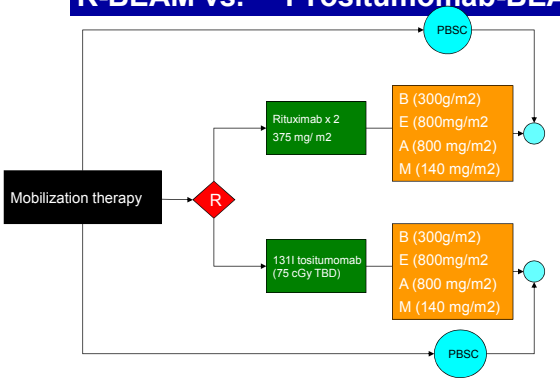
Krishnan, A. et al. J Clin Oncol; 26:90-95 2008

Fig 5. Progression-free survival by disease histology

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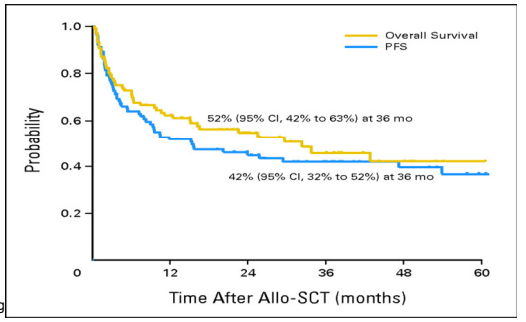
BMT CTN Phase III RCT: R-BEAM vs. ^{131}I Tositumomab-BEAM



IS THERE A PLACE FOR ALLOTRANSPLANTATION IN DIFFUSE LARGE B CELL LYMPHOMA?

Allogeneic Stem-Cell Transplantation As Salvage Therapy for Patients With Diffuse Large B-Cell Non-Hodgkin's Lymphoma Relapsing After an Autologous Stem-Cell Transplantation: An Analysis of the European Group for Blood and Marrow Transplantation Registry

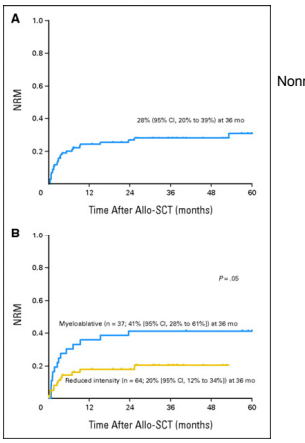
van Kampen R J et al. JCO 2011;29:1342-1348



Prog

©2011 by American Society of Clinical Oncology

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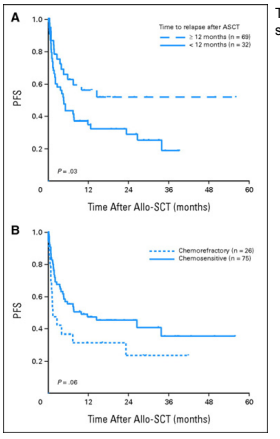


Nonrelapse mortality (NRM).

van Kampen R J et al. JCO 2011;29:1342-1348

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JOURNAL OF CLINICAL ONCOLOGY



Time to relapse and disease sensitivity.

van Kampen R J et al. JCO 2011;29:1342-1348

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CONCLUSIONS

- Prognostic factors in the rituximab era:
  - relapse < 12 months,
  - Secondary aa IPI 2,3,
  - pre-ASCT FDG-PET response

POOR RESULTS : RESPONSE RATE 50%
PFS 20%
BEST RESULTS : RESPONSE RATE 80%
PFS 60%

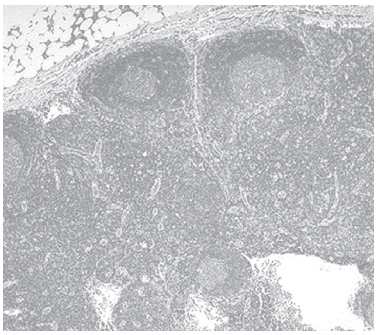
- **Understanding the biology of the disease to incorporate new agents targeting pathways.**
- **Are molecular DLBCL subtypes important**
- **Translational program should be developed**

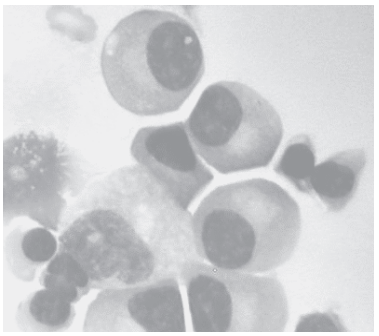
TREATMENT OPTIONS FOR DLBCL

Past	Present	Future Molecular subtypes
ICE	R-ICE	Dense- R
DHAP..	R-DHAP	New molecules: pathways adapted
What Else?	R- Other	(e.g. new anti CD 20, GA 101, CD40…. anti-angiogenics
± ASCT	± ASCT/ PET-evaluation	lenalidomide)
	OS benefit	± ASCT/ RIC allo
		Prolonging OS?

Better tolerability → increasing cure

Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies





Mantle cell lymphoma: How best to approach and treatment: Is there a role for maintenance?

Brad Kahl, MD

Mantle Cell Lymphoma – How best to approach and is there a role for maintenance?

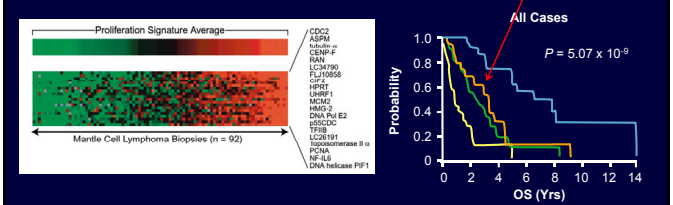
Brad Kahl, MD
University of Wisconsin

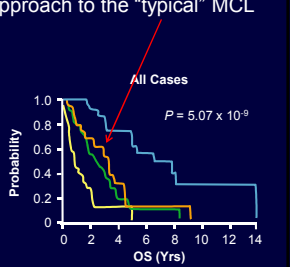
Frontline Treatment Considerations

- MCL not yet shown to be reliably curable with currently available frontline treatments
  - Treat for control rather than for cure in 2011 (like FL)
  - But clearly harder to control than FL
  - Hence the tendency to treat "aggressively"
- Prolongation of survival by frontline treatment choice has not been definitively shown
  - Hence several "reasonable" options (there are tradeoffs)
- There is no "standard of care" in MCL in 2011

Proliferation Signature in MCL

- Today's talk is geared towards the approach to the "typical" MCL





Reprinted from Rosenwald A, et al. Cancer Cell. 2003;3:185-197.

Approach to a newly diagnosed patient

R-CHOP ± MR	Less intensive
R-Bendamustine ± MR	
R-CHOP/RIT	
Modified HyperCVAD	
vs	
R-CHOP/ASCT	More intensive
R-HyperCVAD/MTX/Ara-C	
R-HyperCVAD/MTX/Ara-C/ASCT	
Nordic	

What does R-CHOP do for you in MCL?

Estimate ORR 90%, CR 40%, median PFS 18-24 months

Measure	DFCI[1]	GLGSG[2]	StiL[3]
Trial size	N = 40	N = 62	N = 48
Median age	55 (31-69)	62 (37-78)	70
ORR (%)	98	94	?
CR (%)	48	34	?
mPFS (months)	16	28*	22

[1]Howard O, et al. J Clin Oncol. 2002;20:1288-1294.

[2]Lenz G, et al. J Clin Oncol. 2005;23:1984-1992. Updated ASH 2007.*14 patients received aSCT.

[3]Rummel M, et al. Blood. 2009. ASH abstract #405.

StiL: First-line Bendamustine + Rituximab in Patients With FL, Indolent, and MCL

Stage III or IV CD20+ lymphoma

(N = 549)

Bendamustine-Rituximab
B 90 mg/m² on Days 1, 2 +
R 375 mg/m² day 1
Max 6 cycles, q4w
(n = 260)

R-CHOP
Max 6 cycles, q3w
(n = 253)

Rummel MJ, et al. ASH 2009. Abstract 405.

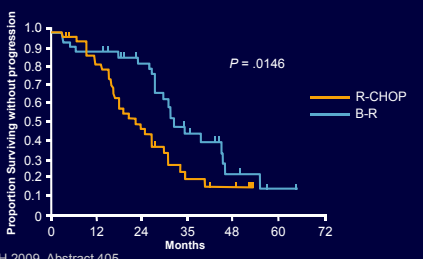
Entities

549 patients randomized. 513 patients evaluable for response and toxicity

		B-R	CHOP-R	Age
Total	n	260	253	64
Follicular	54 %	139	140	60
Mantle cell	18 %	45	48	70
Marginal zone	13 %	37	30	66
Waldenströms	8 %	22	19	64
SLL	4 %	10	11	68
Unclassifiable	2 %	7	5	69

StiL: PFS (Primary Endpoint)

- In subanalysis, B-R superior to R-CHOP in MCL (*P* = .0146)
- mPFS: R-CHOP 22 months. BR 33 months.



Rummel MJ, et al. ASH 2009. Abstract 405.

StiL: Toxicities

Toxicity	B-R (n = 260)	R-CHOP (n = 253)	*P* Value
Paresthesias, n	18	73	< .0001
Stomatitis, n	16	47	< .0001
Erythema, n	42	23	.0122
Allergic skin reaction, n	40	15	.0003
Infectious complications, n	96	127	.0025
Sepsis, n	1	8	.0190
Grade 3/4 myelosuppression, %			
▪ Neutropenia	10.7	46.5	< .0001
▪ Leukocytopenia	12.1	38.2	< .0001
▪ G-CSF administered	4.0	20.0	< .0001

- Less alopecia reported in B-R vs R-CHOP (*P* < .0001)

Rummel MJ, et al. ASH 2009. Abstract 405.

What is the optimal non-intensive approach?

- Hint of data that BR may be less toxic and more efficacious than CHOP-R
  - Clearly more data needed
- How to improve?
  - Limitations in how much one can "intensify" the remission inducing therapy
  - maintenance or consolidation strategies are attractive
    - Relatively easy to establish remission
    - Remission durability is the problem
  - Needs to be a well tolerated post remission therapy

First RCT for MCL Elderly
8 countries, n = 560 (Jan 2004-Oct 2010)

Newly diagnosed, >60 yr; performance 0-2, Stages II-IV, central PA review

8 x R-CHOP

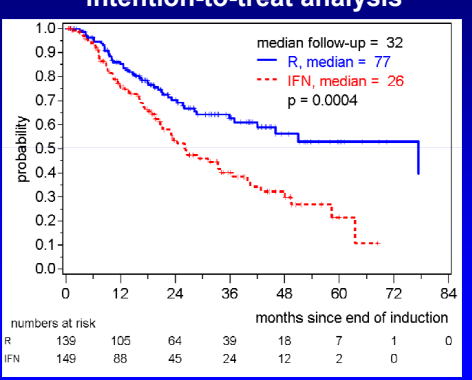
6 x R-FC

CR,CRu,PR

IFN-α maintenance (3 x 3 M IU/week) or Peg-IFN (1ug/kg week)

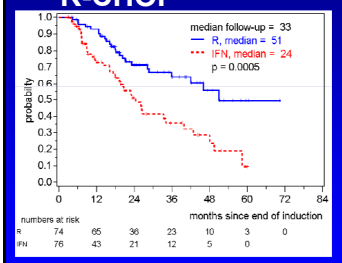
Rituximab maintenance (every 2 mos to PD)

MCL Elderly study
Remission duration maintenance
intention-to-treat analysis

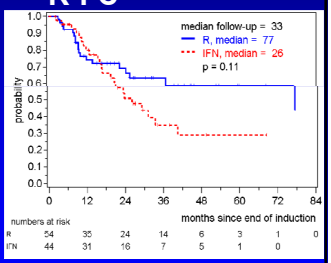


MCL Elderly study
Remission duration related to induction

R-CHOP

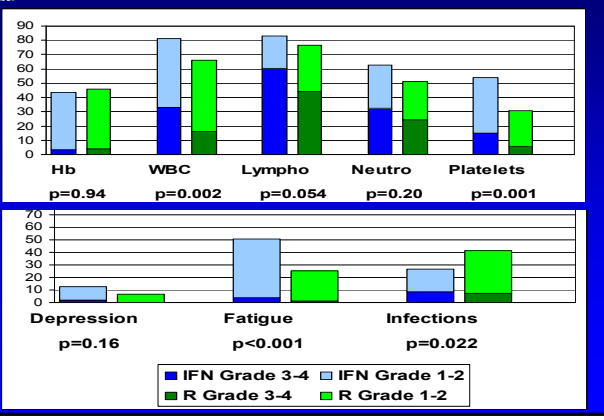


R-FC



p=0.41 for interaction of induction and maintenance

Toxicity of IFN and rituximab



Maintenance Rituximab for MCL

- European study demonstrated MR doubles remission duration compared to IFN (after R-CHOP)
- Benefit not seen after FCR
  - Significant toxicity from FCR. Most patients never made it to 2nd randomization.
- OS benefit noted in R-CHOP subgroup
  - Study stopped early by DSMB
- Study complicated
  - 2 x 2 factorial design with lots of drop out
  - MR compared to IFN

My current approach to patients for whom non-intensive strategies are appropriate

- R-bendamustine followed by MR (for 2 years)
  - Admittedly an extrapolation of existing data
    - Bendamustine MOA is alkylator
    - MR makes sense in non-curative disease where the challenge is keeping patients in remission
    - UW data supports MR notion
      - 2 studies demonstrated median PFS ~ 3 yrs with MR
- R-CHOP followed by MR would be very reasonable
  - And have more data behind it

Patients for Whom a Dose-Intensive Approach Is an Option

Less intensive
- R-CHOP
- Modified HyperCVAD
- R-CHOP/RIT
- R-Bendamustine

vs

More intensive
- R-CHOP/ASCT
- R-CHOP_R-DHAP/ASCT
- R-HyperCVAD/MTX/Ara-C
- Nordic

What does an intensive approach get you in MCL?

Estimate ORR 95%, CR 60-70%, median EFS 4-5 years

Trial	N	Age	3 yr EFS	5 yr EFS	Comments
R-CHOP-ASCT[1]	249	55	60%	40%	Unpublished. Short follow up
R-CHOP/R-DHAP ASCT[1]	248	56	75%	65%	No OS difference.
CALGB 59909[2]	78	57	59%	46%	Median follow up 4.7 years.
Nordic[3]	160	56	70%	60%	Updated Lugano 2011.
MD Anderson[4]	99	61	65%	50%	Single inst. updated 2010

[1]Hermine O, et al. ASH 2011. abstract #110.

[2]Damon LE, et al. J Clin Oncol 2009;36:6101-6108

[3]Geisler CH, et al. Blood 2008;112:2687-2693.

[4]Romeguera JE, et al. J Clin Oncol 2005;23:7013-7023.

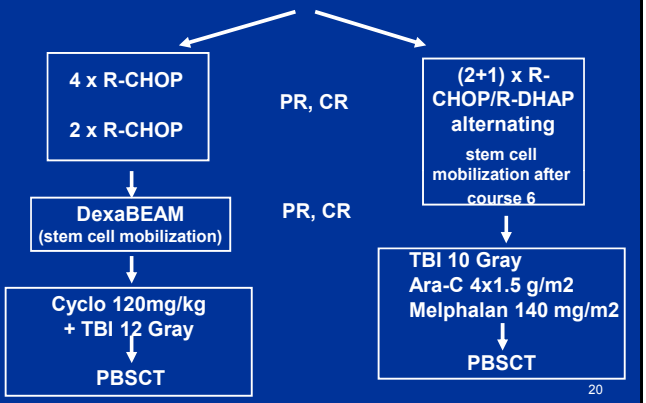
Efficacy of 6 courses CHOP plus Rituximab followed by myeloablative radiochemotherapy and autologous stem cell transplantation versus alternating courses of 3x CHOP and 3x DHAP plus Rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (MCL Younger Trial)

Olivier Hermine, Eva Hoster, Jan Walewski, Vincent Ribrag, Nicole Brousse, Catherine Thieblemont, Reddah Bouabdallah, S. Stilgenbauer, Pierre Feugier, R Forstpointner, Corine Haouin, M Kneba, Mathias Hänel, René Olivier Casasnovas, J. Finke, M Hallek, H. Wandt, A Bosly, Wolfram Klapper, Christian Gisselbrecht, Bertrand Coiffier, Wolfgang Hiddemann, Michael Unterhalt, Martin Dreyling
On Behalf of the *European Mantle Cell Lymphoma Network*

European MCL Network

ClinicalTrials.gov: NCT00209222

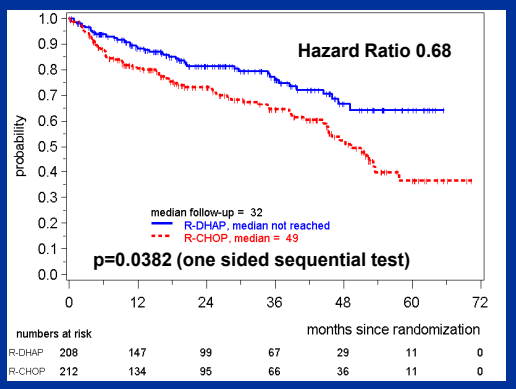
MCL younger Protocol Design



20

Update November 19, 2010, European MCL Network, V0.3 26.11.2010

Time to treatment failure



21

Update November 19, 2010, European MCL Network, V0.3 26.11.2010

Intensive strategies for MCL

- European RCT suggests the way you get to SCT may matter (for PFS)
  - Note the 2 conditioning regimens differed
- In 2011 several reasonable intensive strategies
  - R-CHOP + ASCT (not my favorite)
  - R-CHOP/R-DHAP + ASCT
  - Nordic approach
  - MD Anderson approach

MCL: No standard of care in 2011

- NCCN guidelines
  - Lists 5 intensive options
  - Lists 6 non-intensive options
- Clinical trial usually the best option
  - Hope to define standards of care upon which future regimens can be compared

Intergroup (SWOG/ECOG/CALGB) MCL trial

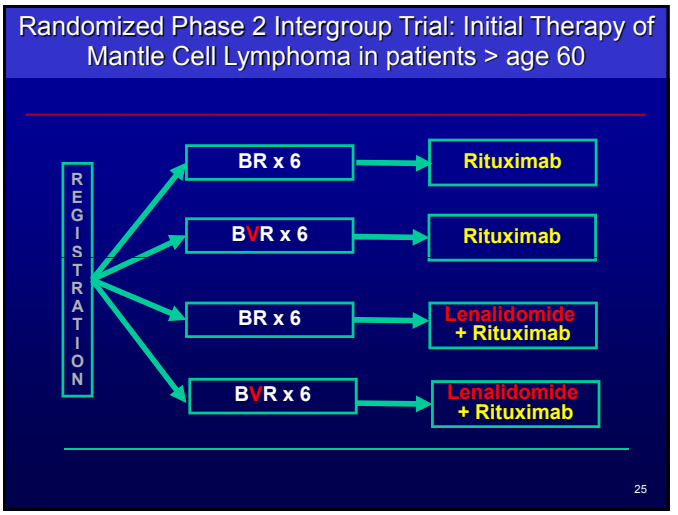
"A Randomized Phase II Trial of R-HCVAD-MTX/ARA-C Induction Followed by Consolidation With an ASCT vs. R-Bendamustine Induction Followed by Consolidation With an ASCT for Previously Untreated Patients ≤ 65 Years of Age With Mantle Cell Lymphoma"

Treatment:

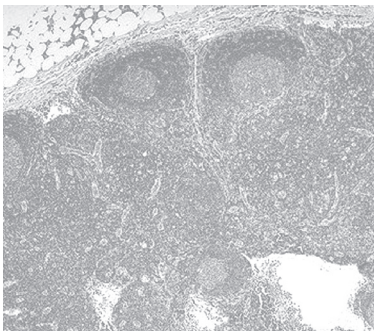
Randomization to one of two regimens:

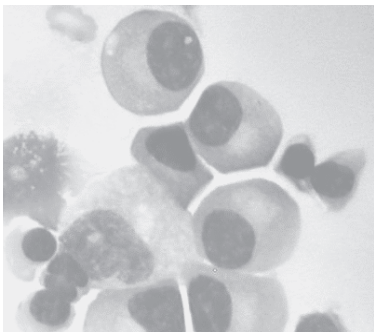
1.R-HCVAD-MTX/ARA-C X 4 cycles; ASCT

2.R-Bendamustine X 6 cycles; R-Cy mobilization; ASCT


Randomized Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma in patients > age 60
REGISTRATION
BR x 6
Rituximab
BVR x 6
Rituximab
BR x 6
Lenalidomide + Rituximab
BVR x 6
Lenalidomide + Rituximab
25

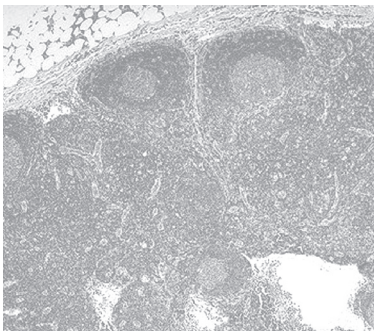
Lymphoma & Myeloma 2011
An International Congress on Hematologic Malignancies

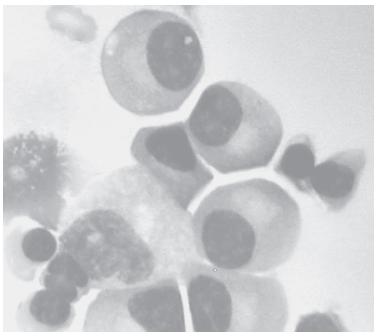




Double hit aggressive lymphoma

Kieron Dunleavy, MD





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Mayo Clinic

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Lochman P[1,2], Leško M[2], Páral J[1,2]

[1]Department of Field Surgery, Faculty of Military Health Sciences, University of Defense, Hradec Kralove, Czech Republic, [2]Department of Surgery, University Hospital, Hradec Kralove, Czech Republic

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[1]Clinical Center of Serbia, Belgrade, [2]Institute for Medical Research, Belgrade, Serbia, [3]Harvard Medical School, Boston, USA

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[1]Department of Medicine, Rhode Island Hospital, Providence, RI, USA, [2]Division of Hematology and Oncology, The Miriam Hospital, Providence, RI, USA, [3]Department of Medicine, Rhode IslandHospital, Providence, RI, USA, [4]Division of Hematology and Oncology, Moffitt Cancer Center, Tampa, FL, USA, [5]Department of Medicine, The Miriam Hospital, Providence, RI, USA, [6]Department of Medicine, The Miriam Hospital, Providence, RI, USA, [7]Division of Hematology and Oncology, The Miriam Hospital, Providence, RI, USA

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[1]Weill Cornell Medical College, New York City, NY, USA, [2]Portola Pharmaceuticals Inc., South San Francisco, CA, USA

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[1]Hematology Department, MD Anderson Madrid. Spain, [2]Cardiology Department, Fundación Jimenez Díaz-Capio, Madrid, Spain.

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[1]The Miriam Hospital, Providence, RI, USA, [2]Edgardo Rebagliati Martins Hospital, Lima, Peru, [3]Pusan National University Hospital, Pusan, South Korea, [4]University Hospital Center Zagreb, Zagreb, Croatia, [5]Helsinki University Central Hospital, Helsinki, Finland, [6]Kurume University School of Medicine, Kurume, Japan, [7]University of Insubria, Varese, Italy, [8]Ruijin Hospital, Shanghai, China, [9]Rhode Island Hospital, Providence, RI, USA

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[1]Hospices Civils de Lyon, Lyon, France, [2]Fox Chase Cancer Center, Philadelphia, PA, USA, [3]Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [4]Yale Cancer Center, New Haven, CT, USA, [5]Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia, [6]Moffitt Cancer Center, Tampa, FL, USA, [7]Royal North Shore Hospital, Sydney, Australia, [8]Hospital Universitario de Salamanca, Salamanca, Spain, [9]Klinikum der Universität zu Köln, Cologne, Germany, [10]Celgene Corporation, Cambridge, MA, USA

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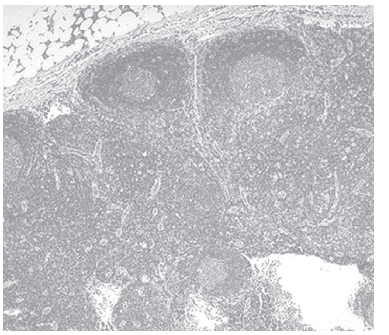
Synchronous Hodgkin Lymphoma and Pregnancy: A Single Institution Experience

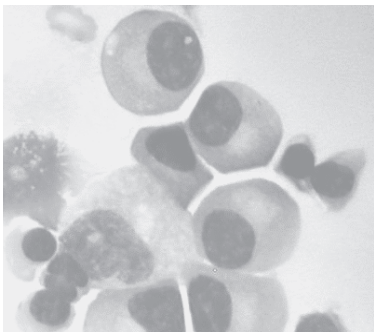
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[1]University of Benin, Benin city. Nigeria, [2]University of Benin, Benin city. Nigeria

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[1]University of Benin

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[1]Serviço de Hematologia, Hospital do Cancer -I, Instituto Nacional de Cancer - Brazil, [2]Serviço de Hematologia, Hospital do Cancer -I, Instituto Nacional de Cancer - Brazil, [3]Laboratório de Hemato-Oncologia Celular e Molecular, Coordenação Técnico Científica,Instituto Nacional de Cancer - Brazil

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[1]University of Birmingham, UK, [2]The Binding Site Group Ltd, UK, [3]Cardiff University, UK, [4]Royal Bournemouth Hospital, UK

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[1]University of Connecticut**,** [2]Hartford Hospital, Hartford, CT

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[1]The Royal Wolverhamptom Hospital Trust, UK, [2]The Binding Site Group Ltd, Birmingham, UK, [3]University of Birmingham, Birmingham, UK

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[1]Stem Cell Laboratory- Clinical Hematology UZ Brussel, Brussels, [2]Department Hematology-Immunology VUB, Brussels, Belgium, [3]Hopital Claude Huriez, Lille, France

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[1]United BioSource Corp., Lexington, MA, USA, [2]Aptium Oncology, Los Angeles, CA, USA, [3]Northwestern University, Chicago, IL, USA, [4]Somerset Hematology Oncology, Somerville, NJ, USA, [5]Providence Cancer Institute, Southfield, MI, USA, [6]Indiana University, Indianapolis, IN, USA, [7]Mayo Arizona, Scottsdale, AZ, USA, [8]Duke University Medical Center, Durham, NC, USA, [9]Alliance Hematology Oncology, Westminster, MD, USA, [10]Rocky Mountain Cancer Centers, Denver, CO, USA, [11]MD Anderson Cancer Center, Houston, TX, USA, [12]Celgene Corporation, Summit, NJ, USA



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[1]Dept. of Hematology, Metaxa Anticancer Hospital of Piraeus, [2]Blood Donation Unit, General Hospital of Florina, [3]Blood Donation Unit, Metaxa Anticancer Hospital of Piraeus

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[1]John Theurer Cancer Center, Hackensack, NJ, USA, [2]University of California, San Francisco, CA, USA, [3]MD Anderson Cancer Center, Houston, TX, USA, [4]Washington University School of Medicine, St. Louis, MO, USA, [5]Emory University School of Medicine, Atlanta, GA, USA, [6]Princess Margaret Hospital, Toronto, ON, Canada, [7]Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta, Canada, [8]H. Lee Moffitt Cancer Center, University of South Florida, Tampa, FL, USA, [9]City of Hope National Medical Center, Duarte, CA, USA, [10]Mayo Clinic, Rochester, MN, USA, [11]Northwestern University School of Medicine, Chicago, IL, USA, [12]Mount Sinai Medical Center, New York, NY, USA, [13]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

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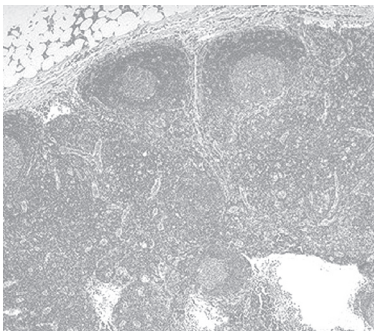
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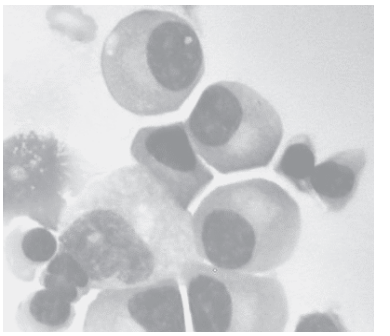
Bakiri N[2], Perez E[2], Pequin A[2], Zunic P[2], Agapé P[2], Saly J[2], Henni T[2], Belkaid I[1]
[1]Hopitaux Civils de Colmar, [2]Centre Hospitalier Régional de la Réunion

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Lahey Clinic Medical Center, Burlington, MA, USA





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The John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ USA

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*Scudla V[1], Herman M[2], Minarik J[1], Pika T[1], Hrbek J[2], Bacovsky J[1], Czech Myeloma Group

[1]Department of Internal Medicine III, [2]Department of Radiology, Palacky University, Olomouc, Czech Republic

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Scudla V[1], Petrova P[2], [1], Pika T[1], Minarik J[1], Bacovsky J[1], Czech Myeloma Group

[1]Department of Internal Medicine III, [2]Department of Clinical Biochemistry, Palacky University, Olomouc, Czech Republic

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[1]University Hospital, Nantes, France, [2]The Binding Site Group Ltd, UK, [3]Institut Curie, Paris, France, [4]University Hospital, Toulouse, France

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Multiple soft tissue lymphoplasmacytic lymphoma associated with Waldenstrom's macroglobulinemia

He X, Narain S, Croopnick J

Metrowest Medical Center, 115 Lincoln St, Framingham, MA 01701

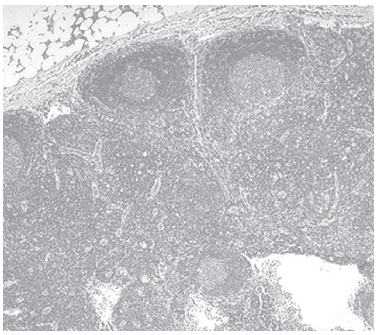
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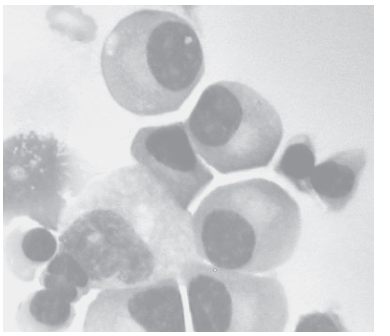
Spindle like morphology of the KSHV- LANA interacting protein one (KLIP1) is necessary for proper mitotic cell division

Bera A[1], Friend S[2], Kuhne K[1], George T[2], Gao SJ[1,3,4,5,6]

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Abstracts

O-1. Synchronous Non-Hodgkin Lymphoma and Pregnancy: A Single Institution Long-Term Experience

Habermann T, Ristow K, Colgan J, Kurtin P, Ansell S, Johansen K, Thompson C, Witzig T

Mayo Clinic

The synchronous presentation of non-Hodgkin lymphoma (NHL) and pregnancy is complex and presents significant challenges. The Mayo Clinic medical registry and the Mayo Clinic Lymphoma Data Base identified a documented histologic diagnosis of non-Hodgkin lymphoma (NHL) with a synchronous pregnancy or in the immediate postpartum period in 15 patients from 1955 to 2011. The median age was 34 years (range 23-43 years). Seven patients were diagnosed in the second, 3 in the first, and 3 in the third trimester with two presentations in the immediate post-partum period. Three patients presented with “B” symptoms. There were eleven mature B-cell neoplasms (diffuse large B-cell lymphoma 4, follicular lymphoma grades 1-3a (FL) 3, primary DLBCL of the CNS 2, MALT 1, and Burkitt lymphoma 1) and 4 T-cell NHL. Patients were managed with a variety of treatment strategies. The median survival of all patients was 4 years 6 months (range 1.2 months to 32 years 2 months). The median survival of patients with FL was 9.5 years (range 8 years 10 months to 32 years 2 months). Three of the four patients with DLBCL were managed in the anthracycline era with a median survival of 22 years 2 months (range 1 year 11 months to 22 years 3 months. The patient with the 1 year 11 month survival died of a secondary acute non-lymphocytic leukemia. There were 4 patients with a T-cell NHL (peripheral T-cell NHL NOS 2, ALK-1 negative anaplastic large cell lymphoma (relapse with disease duration of 7 years and 7 months), and extranodal NK/T-cell lymphoma nasal type 1). The median survival of the three patients with a new diagnosis was 5 years 9 months (range 1.5 months-29 years). The long-term maternal survival revealed 5 alive and disease free, 1 alive and not disease free, 4 died from disease, 4 deaths were related to complications of therapy, and one patient died not as a complication of therapy (cerebral vascular accident 32 years later). There was one stillbirth in the third pregnancy of a patient with FL. Fourteen infants were delivered with a variety of approaches. Four infants were delivered at 31 to 34 weeks, 5 weeks 36 to 39, and 4 at week 40. Four patients had a “flare” in their disease post delivery. In conclusion, the management of patients with synchronous NHL and pregnancy is complex and the histologies are varied favoring aggressive disorders. Prolonged survival times are achievable. Optimal management requires a multi-disciplinary team with knowledge in high-risk pregnancy, the natural history of different lymphoma subtypes, the pharmacology of chemotherapeutic agents, the side effects of radiation exposure (diagnostic and therapeutic) to the patient and the fetus, psychosocial issues, and ethical issues.

O-2. Myeloma-initiating cells are enriched in CD138+/CD38high cells and can be eliminated through an anti-CD47 antibody therapy

Kim D, Wang J, Willingham S, Weiskopf K, Weissman I

Stanford University School of Medicine, Stanford, CA 94305

Purpose of the study: Multiple myeloma is a clonal plasma cell neoplasm that frequently recurs in patients even after initial responses to therapies. This frequent relapse implicates the existence of therapy-resistant myeloma-initiating cells in patients. Therefore, the eradication of these cells may be an important step for the treatment of myeloma patients.

Summarized description of the project: We prospectively identified a long-lived myeloma-initiating cell population in patients, examined the heterogeneity of myeloma cells and the tumorigenicity of subpopulations of myeloma cell line RPMI8226, and investigated the anti-myeloma activity of anti-CD47 antibodies whose target, CD47 is highly expressed in all myeloma cells.

Results and Conclusions: To identify myeloma-initiating cell populations, we transplanted patient myeloma cells into human fetal bone-bearing immunocompromised mice and analyzed the engraftment of patient myeloma cells. These human bone-bearing mice engrafted both $CD19^{+}CD38^{-/low}$ B and $CD138^{+}/CD38^{high}$ plasmablast/plasma cells but the repopulation of cells clonal to patient myeloma cells was observed only in mice transplanted with $CD138^{+}/CD38^{high}$ cells and not $CD19^{+}CD38^{-/low}$ cells (4/4 vs. 0/4, $p<0.01$). Further fractionations and transplantations demonstrated that $CD19^{-}/CD45^{low/-}CD138^{+}/CD38^{high}$ cells but not $CD19^{+}/CD45^{+}CD138^{+}/CD38^{high}$ cells enrich myeloma-initiating cells. These results suggest that myeloma-initiating cells are a subset of fully differentiated plasma cells but not of less-differentiated plasmablasts or B cells. Consistent with the characteristics of patient myeloma-initiating cells, we did not observe B cells in RPMI8226 and NCI H929 myeloma cells based on their immunophenotypes. However, each cell line is composed of heterogeneous plasma cells in their immunophenotype, proliferation ability and morphology. In particular, RPMI8226 is composed of a majority of $CD45^{-}$ cells and a small number of $CD45^{+}$ cells. Serial transplantation studies indicated that both $CD45^{+}$ and $CD45^{-}$ cells have tumor-initiating abilities in the frequency of 1:400 and 1:2,000 in $RAG2^{-/-}\gamma_c^{-/-}$ mice, respectively. Fractionated $CD45^{+}$ cells gave rise to tumors with both $CD45^{+}$ and $CD45^{-}$ cells, but $CD45^{-}$ cells resulted in tumors with only $CD45^{-}$ cells. The $CD45^{-}$ focal pattern in a $CD45^{+}$ tumor, immature morphology and tumor-initiating ability of the $CD45^{-}$ cells suggest that $CD45^{-}$ myeloma-initiating cells might be formed through the clonal evolution process, implying the contribution of clonal evolution to intra-tumoral heterogeneity. In spite of their intra-tumoral heterogeneity, we observed that all myeloma cells - including myeloma-initiating cells - in patients and cell lines expressed CD47 at high levels compared with other bone marrow cells. Blocking CD47, a “don’t eat me” signal, with an anti-CD47 antibody significantly enhanced phagocytosis of myeloma cells in cell lines and patients by macrophages *in vitro*. In addition, anti-CD47 antibody blocked or retarded myeloma growth compared with control immunoglobulin or PBS in xenograft models with or without human bone grafts. Finally, we observed that anti-CD47 antibody inhibited the engraftment of patient myeloma cells into human bone-bearing mice. In conclusion, our studies suggest that myeloma-initiating cells, in spite of their heterogeneity, are enriched in $CD138^{+}/CD38^{high}CD19^{-}CD45^{low/-}$ plasma cells and that anti-CD47 antibodies is a candidate anti-myeloma drugs targeting myeloma cells, including myeloma-initiating cells.

P-1. CD20 Negative Relapse Following Rituxumab Therapy in a Patient with Low Grade NHL-Case report

Stankovic S

University Clinic of Hematology, Skopje, Macedonia

Background: Rituximab is a key molecular targeting drug for CD20 positive B-cell lymphomas. Recently, resistance to Rituxumab has been recognised to be a considerable problem in re-treatment patients .The mechanism of resistance to Rituximab retreatment in non-responding patients is unknown, but it is possible that loss of CD20 expression in the relapsed NHL could be important in some cases.

Aims: Here we present a patient with CD20 positive low grade B-cell NHL that lost the CD20 expression at relapse after Rituxumab therapy.

Case presentation: A 39-year-old female was admitted at our hospital with a diagnosis of Non-Hodgkin lymphoma (CLL/SLL). Immunohystochemical analysis on diagnostic samples of the axilar lymph node biopsy showed CD20 positive expression with proliferative centres positive for Ki67 that responds to pseudofolicular variant. The patient was treated according to R-CVP protocol (Rituxumab 375mg/m² on day 1, Vincristine 2 mg on day 2, Cyclophosphamide 400mg/m² and Prednisolon 50mg daily on days 2-6, every 28 days, eight courses). Maintenance therapy with Rituxumab was continued on three months intervals. At ten months from initial therapy conclusion, a relapse of the lymphoma was found. The second-line therapy according to R-CHOP protocol was started (Rituxumab 375mg/m² on day 1, Vincristine 2 mg, Cyclophosphamide 750mg/m², Doxorubicin 50mg/m² on day 2 and Prednisolon 100mg daily on days 2-6). Partial remission was achieved after 8 cycles of therapy that lasted one year when further recurrence of the lymphoma occurred consisting of lymph nodes enlargement and WBC 94000/mm³. The patient was then treated with 6 new cycles of chemo-immunotherapy according to FCR protocol (Rituxumab 375mg/m² on day 1 and Fludarabine 25mg/m² and Cyclophosphamide 250mg/m² on days 2-4). The achieved partial response lasted 4 months when new lymph node enlargement and leucocytosis of up to 220000/mm³ occurred. Flow cytometric analysis of peripheral blood demonstrated loss of CD20 expression on malignant lymphocytes, while CD19 and CD5 were positive in 80% cells. Father therapy with high-dose Methyl-prednisolon was started.

Conclusions: Our observation confirmed the hypothesis already described in literature, that a CD20 negative phenotypic change could occur in certain number of patients with CD20 positive B-cell lymphomas. As such, CD20 expression by both flow cytometry or immunochisochemistry should be undertaken to document CD20 expression prior to considering repeated courses of Rituxumab in relapsed Non-Hodgkin lymphomas.

P-2. Results of Radiation Therapy for Primary Extranodal Lymphoma of the Head and Neck: A Report of Case Series.

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Purpose: Radiation therapy is an important treatment modality for the extra-nodal lymphoma (ENL) of the head and neck. Intensity Modulated radiation therapy (IMRT) has been shown for head and neck cancers to be associated with decreased late side effects like Xerostomia compared with conventional RT techniques (Conv.RT). The purpose of the study is to determine the clinico-pathological features, treatment outcomes and late toxicities in patients (pts) with ENL of head and neck treated with different RT techniques.

Methods: Retrospective review of records from 2007-2010 identified 14 pts with ENL of the head and neck treated with RT at Fox Chase Cancer Center. Eight were treated with IMRT and 6 with conventional RT technique. Thirteen had CD20+ non-Hodgkin lymphoma [NHL; 7 diffuse large B cell (DLBCL), 3 MALT, 3 others], and one Hodgkin's lymphoma (HL; classic). All pts underwent routine staging work-up with negative bone marrow biopsy for all. Pre and post-treatment PET scan was done in 7 pts. Initial chemotherapy (R-CHOP x 4-6 courses for DLBCL, ABVD x 4 for HL), or no chemotherapy (MALT) was followed by involved field radiation therapy (median RT dose: 36 Gy for NHL, 30 Gy HL, 150- 180 cGy per fraction in 20 fractions over 4 weeks).

Results: The median follow up was 28 months (range: 1- 52). The median age was 60 years (range: 42-95; 7 males and 7 female). Nine had stage IEA disease, 3 had stage II and 2 stage IV. Five had oropharynx involvement, two had paranasal sinus (DLBCL) 2 nasopharynx (1 DLBCL, 1 MALT) and 1 vallecula (HL). The overall response rate after combined modality treatment was 100%. There were no FDG avid lesion noted on post-treatment PET. There were no local or neck node relapses at last follow up. The 2-year actuarial survival rate was 80%. One DLBCL patient had systemic relapse involving stomach and bilateral testes, was treated with second-line chemotherapy and radiation therapy. At the last follow up, 12/14 were alive. RTOG grade 2 acute skin changes were noted in 6 pts (3 by each RT technique), grade 2 mucositis in 5 pts (3 with Conv.RT) and grade 2 xerostomia in 6 pts. None of the pts developed grade 3 xerostomia (both acute and late). Late grade 2 Xerostomia was seen in 5 pts treated with Conv.RT but not with IMRT.

Conclusions: RT following chemotherapy or used alone in ENL of head and neck was associated with local and distant disease control in the majority of patients, with a toxicity profile that appears favorable for IMRT compared with conventional radiotherapy techniques. Larger studies are required to confirm that IMRT is as effective as conventional involved-field RT.

P-3. Primary gastric lymphoma invading spleen, pancreas and transverse colon

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Introduction:

Primary gastric lymphoma involves only 5 % of all gastric malignancies, but it is the commonest extranodal lymphoma at all. Chemotherapy, actinotherapy, surgery or their combination play role in the treatment, however optimal method, especially in early stages, still remains controversial.

Case Report:

55-year-old man was examined for 2 months lasting abdominal pain in the left flank, weight loss and melena. Gastroscopy had shown ulcer lesion of proximal third of stomach which penetrated to the spleen. Multiple biopsies taken revealed diffuse large B cell lymphoma that invaded the spleen, pancreas and transverse colon according to abdominal CT scan. Patient underwent proximal gastrectomy with splenectomy, left side pancreatectomy and extended left colectomy. The postoperative course was complicated with subphrenic abscess formation on the left side, which was managed conservatively, and laparotomy healing by secondary intention.

Conclusion:

Opinions regarding optimal method of treatment have been evolving within recent years. Thanks to improvement of diagnostics number of surgeries is continually decreasing. The next reason is undoubtfully relatively high postoperative morbidity and comparable results of non-surgical methods of treatment. Surgery is currently not method of choice in the treatment of primary gastric lymphomas. It has been still reserved for complicated cases (obstruction, bleeding, perforation etc.) and those ones where local disease persists after non-surgical treatment.

P-4. Disappearance of the Bcl6 positivity as a marker of germinal center in relapsed diffuse large B-cell lymphoma

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Purpose of the study: Diffuse large B-cell lymphoma (DLBCL) is the most complex and heterogeneous lymphoma in adulthood presented as a biologically and clinically distinct subtypes including germinal centre B-cell-like (GCB) and activated B-cell-like (ABC). In DLBCL BCL-6 is associated with the germinal centre subtype and has a good response to modern chemotherapy. It is known that BCL-6 expression is a favorable prognostic factor in DLBCL. However, the effect of BCL-6 expression on relapse of the DLBCL was not studied. The aim of this study was to show Bcl-6 gene expression changes and biological response in relapsed DLBCL and their patterns which include: LDH, b2M, CRP, Fe, ferritin, TIBC, hemoglobin, uric acid and International Prognostic Index (IPI).

Summarized description of the project: We investigated 43 (21F/20M) patients with relapsed DLBCL and role of immunohistochemically determined Bcl6 tested in 22 patients. All patients were treated with R-CHOP protocol. We also investigated biological parameters such as LDH, b2M, CRP, Fe, ferritin, TIBC, hemoglobin, uric acid level as well as IPI at the presentation of DLBCL and at the time of relapse. Mean age of female patients was 53.1±12.7 vs. male 52.8±12.1 and overall age of patients was 53.0±12.3SD years with no significant difference. Investigated relapsed group of 41 patients with DLBCL had own control at the beginning of diseases.

Results and conclusions: From 22 immunohistochemically (IHC) investigated patients for Bcl6 protein expression, 19/22 was positive and 3/22 was negative at the beginning. DLBCL was diagnosed in gastrointestinal tract (13), liver and spleen (7) lungs (5), CNS (4), ovarian (2), vertebral (1), and lymph nodes (9). Patients with Bcl6 negative relapses of DLBCL had very aggressive lymphoma, malignant in nature with the biological responses including significant higher levels of the LDH (1832.5±443.8 SD in relapsed vs. 457.3±88.3 SD U/L at presentation) ($p<0.0001$), b2M (8.4±0.8 vs. 2.5±0.8 mg/L) ($p<0.0001$), CRP (35.9±11.4 vs. 2.5±0.7 mg/L) ($p<0.0001$), uric acid (287.2±65.7 vs. 153.9±33.1 µmol/L) ($p<0.0001$), and significantly low ($p<0.01$) Fe (11.2±4.4 vs. 21.8±7.6 µmol/L) ($p<0.008$), TIBC (35.5±9.2 vs. 46.8±7.0 µmol/L) ($p<0.009$), hemoglobin (91.7±13.2 vs. 126.5±8.6 g/L) ($p<0.0001$), and significantly higher ferritin (2735.6± 628.2 vs. 88.5±20.2 µg/L) ($p<0.0007$) at the time of relapse DLBCL. At diagnosis all 19/22 patients were Bcl6 positive (IHC) and switched to Bcl6 negative at the time of relapse. IPI index as biological indicator was initially vs. relapse 2.01±0.8 vs. 4.4±0.6 respectively ($p<0.0001$). The Bcl-6 negative relapses of DLBCL was associated with very aggressive lymphoma and significant increase of the biochemical parameters such as LDH, B2M, CRP, uric acid, ferritin and significant decrease of serum Fe, TIBC, hemoglobin resulting in anemia of chronic disease. Expression of the single gene Bcl-6 strongly predicts poor outcome of relapsed DLBCL. In human genome it is very rare that single gene can predict outcome of diseases such as Bcl6, but also can predicts relapse as showed in this report. Switching positive into negative Bcl6 expression was strong indicator of DLBCL relapse.

P-5. Association between body mass index and incidence of lymphoma: A meta-analysis of prospective cohort studies

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Introduction: Obesity and overweight have been associated with an increased risk of developing lymphoma. The main objective of this meta-analysis is to evaluate the relationship between overweight and obesity and the development of lymphoma in adults. Secondary objectives are to evaluate the risk of lymphoma types, such as Hodgkin (HL), and non-Hodgkin lymphoma (NHL) and the most common NHL subtypes – diffuse large B-cell (DLBCL) and follicular lymphoma (FL) – in overweight and obese individuals.

Methods: A MEDLINE search from January 1950 to December 2010 was undertaken using: *(obesity OR "body mass index" OR BMI OR overweight) AND (leukemia OR lymphoma OR myeloma).* Prospective cohort studies reporting on the incidence of lymphoma were included. Case-control and cross-sectional studies were excluded. The outcome was calculated as relative risk (RR). Overweight was defined as body mass index (BMI) 25-29.9 kg/m^2 and obesity as BMI ≥30 kg/m^2, according to the WHO criteria. The quality of the studies was determined by the Newcastle-Ottawa scale (NOS). The random effects model was used to calculate the combined outcome. Heterogeneity was assessed by the I^2 statistic. Publication bias was assessed by the trim-and-fill analysis. Meta-regression analyses were performed to evaluate the association between BMI, as a continuous variable, and the incidence of lymphoma in general and lymphoma subtypes. Literature search, data gathering and study quality assessment were performed independently by at least 2 of the investigators. All the graphs are calculations were obtained using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

Results: From 758 returns, 22 prospective cohort studies evaluating the association between obesity and lymphoma were identified. All the studies were of high quality (NOS >7 points). For NHL, the overall RR was 1.06 (95% CI 1.02-1.10; p=0.001). For overweight and obese patients, the RR were 1.04 (95% CI 1.01-1.07; p=0.02) and 1.11 (95% CI 1.06-1.16; p<0.001), respectively. Meta-regression showed a linear association between BMI and incidence of NHL (p<0.001). For DLBCL, the overall RR was 1.14 (95% CI 1.01-1.29; p=0.03). Overweight and obese patients had a RR of 1.08 (95% CI 0.96-1.22; p=0.22) and 1.24 (95% CI 1.08-1.44; p=0.003), respectively. Meta-regression showed a trend towards a significant association between BMI and incidence of DLBCL (p=0.1). For FL, the overall RR was 1.11 (95% CI 0.99-1.25; p=0.08). Overweight and obese patients had a RR of 1.10 (95% CI 0.94-1.28; p=0.25) and 1.15 (95% CI 0.97-1.36; p=0.11), respectively. Meta-regression showed no association between BMI and incidence of FL (p=0.78). For HL, the overall RR was 1.10 (95% CI 0.97-1.26; p=0.15). Overweight and obese patients had a RR of 0.91 (95% CI 0.80-1.03; p=0.13) and 1.23 (95% CI 1.05-1.44; p=0.009), respectively. Meta-regression showed a statistically significant linear relationship between BMI and incidence of HL (p=0.009).

Conclusions: Obesity was associated with a mild increased risk of developing HL (23%), NHL in general (11%) and DLBCL (24%), but there was no association with FL. There was a statistically significant linear association between BMI and HL as well as for NHL in general, but only a trend towards an association with DLBCL.

P-6. Incidence of bleomycin hypersensitivity in patients receiving doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) for the treatment of Hodgkin's lymphoma

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Incidence of bleomycin hypersensitivity in patients receiving doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) for the treatment of Hodgkin's lymphoma

Study Purpose: Present a retrospective analysis of our institution's experience with bleomycin hypersensitivity reactions in patients receiving ABVD for the treatment of Hodgkin's lymphoma after elimination of a test dose of bleomycin.

Description: The routine utilization of a bleomycin "test dose" was a result of several reported incidences of hypersensitivity reactions in patients during the 1970's and 80's. However, very few reactions have been reported over the last couple decades and our institution eliminated routine administration of a test dose. This is a retrospective chart review of all patients who received bleomycin as part of the ABVD regimen for the treatment of Hodgkin's lymphoma within our institution between January 2005 and September 2010 before and after the elimination of the bleomycin test dose.

Results: A total of 94 consecutive patients were included in our analysis; 39 patients received a test dose and 55 patients did not receive a test dose. The average number of ABVD cycles was 4.9 vs. 5.1 and the total number of bleomycin doses was 532 vs. 371 among those who received a test dose and those who did not, respectively. The majority of patients in both groups had nodular sclerosing subtype of Hodgkin's lymphoma (69.2% vs. 67.3%, respectively). There was no difference in the primary outcome of hypersensitivity reactions (0% vs. 0%, respectively).

Conclusion: Administration of bleomycin as part of ABVD regimen without a test dose is safe, and has become the standard of practice at our institution.

P-7. SYK inhibition and response prediction in diffuse large B-cell lymphoma

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Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma and the role of SYK in its pathogenesis is not completely understood. Using tissue microarray, we demonstrated for the first time that SYK protein is activated in 27 of 61 (44%) primary human DLBCL tissues. Among DLBCL cell lines, seven were sensitive and three were resistant to a highly specific SYK inhibitor, PRT060318. In sensitive DLBCL cells, SYK inhibition blocked G_1-S transition and caused cell cycle arrest. This effect was reproduced by genetic reduction of SYK using siRNA. A detailed analysis of the BCR signaling pathways revealed that the consequence of SYK inhibition on PLCγ2, and AKT, as opposed to ERK1/2, was responsible for cell cycle arrest. Genetic knock-down of these key molecules decelerated the proliferation of lymphoma cells. Additionally, BCR signaling can be blocked by PRT060318 in primary lymphoma cells. Together, these findings provide insights into cellular pathways required for lymphoma cell growth and support the rationale for considering SYK inhibition as a potentially useful therapy for DLBCL. The results further suggest the possibility of using PLCγ2 and AKT as biomarkers to predict therapeutic response in prospective clinical trials of specific SYK inhibitors.

P-8. The prevalence of 7q32 deletions in small B-cell lymphomas

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Background: Splenic marginal zone lymphoma (SMZL) is a low grade B-cell lymphoma that is a unique clinicopathologic entity in the World Health Organization classification. Deletion of the long arm of chromosome 7 (del(7q)), specifically from 7q31.33 to 7q33, is thought to be common in SMZL and therefore may be useful for diagnostic purposes, but its prevalence in other small B-cell lymphomas is unknown.

Materials and Methods: Tissue microarrays (TMA) containing paraffin-embedded tissue cores of morphologically and immunophenotypically proven small B-cell lymphomas, including SMZL (n=53), follicular lymphoma (FL; n=113), extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma; n=112), lymphoplasmacytic lymphoma (LPL; n=30), mantle cell lymphoma (MCL; n=19) and nodal marginal zone lymphoma (NMZL; n=18), were constructed. Thin sections of all specimens were screened for del(7q) using a homebrew two-color fluorescence in situ hybridization (FISH) probe for 7q32.1 (locus of interest) and 7p22.3 (control).

Results: FISH was successful in 91% of specimens overall. Del(7)(q32) was present in 9/48 (19%) SMZL, 0/108 (0%) FL, 1/95 (1%) MALT lymphoma, 1/29 (3%) LPL, 1/17 (6%) MCL and 0/15 (0%) NMZL. The sensitivity of del(7)(q32) in SMZL is 19%, its specificity is 99%, its positive predictive value is 75% and its negative predictive value is 87% . Extra 7q32.1 and 7p22.3 signals, consistent with trisomy 7, were present in 12/108 (11%) FL and 3/17 (18%) MCL but were absent in the other tumors.

Conclusion: Deletion of 7q32 is present in 19% of SMZL. Identification of del(7)(q32) may be helpful in establishing a diagnosis of SMZL but correlation with the remaining morphologic, phenotypic and genetic findings is essential as del(7)(q32) is also occasionally present in other small B-cell lymphomas such as MALT lymphoma, LPL and MCL. Trisomy 7 is common in FL and MCL but rare in SMZL, LPL, MALT lymphoma and NMZL.

P-9. Esophageal perforation, an atypical presentation of non-Hodgkin's lymphoma

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Large B cell lymphoma can involve virtually any organ. The incidence has increased substantially in the last few decades. However, timely diagnosis could be a challenge due to atypical presentations. Here we report a case of large B cell lymphoma that presented as esophageal perforation.

P-10. CENTROBLASTIC SUBTYPE HAS A PARTICULAR EXPRESSION PROFILE OF P53, BCL-2, XIAP, SURVIVIN AND KI-67 AMONG DIFFUSE LARGE B CELL LYMPHOMA

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Purpose of the study: The imunohistochemical detection of the apoptosis modulators p53, Bcl-2, survivin and XIAP and the cell proliferation antigen Ki-67 have been reported to correlate with prognosis in some series of diffuse large B cell lymphoma (DLBCL). Nevertheless, the immunoblastic variant exhibits an anti-apoptotic expression profile and the centroblastic subtype exhibits a proliferative expression profile. However, the subtypes expression pattern of these apoptosis modulators is not established which raises doubts if these proposed biological prognostic factors analysis could be applied to each of the DLBCL morphological subtypes. Therefore, to overcome this potential bias, the aim of this study was to analyze the expression pattern and the prognostic impact of p53, Bcl-2, survivin, XIAP and Ki-67 expression exclusively in centroblastic DLBCL.

Materials and Methods: Samples from 81 DLBCL patients were selected according to the tumor sample quality. From those, 69 were treated with standard anthracycline-based protocol and where therefore eligible for entering the prognostic analysis. Detection of p53, Bcl-2, survivin, XIAP and Ki-67 was performed by immunohistochemistry. Statistical analysis was performed in SPSS 17.0 software. Co-expression was investigated by the Pearson Qui-square test and the observed probabilities of survival were compared by Kaplan-Meier survival curve and Log-rank test methods. Further confirmation was investigated by the Mann-Whitney test.

Results and Conclusions: In all positive centroblastic DLBCL analyzed samples the localization of p53, XIAP and Ki-67 was nuclear while the localization of Bcl-2 and survivin was cytoplasmic. However, unlike other studies regarding DLBCL not considering the morphological subtype, p53, Bcl-2, XIAP and Ki-67 expression did not predict the progression free survival or the overall survival of the centroblastic DLBCL patients. Survivin expression was the only protein with a possible prognostic impact in our series (PFS p=0.077 and OS p=0.054). Interestingly, although a trend for survivin and XIAP co-expression was also observed (p=0.059), nuclear localization of XIAP has been reported to prevent its anti-apoptotic activity which might explain the lack of prognostic impact in our analysis, while survivin which localized in the cytoplasm appears to have a more important role in the prognosis of centroblastic DLBCL patients.

Taken together these results corroborate with parallel observations in literature indicating that centroblastic DLBCL may be a particular disease with characteristic biology and clinical course and, therefore, specific prognostic factors.

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P-11. Liposomal Doxorubicin in Aggressive B Cell Lymphoma. A Retrospective Study

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Introduction: R-CHOP (Rituximab, Cyclofosfamide, Doxorubicin, Vincristine and Prednisone) is the current standard of treatment in aggressive B cell lymphoma.

Doxorubicin has an essential role but is associated with cardiac toxicity. The omission of doxorubicin in patients who are frail, have poor baseline cardiac function or who have previously received antracicline therapy may compromise outcome.

Liposomal Doxorubicin has demonstrated less toxic profile compared to the standard formulation in breast cancer studies.

Aims: To evaluate the effectiveness and toxicity of R-COMP21 treatment (Rituximab 375 mg/m2/, Cyclofosfamide 750 mg/m2/day1, Vincristine 1.4 mg/m2/day1, Liposomal Doxorubicin 50 mg/m2/day1 and Prednisone 60 mg/m2/day1-5) in elderly DLBCL and grade 3 Follicular Lymphoma patients (pt).

Methods: In this single-center retrospective study, we analyzed patients aged 70 and above diagnosed of Aggressive B Cell Lymphoma treated with R-COMP21 regimen and primary G-CSF prophylaxis.

We evaluate responses with PET-TAC following *The Revised International Workshop Response Criteria*, and toxicity as *CTCAE v3.0 of NCI* scale. Left ventricular ejection fraction (LVEF) was assessed by *echocardiogram visual estimation method* prior to and after R-COMP21 treatment.

Results: From November 2006 to April 2010, a total of 30 aggressive B cell lymphoma over 70 year-old patients were treated with R-COMP and G-CSF prophylaxis. As front line 26 pt and as salvage therapy 4 pt. Mean age was 76.8 years old, male/female 16/14. DLBCL 23 pt and Grade 3 Follicular Lymphoma 7 pt. Patients characteristics were: Ann Arbor stage III or IV 22 pt (73%), hypertension 17 pt, cardiomyopathy 11 pt, and previous antracicline treatment 4 pt. All the patients showed a LVEF over 50%. Mean R-COMP21 cycles were 5.6 (3-6).

Effectiveness: 29 patients completed the treatment and were evaluated: 26 pt(86%) CR, 2pt PR and 1pt PD. In 11 cases the response was consolidated, 8 radiotherapy and 3 radio-inmunotherapy (90Y Ibritumomab Tiuxetan)

With a mean follow up of 25.8 months, 24 pt (80%) are alive and in CR.

Toxicity: Grade 3 or 4 neuthropenia 100%, febrile neuthropenia 8 (26%) 1 septic shock.

Cardiac adverse events in 3 cases: 2 patients received a pacemaker implant and 1 case of heart failure was documented. Only this latter case developed mild left ventricular dysfunction.

Exitus causes were: 1 Septic shock (effectiveness non evaluated patient) 3 cases of systemic progression and in 2 patients other causes (non filiated entheropathy and acute bronchitis, 18 and 8 month after R-COMP respectively).

Conclusions: In our experience R-COMP21 and G-CSF prophylaxis in elderly aggressive B cell lymphoma patients is effective, showing a 86% CR rate, and well tolerated.

P-12. Clinicopathological differences between Asian and Western patients with de novo DLBCL treated with R-CHOP

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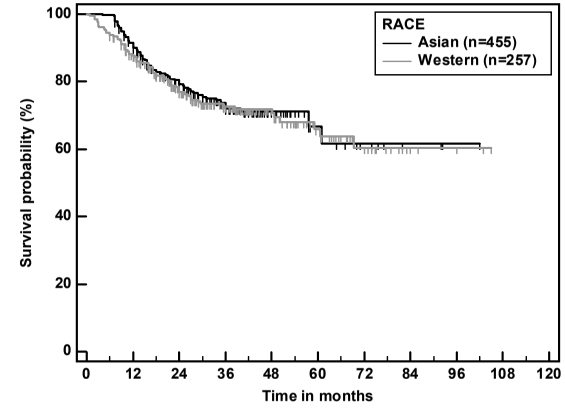
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Introduction: Little is known on the racial differences in characteristics and outcomes of patients with a diagnosis with diffuse large B-cell lymphoma (DLBCL) treated with rituximab-containing regimens. The aim of this retrospective study is to compare the clinico-pathological characteristics, prognostic factors and outcomes of Asian and Western patients with a diagnosis of *de novo* DLBCL treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).

Patients and Methods: Patient-level data was collected from 8 centers (USA, Italy, Sweden, Finland, Croatia, Japan, Korea and China). This study was approved by IRB at each of the participant centers. All patients were diagnosed with *de novo* DLBCL and treated with R-CHOP administered every 3 weeks. The requested clinical data included age, sex, race, performance status, LDH levels, number of extranodal sites, clinical stage, expression of CD10, BCL6 and MUM1/IRF4, response, outcome and overall survival (OS). Patients were divided in Asian and Western, according to the country of report. Comparison between groups was performed with Mann-Whitney and Chi square tests for continuous and categorical variables, respectively. Univariate survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was performed using the Cox proportional-hazard regression test. P-values of <0.05 were considered statistically significant.

Results: A total of 712 patients, 455 Asian and 257 Western patients were included in this study. Western patients were more likely to present with elevated LDH levels (70% vs. 48%; $p<0.001$), advance clinical stage (58% vs. 49%; $p=0.02$) and a non-germinal center immunohistochemical profile (53% vs. 43%; $p=0.01$). Additionally, Western patients were more likely to present with low risk IPI scores ($p=0.003$ for trend), and had higher complete response (CR) rates (91% vs. 76%; $p<0.001$). There were no statistical differences between the 2 groups on age at diagnosis, sex distribution, ECOG performance status, number of extranodal sites, overall response rates and proportion of deaths. After a median follow-up of 36 months, there was no difference in median overall survival (OS; not reached in both groups) or estimated 5-year OS (66% vs. 62%; $p=0.67$). In the univariate analyses, ECOG >1, elevated LDH levels and advanced stage were significantly associated with a worse survival in Westerners ($p<0.01$ each factor) while ECOG >1, >1 extranodal sites and advanced stage were significant for Asians ($p<0.01$ each factor). In the multivariate analyses, ECOG performance status and stage were independently associated with survival in Westerners and Asians ($p<0.01$, $p=0.03$, and $p<0.01$, $p<0.01$, respectively). Elevated LDH level was independent for Western patients only ($p=0.04$).

Conclusions: Asian and Western patients with DLBCL present with distinct clinical and pathological characteristics, and although the CR rate to standard R-CHOP was higher in Westerners than in Asians, the final outcome, prognostic factors and median and 5-year OS rates are similar in both populations.



P-13. Value of sonography in monitoring the therapeutic response of mediastinal lymphoma.

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Lymphomas are among the important causes of disabilities and mortalitys of population. Morbidity with them is uneven. Lymphogranulomatosis or Hodgkin's lymphoma (LGM) is in the 9th place among oncological diseases. Morbidity with LGM is 3.0 per 100 000 population, and primary malignant Non-Hodgkin's lymphomas (NHL) is 2.5-4 times higher than morbidity with LGM and is the basis of adverse tendencies in the growth of lymphoid neoplasia. On the contribution that made lymphomas in the reduction of lifetime, they are in the 4th place among malignant neoplasms causing great social and economic damage. According to precocious studies for the period 1966-1971 and 1998-2004 there was a statistically significant increase of total morbidity with leukaemias and lymphomas in the Republic of Armenia (9.19 vs. 13.2, t = 7.3, p ≥ 99%) at the cost of portion increase of lymphoma and multiple myeloma (MM).

From 2006 to 2009 at "Haematology center", (Republic of Armenia, Ministry of health), 209 primary patients, diagnosed with lymphoma, were examined - 91 (43,5%) of them diagnosed with LGM, 118 (56.5%) of them diagnosed with NHL. Staging was distributed as follows: in case of LGM 2A - 5 patients, 2B-12, 3A - 5, 3B - 5, 4A - 4, 4B - 5.

Injury pattern of tissue version is the following: 27 patients with LGM were with nodular sclerosis, 3 with mixed cellular type, 3 with lymphocytic predominance, and 6 with indeterminate variant. In 6 patients diagnosed with NHL tissue version was distributed as follows: large cell – 4, follicular, small-celled – 1, lymphocyte predominance – 1.

The exactness and timeliness of diagnosis of these diseases determine the tactics and the effectiveness of treatment. The results of treatment and prognosis of these diseases are largely dependent on the extent of the pathological process that may involve many organs and systems including the mediastinum.

According to the data of our study, among the examined patients there was mediastinum injury in 39 (42.9%) patients diagnosed with LGM and in 6 (5.1%) patients with NHL. Isolated injuries were singular, only 3 cases of patients with LGM.

Thus, the role of sonography, particularly in the dynamic monitoring of the treatment process, is invaluable and necessary, because of invasiveness in multiple studies.

P-14. Synchronous presentation of male breast carcinoma and axillary lymphoma: an unique case report

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Summary (mini abstract)

Breast cancer is very uncommon in people under 40 years of age. Male breast cancer is even a more rare occurrence, and particularly rare is the simultaneous presentation of two malignancies. A 39 years old man has been diagnosed with both breast cancer and axillary lymphoma. To our knowledge, this is the first synchronous case reported in literature of male breast cancer and axillary lymphoma simultaneously confirmed in the same patient

Breast cancer is very uncommon in people under 40 years of age. Male breast cancer is even a more rare occurrence, and particularly rare is the simultaneous presentation of two malignancies. A 39 years old man has been diagnosed with both breast cancer and axillary lymphoma. Familiar history revealed that his mother died because of breast cancer. The patient underwent fine needle aspiration leading to the diagnosis of malignant lesion.

Modified radical mastectomy was performed, and histology revealed an infiltrating ductal carcinoma 2,8 cm wide, Grade 2, with vascular and lymphatic invasion. Surprisingly, one of the second level nodes was confirmed as a high grade large B cell non Hodgkin's lymphoma. The patient was treated with local radiotherapy, followed by 6 courses of chemotherapy (RCHOP) before starting a treatment with tamoxifen using a dosage of 20 mg daily.

To our knowledge, this is the first synchronous case reported in literature of male breast cancer and

axillary lymphoma simultaneously confirmed in the same patient.

P-15. Complete Responses on a Phase 2 Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma

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Background: Romidepsin, a potent histone deacetylase inhibitor, has shown durable clinical benefit and tolerability in patients with relapsed or refractory peripheral T-cell lymphoma (R/R PTCL). In two phase 2, single-arm, open-label trials, objective response rates of 38% (17/45) and 25% (33/130) and median durations of response (DOR) of 9 months and 12 months have been published for NCI1312 andGPI-06-0002, respectively. This abstract provides a subset analysis of patients who achieved confirmed/unconfirmed complete responses (CR/CRu) on the GPI-06-0002 trial.

Methods: Patients with R/R PTCL received romidepsin 14 mg/m^2 as a 4-hour intravenous infusion on days 1, 8, and 15 every 28 days. An Independent Review Committee made blinded efficacy assessments in a 2-step process: initial radiographic review followed by an overall clinical assessment based on radiology and relevant clinical parameters.

Results: The CR/CRu rate was 15% (19/130); median time to CR/CRu was 3.7 months (range 1.6-13.7 months). Similar CR/CRu rates were observed across the 3 major PTCL subtypes (NOS, AITL, and ALK-1 negative ALCL). At the data cut-off (October 31, 2010), median DOR for patients that achieved CR/CRu was 17 months with longest DOR of 34+ months. With a median follow-up of 13.4 months, 17/19 (89%) patients remained in remission and 9/19 (47%) patients continue on romidepsin therapy with DORs of ≥ 9 months. Patients who achieved CR/CRu were representative of the overall patient population (Table). Baseline characteristics including age (< 65 vs. ≥ 65), receiving > 2 prior systemic therapies, prior stem cell transplant, or being refractory to last prior therapy did not impact CR/CRu rate. Overall (N = 131), the most common grade 3/4 adverse events were thrombocytopenia (24%), neutropenia (20%) and infections (all types summed; 19%). Rates of grade 3/4 adverse events were similar for patients who did or did not achieve CR/CRu.

Conclusions: Durable CR/CRu rates were observed with single-agent romidepsin in patients with R/R PTCL, including those with advanced and heavily pretreated disease.

Baseline Characteristics		
	CR/CRu (n = 19)	Other (n = 111)
Age in years, median (range)	61 (37-78)	61 (20-83)
PTCL subtype, n (%)		
PTCL NOS	10 (53)	59 (53)
AITL	5 (26)	22 (20)
ALK1-negative ALCL	4 (24)	17 (15)
Bone marrow disease, n (%)	7 (37)	29 (26)
International prognostic index, n (%)		
< 2	3 (16)	28 (25)
≥ 2	16 (84)	83 (75)
Number of prior systemic therapies, n (%)		
≤ 2	11 (58)	71 (64)
> 2	8 (42)	40 (36)
Refractory to last prior systemic therapy, n (%)	9 (47)	40 (36)
Prior stem cell transplant, n (%)	2 (11)	19 (17)

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK1, anaplastic lymphoma kinase 1; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma.

P-16. Synchronous Hodgkin Lymphoma and Pregnancy: A Single Institution Experience

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Mayo Clinic

The synchronous presentation of Hodgkin lymphoma (HL) is rare and incorporates different approaches than non-Hodgkin lymphoma (NHL). The Mayo Clinic medical registry and the Mayo Clinic Lymphoma Data Base identified a documented diagnosis of HL with synchronous pregnancy or in the immediate postpartum period in 32 patients from 1954 to 2011. The median age was 26 years (range 18 to 37 years). The histology was nodular sclerosis in 28, mixed cellularity in 2, and lymphocyte predominant in 2. The stage, as determined clinically and by the time period was I in 8, II in 22, III in 1 and IV in 1. One patient had “B” symptoms. Twelve patients were observed during the pregnancy. The median time to delivery was 39 weeks (range 34 to 41 weeks). Four patients delivered at 34 to 35 weeks. Six patients had a “flare” after delivery. Twenty patients were treated during the pregnancy. Sixteen patients were managed since 1980. Individualized radiation therapy approaches were employed with patients managed with a pregnancy radiation table and lead aprons to avoid fetal radiation therapy exposure. The median overall survival (OS) of all patients was 17 years (range 6 months to 44 years). The median OS of all patients since 1980 was 13.5 years (range 0.5 to 25 years). The management of the 16 patients treated since 1980 was as follows: observation 6, split doses of radiation therapy 4, full dose radiation during pregnancy 2, radiation therapy before delivery followed by chemotherapy after 3, ABVD x one cycle followed by delivery. Since 1980, 14/16 (88%) patients are alive and disease free long-term. One patient died of disease, and one patient died over 20 years later with disease status at the time of death unknown. Since 1980, four patients relapsed and were treated with chemotherapy. Fetal complications included one case each of Down’s Syndrome and retained dead fetus. In conclusion, an individualized approach to the patient and fetus can result in favorable outcomes.

P-17. Pilot Study Consisting of Rituximab, Ofatumumab, Bendamustine, and Sargramostim (ROBS) to Eradicate Minimum Residual Disease (MRD) in Chronic Lymphocytic Leukemia (CLL) with high risk factors

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Purpose: CLL is considered to be an indolent disease process with patients having long term survival. However, patients presenting with high-risk factors have a median survival of 2 to 3 years. High-risk patients appear to have improved survival with therapies that induce high remission rates leading to eradication of MRD, an important factor in leading to the prolongation of survival and eventual cure of CLL. Thus, we developed a pilot study designed to eliminate MRD for patients with high-risk CLL.

Description: The backbone of this novel biochemotherapy protocol is the active combination of rituximab and bendamustine. Sargramostim was added before and after the start of each cycle because it has been reported to potentiate the activity of rituximab and has the ability to decrease neutropenia. Ofatumumab was given as consolidation due to its activity in rituximab refractory disease. Previously untreated, symptomatic CLL patients with at least one high risk factor (<6 month doubling time, trisomy 12, zap 70 positive, unmutated status) were given an induction regimen consisting of three, 28 day cycles of rituximab (375mg/m2, D1) and bendamustine (90mg/m2 D1, D2) preceded and followed by 4 daily doses of sargramostim (500mcg). 4 weeks later a consolidation regimen consisting of 300mg ofatumumab followed 1 week later by 2000mg monthly x 3. Patients were considered free of MRD when the malignant clone was below the detection of both FISH and 5-color flow cytometry.

Results: To date, four patients have been treated. Each had a rapid response achieving a normal absolute lymphocyte count after the first induction cycle. At the end of treatment all patients had a normal hemogram and normal bone marrow morphology. By the above criteria, 50 percent achieved elimination of MRD in bone marrow and 100 percent achieved elimination of MRD in the peripheral blood. The two patients with residual disease in the bone marrow were negative by FISH, but had a reported 1% clone by flow. All patients continue the same depth of response by peripheral blood flow, with an average duration of 8 months. The regimen was well tolerated with fatigue and infusion reactions representing the most common adverse effects. No grade 3 or 4 hematologic toxicity was seen.

Conclusions: The results of this pilot study show that ROBS can eliminate MRD in CLL patients, and holds the promise of prolonging survival in high risk disease. A larger trial with longer follow-up will be needed to confirm the validity of this study.

P-18. Increased Response of Acute Phase Markers in Lymphoid Leukemias – A Probable Diagnostic Tool

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OBJECTIVES: Diseases which alter plasma proteins composition such as leukaemia and some inflammatory conditions have been linked with altered hemorheology and vascular dynamics. The association of various forms of Leukaemias with rheological determinants especially in Africans are few, therefore we have designed this study to primarily identify any possible changes in blood flow dynamics in newly diagnosed leukaemic patients.

METHODS: Blood samples were taken from 20 leukaemic patients (5 in each group of FAB classification) together with 20 apparently healthy individuals (age and sex -matched) as controls. Rheological determinants such as Plasma Fibrinogen concentration (PFC), Plasma Viscosity (PV) and erythrocytes sedimentation rate (ESR) were measured with standard laboratory methods. Hematocrit (HCT) was also measured to validate the sedimentation results.

RESULTS: We recorded statistically significant increases in the levels of PFC, PV and ESR ($P<0.05$, respectively) in all cases and in the following orders:

(PFC: ALL>>CLL>>CML>>AML>>controls),

(PV:CLL>>ALL>>CML>>AML>>controls)

(ESR: ALL>>AML>>CML>>CLL>>CONTROLS).

CONCLUSIONS: Hyperfibrinogenaemia coupled with hyperviscosity could be associated with reduced blood flow and tissue perfusion of blood in leukaemias especially in the Lymphoid series. This combination could trigger stasis and abnormal thrombogenesis in these patients. The use of Plasma viscosity as a better assessment of inflammatory syndromes than ESR is re-iterated.

P-19. Negative Rheologic evidence in Lymphoid Leukemias

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(PFC: ALL>>CLL>>CML>>AML>>controls),

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P-20. Relevance of Immunophenotype on Clinical features and Outcome of patients with T-cell Lymphoma/Leukemia

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Purpose of the Study: T-cell lymphoblastic lymphoma (T-LBL) and leukemia (T-ALL) are distinct clinical presentations of related malignant diseases that arise in developing thymocytes. The clinical distinction between T-LBL and T-ALL is based on the extent of tumor cell dissemination within the bone marrow and peripheral blood. Investigations into the molecular prognostic factors of T-LBL derive from T-ALL. The risk stratification is still difficult by the lack of well-established prognostic factors, especially concerning T-LBL. Furthermore, T-LBL biopsies are often classified histologically only, without phenotyping. Immature phenotypes have been associated with poor prognosis predominantly occurring in adults but not pediatric cases. We analyzed the impact of age, clinical and immunophenotype features on treatment response and survival of T-LBL/T-ALL.

Material and Methods: Patients with T-LBL (n=48) and T-ALL (n=42) diagnosed at the Instituto Nacional de Câncer, Brazil from 1997 to 2009 were classified according to the WHO 2008 classification. The immunophenotype of T-cells from bone marrow, peripheral blood and tissue micro-array biopsy material was based on the results of flow cytometry and immunohistochemical staining. The maturational stages of T-LBL and T-ALL were analysed regarding to age-groups and survival.

Results and Conclusions: The median age was 15.5 years (range 1-60 years) and there was a male predominance. Concerning the immunophenotypic profile, the cortical phenotype predominated (T-LBL, 62%; T-ALL, 65%) with tendency for difference between age-groups (childhood versus adult patients, p= 0.07) in T-LBL. Non-cortical phenotype increased with age among T-LBL cases. The CD34 was expressed in 5% of T-LBL and 28% of T-ALL cases (p = 0.01). Cortical phenotype was associated with a better survival for T-ALL (p=0.07), but not for T-LBL (p=0.38). The 5-year overall survival rate was 52% for both clinical forms, but comparatively a higher rate of initial failure was observed in T-LBL. Treatment response was the only prognostic factor identified in T-LBL patients.

Although the survival rates were similar, the events related to death were not the same for T-LBL and T-ALL. The clinical presentations of T-LBL and T-ALL are similar in many aspects, however it remains unknown whether there might be additional differences distinguishing T-LBL from T-ALL.

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Keywords: T-Cell Lymphoblastic Lymphoma- Leukemia. Phenotype. Survival.

P-21. Clinical success of the treatment of invasive fungal sepsis with antimycotic drugs and rHuG-CSF plus Dexametasone mobilized granulocytes after autologous stem cell transplant

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Purpose of the study: Severe bacterial and/or fungal infections are serious complications of high-dose preconditioning chemotherapy due to autologous stem cell transplant (SCT). Particularly during longstanding neutropenia, patients are at risk for life-threatening sepsis. The aim of this study was to assess the efficacy and safety of recombinant human Granulocyte-Colony Stimulating Factor (rHuG-CSF) plus Dexametasone mobilized granulocyte transfusions (GTX) combined with antimycotic drugs in severe neutropenic patient with fungal sepsis after autologous SCT.

Summarized description of the project: Male patient age 42 was treated for lymphoblastic lymphoma at Clinical center of Serbia with Hyper-CVAD and due to high risk disease consolidated with autologous SCT in the complete remission in 2010. The number of reinfused CD34+ cells was 3.8x10E6/kgtm. Before GTX, severe neutropenia (absolute neutrophil count - ANC = 0.1x10E9/L) related to autologous SCT was persisted three weeks, complicated with fungal sepsis (Stephanoascus citerii and Candida guilliermondi) despite combined antimycotic (Voriconasol and Caspofungin), antibiotic, antiviral therapy and rHuG-CSF applying. Using our own granulocyte-donor preconditioning incorporated: rHuG-CSF 5 μg/kgbm for two days and Dexametasone 6 mg per os 12 h prior to apheresis. Polymorphonuclears (PMN) for supportive treatment were collected by Cobe Spectra (CaridianBCT, USA).

Results and conclusions: The processed blood volume was 6250 mL, the quantity of collected cell suspension was 360 mL, and the number of harvested PMNs was 6.2x10E10/Unit. After cell collection, PMNs were irradiated with 25 Gy to prevent transfusion associated GvHD, and after that applied across central venous catheter. Patient was premedicated with Methylprednisolone, Ranitidine and Loretadine. The in vivo recovery, that is mean increase of the PMN count 1 h after GTX was 0.9x10E9/L (i.e. from 0.5 on 1.4x10E9/L), with consecutive rising until normalization in seven following days. To prevent of CMV infection, Gancyclovir was applied with resolving fungal sepsis, significant decrease of C-reactive protein (CRP) and patient's condition complete clinical recovery. The use of GTX and antimycotics can be a satisfactory and safe therapeutic approach with advantageous effects on invasive fungal sepsis in immunosuppressed neutropenic patients following SCT.

P-22. Elevated serum free light chains independently identify stage A chronic lymphocytic leukaemia patients with aggressive disease

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Background: Chronic lymphocytic leukaemia (CLL) is a heterogeneous disease and identifying early stage patients who are likely to progress remains difficult. We have previously shown that elevated combined free light chains (κ + λ FLC; cFLC) are independently prognostic in a mixed population of CLL patients (treated and untreated Binet stage A-C).

Purpose of the study: To investigate if elevated cFLC identify aggressive disease in newly diagnosed, untreated stage A CLL patients.

Methods: 167 Binet stage A, untreated CLL patients were retrospectively analysed. The levels of FLC and beta 2-microglobulin (β_2M) were assessed using nephelometric immunoassays. Previously recorded measurements for clinical markers (age (< or > 65 years), sex, CD38$^{+/-}$, ZAP-70$^{+/-}$, lymphocyte doubling time (LDT< or > 12 months), *IGVH* mutational status (< or > 98% homology)) were used to perform Kaplan Meier and Cox regression survival analysis.

Results: Elevated cFLC were significantly associated with a shorter time to first treatment (TTFT) and was a more significant prognostic marker than an abnormal FLC ratio. A cut-off of cFLC>50mg/L identified 36 CLL patients with a significantly shorter TTFT compared to patients with cFLC<50mg/L (median 115 months v 175 months respectively; p=0.043). Univariate analysis identified CD38^{+ve} (hazard ratio (HR) 2.26, p=0.002), ZAP-70^{+ve} (HR 3.71, p<0.0001), *IGVH* mutational status (HR 3.86, p<0.0001), LDT<12 months (HR 4.3, p<0.0001), and FLC>50mg/L (HR 1.73, p=0.046) were all significantly associated with TTFT. Multivariate analysis indicated that LDT<12 months (HR 4.1, p<0.0001), ZAP-70^{+ve} (HR 2.3, p=0.004) and cFLC>50mg/L (HR 2.0, p=0.024) were independently associated with shorter TTFT.

A two tiered risk model using cFLC>50mg/L and ZAP-70^{+ve} identified patients with aggressive disease and was significantly associated with TTFT. Patients with 1 or 2 risk factors (FLC>50mg/L and / or ZAP-70^{+ve}) had a much shorter TTFT than patients with 0 risk factors (FLC<50mg/L and ZAP-70^{-ve}; median TTFT 113 v 218 months respectively, p<0.0001).

Patients with cFLC>50mg/L also had a significantly shorter overall survival (OS) than patients with FLC<50mg/L (75% survival 101 v 170 months respectively, p=0.005). Univariate analysis identified CD38^{+ve} (HR 4.25, p=0.001), ZAP-70^{+ve} (HR 5.14, p<0.0001), *IGHV* mutational status (HR 5.72, p=0.0001), LDT<12 months (HR 3.01, p=0.046), β_2M>3.5mg/L (HR 3.41, p=0.003), abnormal FLC ratio (HR 3.25, p=0.002), and FLC>50mg/L (HR 3.00, p=0.008) were all associated with shorter OS.

Conclusion: Elevated cFLC>50mg/L aids in the identification of untreated CLL stage A patients with aggressive disease.

P-23. A unique presentation of a rare disease: T-cell prolymphocytic leukemia

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Purpose: To report the first case of T-cell prolymphocytic leukemia (T-PLL) presented initially with acute renal failure.

Method: Case report

Description: Prolymphocytic leukemias are rare chronic lymphproliferative disorders that include B cell and T cell subtypes. With less than 120 cases reported annually (or less than 2 % of all mature lymphocytic leukemia in adults), T-PLL is extremely rare T-cell lymphoid malignancy .The name "prolymphocytic" is a misnomer, as the clonal cells are derived from mature or postthymic T cells. Clinical presentation usually includes leukocytosis, Hepatosplenomegaly (75%), generalized lymphadenopathy (50%), anemia (36%), thrombocytopenia (51%), skin infiltration and serous effusion (20%). CNS involvement is rare. Here we describe the first case of T-PLL presenting as acute renal failure. Case presentation: A 67- year-old man was admitted to the hospital with acute renal failure (BUN/Cr of 57/3.8 mg/dL). Physical exam showed generalized lymphadenopathy. His renal ultrasound was negative for hydronephrosis and urine analysis did not show nephritis/ nephrotic findings. Despite aggressive IV hydration, His renal function did not improve. interestingly, his LDH was normal and the PET- CT revealed some cervical, retroperitoneal, portacaval and lymphadenopathies but no hepatosplenomegaly. The peripheral blood flow cytometry showed CD4 positive, T-cell population with bright expression of CD5 and CD7. The bone marrow molecular studies revealed chromosome14q inversion and multiple complex abnormalities were detected. Right kidney biopsy (as well as cervical node and bone marrow biopsies) showed extensive involvement with T-PLL. He was treated with Campath. After 3 cycles of Campath, patient's renal function improved to 1.9 mg/d and after 6 cycles, his bone marrow showed morphologic and molecular remission . He is on Campath maintenance as a bridge for an allogenic sibling bone marrow transplant. Conclusion: While majority of T-PLL patients require aggressive treatment, approximately 30% of patients only need to be closely monitored. However, this is the first and only reported case of T-PLL presented in a scenario of acute renal failure. This was an aggressive presentation of T-PLL infiltrating the kidney parenchyma and causing acute renal failure, which was successfully resolved after chemotherapy.

P-24. Immunoglobulin ratios are a rapid, sensitive alternative to immunofixation for the identification of monoclonal proteins

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Introduction: Historically, serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP) and immunofixation (IFE) have been used to quantify and identify monoclonal proteins (M-proteins). While this approach is adequate for the identification of intact immunoglobulin multiple myeloma (MM), it is not sensitive enough to detect light chain MM (LCMM). Therefore, an algorithm that utilises SPE, serum free light chain (FLC) immunoassays and IFE for the identification of M-proteins has been suggested. Assays have now been developed that utilise polyclonal antisera raised against the κ and λ light chain types of IgG, IgA and IgM immunoglobulins (heavy/light chains; HLC).

Purpose of the study: To investigate the use of HLC assays as an alternative to IFE for identification of monoclonal immunoglobulins.

Methods: 1495 patient sera were screened using SPE and FLC. Electrophoresis was performed using a SEBIA HydrasysII in accordance with the manufacturer's instructions. FLC κ/λ ratios, IgGκ / IgGλ, IgA κ / IgAλ and IgMκ / IgMλ HLC ratios were measured nephelometrically using commercial assays (The Binding Site Group Ltd), and compared to historic IFE results.

Results: 198/1495 patients had an abnormal SPE or FLC result, of which 106/198 patients were positive by IFE and 81/198 had an abnormal HLC ratio (HLCr). 25/106 IFE positive patients had symptomatic haematological malignancies (14 MM, 4 Waldenstrom's Macroglobulinemia (WM) and 7 non-Hodgkins lymphoma (NHL)). Abnormal HLCr were identified in 22 of the 25 symptomatic patients. Moreover, abnormal HLCr identified 7 additional patients that, at the time of testing, were negative by IFE, but where subsequently diagnosed with a haematological malignancy (1 AL Amyloidosis, 1 IgAλ MM and 1 IgMκ WM and 4 NHL). 74/106 IFE positive patients had monoclonal gammopathy of undetermined significance (MGUS), 42/74 had an abnormal HLCr. 32 MGUS patients had 'normal' HLCr, but using the Rajkumar MGUS stratification model (Rajkumar et al, Blood 2005, 106, 812-817), these were all in the low or low/intermediate MGUS risk category.

Conclusion: We conclude that HLCr can detect most symptomatic haematological malignancies and offers a rapid and quantitative alternative to IFE.

P-25. Upregulation of miR-135b expression in bone marrow derived mesenchymal stem cells of Multiple Myeloma patients is associated with impaired osteogenic differentiation potential

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Mesenchymal stem cells from multiple myeloma patients (MM-hMSCs) possess abnormal characteristics compared to their counterparts from normal donors (ND-hMSCs), exhibited by an enhanced spontaneous and myeloma cell-induced production of cytokines and a distinctive gene expression profile. MicroRNAs (miRNAs) are endogenous non-coding RNA molecules which are crucial in regulating stem cells fate and involved in the differentiation process of MSCs.

In this study, we performed a miRNA microarray to determine the miRNA expression profile in hMSCs from MM patients and normal donors. Among 755 miRNAs tested, 25 were significantly upregulated and 9 were downregulated in MM-hMSC as compared to ND-hMSC. One upregulated miRNA, miR-135b, has been described in previous studies to be involved in the regulation of osteogenic differentiation. By real time PCR we analyzed miR-135b expression in more samples (9 MM-hMSCs and 5 ND-hMSCs) and confirmed that miR-135b was significantly upregulated in MM-hMSCs Noticeable, all tested MM-hMSC samples showed impaired osteogenic potential as demonstrated by lower alkaline phosphatase (ALP) activity. During *in vitro* hMSCs osteogenic differentiation, we observed by real time PCR a considerable decrease in miR-135b expression after osteogenic induction. In addition, by means of ALP and mineralization staining, as well as qPCR for osteogenic differentiation markers (BSP, COLA1 and OPN), we could demonstrate that loss or gain of miR-135b did result in enhanced or reduced osteogenic differentiation, respectively. Even more importantly, the impaired osteogenic differentiation of MM-hMSCs could be corrected by a miR135b inhibitor, as confirmed by ALP activity, osteogenic genes expression and mineralization deposition.

In conclusion, in this study we demonstrate for the first time, that hMSCs derived from the MM bone marrow microenvironment have a differential miRNA expression profile as compared to their normal counterparts. Abnormal expression of miR-135b in MM-hMSCs is associated with their lower osteogenic potential. Targeting MM-hMSCs by miR-135b inhibitors might be an interesting strategy to correct the impaired MSC osteogenic differentiation and to control bone disease in MM.

P-26. Association of health-related quality of life with bone disease in multiple myeloma

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Purpose of the Study. Bone disease in patients with multiple myeloma has rarely been evaluated with respect to its association with health-related quality of life (HRQOL) in the United States (US). In this study, baseline HRQOL of patients with active, symptomatic MM was assessed by bone disease status.

Summarized Description of the Project. As part of Connect MM®, an ongoing prospective US disease registry of patients with MM, clinicians reported patient demographics and clinical characteristics. Patients reported HRQOL within 2 months of diagnosis by completing a battery of three validated instruments: Brief Pain Inventory (BPI), EQ-5D, and Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM). Mean (Standard Deviation [SD]) BPI, EQ-5D and FACT-MM scores were analyzed by bone involvement. Statistical significance was assessed by ANOVA using SAS 9.1.

Results and Conclusions. Data were collected on 781 patients at 189 clinical centers. Patients were mostly male (57.4%) and white (81.2%) with mean age 66.9 yrs (SD 11.5). Patients were characterized as having no bone lesions (n=213), presence of bone lesions (n=405), or severe osteopenia and/or fracture (n=163). EQ-5D pain/discomfort and usual activities scores were most compromised. Increasing bone involvement was associated with worse BPI; EQ-5D scores (except anxiety/depression); FACT-MM physical and functional domain scores; and FACT-G and FACT-MM scores. Connect MM® baseline findings indicate that bone involvement is associated with greater HRQOL degradation overall, and specifically in physical and functional areas, but not in psychological areas. Future study should be conducted as patients undergo treatment to observe effects of disease and treatment on HRQOL over time.

P value from ANOVA for comparison among three groups.

HRQOL Scores Mean(SD)	No bone lesions (n=213)	Presence of bone lesions (n=405)	Severe osteopenia and/or fractures (n=163)	P Value[1]
BPI-Average Pain	2.5(2.8)	3.6(2.8)	4.2(2.9)	<.0001
EQ-5D				
Mobility	1.5(0.5)	1.6(0.5)	1.7(0.5)	0.0002
Self Care	1.2(0.4)	1.3(0.5)	1.5(0.6)	<.0001
Usual Activities	1.5(0.6)	1.8(0.6)	2.0(0.7)	<.0001
Pain/discomfort	1.5(0.6)	1.8(0.5)	2.0(0.6)	<.0001
Anxiety/Depression	1.3(0.5)	1.4(0.5)	1.5(0.6)	0.1465
FACT-MM				
Physical	21.2(5.6)	19.7(5.8)	18.3(5.8)	<.0001
Social/Family	23.5(4.5)	23.0(5.2)	23.2(4.4)	0.4946
Emotional	18.2(3.8)	18.2(4.3)	17.7(4.4)	0.5834
Functional	18.0(6.3)	15.9(6.7)	13.7(6.1)	<.0001
MM subscale Score	38.4(10.8)	36.1(10.7)	33.6(11.0)	0.0006
FACT-G Total	81.0(14.6)	76.8(16.4)	72.9(15.6)	<.0001
FACT-MM Total	119.3(23.9)	112.9(25.2)	106.4(25.2)	<.0001

P-27. The summary of 15 years own experience with stem cell transplantation for multiple myeloma

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Introduction: Autologous stem cell transplantation (ASCT) became standard of care for patients with multiple myeloma (MM) under the age of 65 years. We routinely perform ASCT for newly diagnosed MM since 1996 in our department, the first ASCT for MM in Czech republic was done in Hradec Kralove.

Patients and methods: We retrospectively analyzed all 285 transplants in 185 patients done for MM from January 1996 till December 2010. 270 transplants were autologous (255x Mel200, 15x Mel100 for elderly patients), 15 transplants were allogenic (13x reduced-intensity conditioning Bu-Flu-ATG or Flu-Cy, 1x myeloablative Bu-Mel, 1x twin sibling). Median age of patients was 57 years (27-75). We analyzed overall survival (OS) and progression-free survival (PFS) regarding conditioning, stage, complete or very good partial remission (CR, VGPR) achievement, renal impairment, single vs. double transplant.

Results: Estimated 10-years survival of the whole set of patients is 39% (median survival 55 months). Patients with renal impairment show same OS as those without (p=0.22). Patients show similar overall survival and event free survival regardless of type of transplant. We observed better outcome in terms of overall survival in patients treated with new drugs (p=0.0014). Reaching CR or VGPR was surprisingly not translated into better OS (p=0.30) and EFS (p=0.10). Also stage of the disease and whether single or double trasnplant was used did not make any significant difference in the outcome.

Conclusion: Stem cell transplantation greatly improved outcome of patients with MM. Poor outcome of allogenic transplantation in our group of patients is related to high transplant related mortality (20% vs. 0%) and unexpected high relapse rate. However in this group are two long term survivors who are disease free for more than 10 years. There is an obvious trend towards better survival, when new drugs are incorporated at any time in the course of the disease as an addition to ASCT. This fact supports hypothesis that use of these drugs with ASCT should translate into better long-term outcome in all patients.

P-28. The results of maintenance therapy with alpha interferon after autotransplant in multiple myeloma – a single center experience

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Background: alfa interferon was an option for maintenance therapy after auto stem cell transplant before the era of new immunomodulatory drugs; it still remain a good alternative of treatment in those countries with low socioeconomic status, where Thalidomide, Lenalidomide and Bortezomib are not available for extended use because of their costs.

Aim: to evaluate the role of alfainterferon as maintenance therapy after autostemcell transplant in a limited group of multiple myeloma patients , diagnosed and treated in Fundeni Clinic Of Hematology & Transplant.

Material & Methods: a retrospective clinico-evolutive study of 15 patients with multiple myeloma who were transplanted in our center between 2001-2006.

(2 patients with double auto); 6 from 15 were treated with interferon after stem cell transplantation 6-12 months. The sex distribution was equal. The age at diagnosis range between 28-67 years . 3 patients were IgA multiple myeloma , 3 with IgG type multiple myeloma. All of them were treated with VAD as induction therapy and achieved a VGPR before autotransplant ; conditioning was Melphalan 200 mg/sm and mobilization with Cyclophosphamide 3 g/sm.

Results: 4 from them are still alive, in plateau phase, with no treatment at 5 years from the end of study period. 2 patients relapsed and they were treated with new drugs combinations.

Conclusions: although the study group is very small, we believe that maintenance therapy with interferon after performing autostem cell transplant may be beneficial. Complete remission cannot be achieved in all patients, so maintenance therapy should be considered in order to prolong disease free survival after transplantation. New immunomodulatory drugs proved their efficacy not only as induction but also as maintenance therapy. Unfortunately, due to their limited free availability, not all the patients could be treated , so interferon may be an alternative.

P-29. Does the addition of Anthracyclin to the Bortezomib-Dexamethasone combination in the front-line therapy of Multiple Myeloma patients lead to better results after Autologous bone marrow transplantation?

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Purpose of the study: The comparison of response to front-line therapy and Autologous Bone Marrow Transplantation (ABMT) of Multiple Myeloma (MM) patients who received Bortezomib-Dexamethasone (VD) combination versus those who received Bortezomib-Dexamethasone plus Pegylated Adriamycin (PAD).

Summarized description of the project: A retrospective study of 24 patients (21 with MM, 3 with Plasma cell leukemia), of whom 19 were men, with a median age of 57y.o (44-71) who were diagnosed in our Clinic from 2007-2010 and considered as candidates for ABMT. Eight patients had IgG-k myeloma, 7 IgG-l, 2 IgA-k, 6 light-chain disease and 1 IgD-l. With regard to the ISS, 7 had Stage I disease, 6 Stage II and 11 Stage III. The efficacy and toxicity of the front-line therapies were studied, the number of Peripheral Blood Stem Cells (PBSC) collected was recorded and a statistical analysis was performed to study the correlation of the response to ABMT in regard to front-line therapy or other patient and disease parameters.

Results and conclusions: Eleven patients received VD and 13 PAD. All patients underwent PBSC collection after Cyclophosphamide mobilization, but 3 patients (all in the VD group) did not undergo ABMT (1 due to bad Performance Status, 2 are pending). Patients in the PAD group presented with significantly higher grade 3-4 toxicity compared with the VD group, as summarized in table 1.

Table 1: Percentage of patients who presented grade 3-4 toxicity

	PAD	VD
Hematologic	100%	56%
Metabolic	23%	11%
GI	23%	0
Renal	15%	11%
Infections	8%	0
Cardiologic	0	11%
Hospitalisation	23%	11%

The mean number of PBSC collected (in 10^6 cells/kg of patient weight) was 9.15 (4-24) for the PAD group and 10.73 (4-19) for the VD group. Response to treatment before and after ABMT in regard to front-line therapy is summarised in table 2.

Table 2: Response before and after ABMT with regard to front-line therapy

	PAD		VD	
	Before ABMT	After ABMT	Before ABMT	After ABMT
sCR	2/13 (15.4%)	9/13 (69.2%)	4/8 (50%)	6/8 (75%)
>VGPR	10/13 (76.9%)	12/13 (92.3%)	5/8 (62.5%)	7/8 (87.5)
PR	2/13 (15.4%)	0/13 (0%)	2/8 (25%)	1/8 (12.5%)
RD	1/13 (7.7%)	1/13 (7.7%)	1/8 (12.5%)	0/8 (0%)

sCR: stringent Complete Remission, >VGPR: Sum of patients who achieved sCR, CR (Complete Remission) or VGPR (Very Good Partial Remission), PR: Partial Remission, RD: Refractory disease

It is noticeable that 12 patients improved the depth of their remission and 9 remained stable after ABMT. Even though the PAD group seems to achieve better results concerning remissions >VGPR, this did not prove statistically significant in our study. Likewise, no statistically significant correlation was observed regarding patient age, disease stage or type of paraprotein. As a conclusion, the addition of Anthracyclin to front-line therapy does not seem to improve the final response to ABMT and, as it adds on toxicity, it is better to be avoided. Both protocols, however, permit the collection of adequate number of PBSC and are, thus, suitable for patients who are candidates for ABMT.

P-30. Long-term Follow Up of PX-171-003-A1, an Open-label, Single-arm Phase 2 Study of Carfilzomib in Patients with Relapsed and Refractory Multiple Myeloma

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Carfilzomib is a next-generation proteasome inhibitor that selectively and irreversibly binds to its target resulting in sustained inhibition absent the off-target effects observed with bortezomib. It has demonstrated durable anti-tumor activity and an acceptable tolerability profile in patients with multiple myeloma. PX-171-003-A1 was an open-label, single-arm, phase 2b trial to evaluate the efficacy and safety of carfilzomib in patients with relapsed and refractory multiple myeloma. Here, we present the final Independent Review Committee's mature response data for this study.

Patients had received ≥2 prior therapies (bortezomib, either thalidomide or lenalidomide, and an alkylating agent), must have been responsive (≥minimal response [MR]) to a prior therapy, and were refractory to their most recent therapy. Refractory disease was defined as ≤25% response to, or progression during or within 60 days after completion of therapy. Carfilzomib was given on days 1, 2, 8, 9, 15, and 16 of 28-day cycles and patients received stepped up dosing consisting of 20 mg/m^2 in Cycle 1 and 27 mg/m^2 in Cycles 2 through 12. The primary endpoint was overall response rate (ORR). Secondary endpoints were clinical benefit response rate (CBR), duration of response (DOR), overall survival (OS), progression free survival (PFS) and safety. Responses were assessed per International Myeloma Working Group Uniform Response Criteria, with additional assessment of MR per European Blood and Marrow Transplant Group criteria, and were confirmed by an Independent Review Committee.

Of 266 patients enrolled, 257 were response-evaluable. Patients had a median age of 63 years and a median time since diagnosis of 5.4 years. They had received a median of 5 prior treatment regimens with 95% refractory to their most recent regimen. Seventy-seven percent had baseline Grade 1/2 peripheral neuropathy, 31% were classified as ISS stage III, and 234 had cytogenetic data available with 32% showing unfavorable characteristics. ORR was 24% (95% CI 18.7–29.4) with a median DOR of 7.8 months and CBR (ORR + MR) was 37% (95% CI 31.1–43.2) with a median DOR of 8.3 months. There were 81 (32%) patients with stable disease. Median PFS based on Kaplan-Meier estimate was 3.7 months (95% CI 2.8-4.6). Median OS was 15.6 months (95% CI 13.0-19.2). When patients were stratified by subgroups, ORR showed consistency across different subgroups including in patients with pre-existing neuropathy, poor prognosis cytogenetics/FISH, renal dysfunction, and in those who were refractory to bortezomib. The most common treatment-emergent adverse events (AEs) ≥G3 were primarily hematologic: thrombocytopenia (29%), anemia (24%), lymphopenia (20%), and neutropenia (11%). New-onset PN was infrequent and PN ≥G3 occurred in 1.1% of patients. There was one treatment discontinuation due to neuropathy in a patient with pre-existing PN. Forty patients completed 12 cycles and 31 continued on extension protocol PX-171-010 with no evidence of cumulative toxicities.

In summary, single-agent carfilzomib demonstrated durable activity and an acceptable safety profile in heavily pre-treated patients with relapsed and refractory multiple myeloma, including those with pre-existing peripheral neuropathy and unfavorable cytogenetics/FISH.

P-31. Non-Frozen Autologous Peripheral Blood Stem Cells Transplantation in Multiple Myeloma

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The goal of the study was to assess hematologic recovery and outcome of patients (Pts) with multiple myeloma (MM) after non-frozen autologous peripheral blood stem cells (PBSC) transplantation.

These transplants were performed in 30 Pts with MM and of age ranging 36 to 71years (median, 58 years). Twenty-two of them were IgG MM, 5 IgA, 2 light chains and one non-secretory MM. According to Durie-Salmon, all were stage III. All Pts but two, had been newly diagnosed and had been induced by VAD regimen before autografting. Stem cells mobilization was carried out with ciclophosphamid (4 g/m^2) Followed by administration during at least five days of G-CSF (filgrastim) until the peripheral stem cells harvest. PBSC collections were performed with cells separators. Pts were conditioned with high dose melphalan, 200 mg/m^2 for 26 of them, 140 mg/m^2 for four. Non-frozen, non-purged mononuclear cells were stored at room temperature for less than 24 hours.

The harvest contained a median of 7.2 x 10^6 CD34+ cells/kg (range, 2.2 - 18.6). The median time for recovery a polynuclear neutrophil count > 0.5 G/L was 11 days (range, 9 - 22), the median duration of neutropenia was 7 days (range, 5 - 16 days). Two Pts died during neutropenia, the first of a heart failure after a systemic capillary leak syndrom, the second of a septicemia. Sixteen Pts relapsed between 3 and 50 months after PBSC transplantation (1 plasma cell leukemia). Two other Pts died in remission, 1 of septicemia, the other of myocardial infarction. Eight Pts are alive in complete remission, median 43 months (range, 19 - 81 months). Median EFS, 26 (range, 3 - 81).

This study shows that simplified schedules for high dose chemotherapy administration together with simple PBSC collection procedures provide safe and effective methods for administrating myeloablative chemotherapy treatment. With this method, the restrictions made necessary by cell freezing, to PBSC autotransplant programs, may be overcome and cost may be reduced.

P-32. Second Hematologic Neoplasms in the Bone Marrow of Patients with Plasma Cell Dyscrasia or Multiple Myeloma

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The frequency of second hematologic neoplasms in the bone marrow of pts with plasma cell dyscrasia (PCD) or multiple myeloma (MM) is not established. The most frequently reported second diagnosis is CLL; but myeloid neoplasms have also been reported. Most reports are of individual pts, and a systematic review has not been reported. Therefore, we retrospectively reviewed bone marrow biopsy specimens performed in patients with PCD or MM at our institution to determine the prevalence of dual diagnoses and to identify the second disorders that occurred. PCD was defined as a monoclonal serum protein with <10% phenotypicaly abnormal plasma cells in the marrow. The presence of ≥10% clonal plasma cells was diagnostic of MM. From January 2007 through December 2009, 1655 pts had bone marrow biopsies, and 115 pts were diagnosed with PCD (n = 46) or MM (n = 69). In 7 pts a second hematologic disease was identified.

Age/ Gender	M-protein	Biopsy Indication	Marrow Diag 1	Marrow Diag 2	Indication for Treatment
57/M	IgG kappa	M-spike & splenomegaly	MM	MCL	MCL
85/M	IgG lambda	lytic bone lesion	MM	MDS	MDS
77/M	IgG lambda	anemia & thrombocytosis	PCD	JAK-2 (+) ET	ET
59/M	IgG kappa	M-spike	PCD	MPN, JAK-2 (+) ET	MPN
80/F	IgA kappa	M-spike & hypercalcemia	PCD	Low grade lymphoma	Not yet initiated
66/F	IgG kappa	M-spike	PCD	MDS	MDS/secondary AML
66/M	IgG lambda	neutropenia	MM	MDS	MDS

An M-protein was present in all 7 pts prior to bone marrow biopsy: IgG-kappa (n = 3), IgG-lambda (n = 3), and IgA-kappa (n = 1). In 2 pts bone marrow biopsy was performed solely because of the M-spike. In 4 pts the indication was an M-spike plus another abnormality: splenomegaly, lytic bone lesion, hypercalcemia, and neutropenia. In one of the 2 JAK-2 positive pts the biopsy was done for a reason unrelated to the monoclonal gammopathy: anemia and thrombocytosis. The hematologic conditions identified were: MDS (n = 3), MPN (n = 2), and lymphoma (n = 2). The second disease was unknown prior to biopsy in all pts except for one pt with ET and one pt with MDS. Six pts required treatment, and in all 6 the indication was the second hematologic disorder. **Conclusion:** In our experience, the frequency of second neoplasms in bone marrow of pts with PCD or MM was 6.1%. Unlike previous reports there were no cases of CLL. Interestingly, the majority of second neoplasms were myeloid (5/7). In 5 pts the biopsy identified a previously undiagnosed condition. Importantly, the second disorder was always the indication for treatment, and no pt was treated for PCD or MM. Our findings highlight the significance of the second marrow diagnosis. A bone marrow biopsy should be performed in pts with a monoclonal gammopathy and another hematologic abnormality such as JAK-2 mutation, neutropenia, or splenomegaly.

P-33. A Phase I/II Study of Escalating Doses of Thalidomide in Conjunction with Bortezomib and High Dose Melphalan As a Conditioning Regimen for Autotransplant in Patients with Advanced Multiple Myeloma

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Background: Recently, it has been shown that the combination of melphalan (Mel) and bortezomib (Vel) is an active regimen for high dose therapy with autotransplant in MM. In vitro studies on myeloma cells demonstrated potential synergy of the combination of MelVel with thalidomide (Thal) within the BM microenvironment. We designed a Phase I/II trial of high dose Mel Vel with escalating dose Thal with ASCT in patients with relapsed/refractory MM or with evidence of residual MM after high dose Mel.

Objective: To evaluate the toxicity, engraftment kinetics, response rate, progression-free survival and overall survival of the combination of MelVelThal.

Patient characteristics: All patients had pathological proven and symptomatic myeloma. They had either relapsed/refractory (n=6) myeloma or had not achieved at least a PR (n =3) with their most recent therapy. The median age was 60 years. Male: female ratio was 1:2; median number of prior therapies was 3. 8 patients had 1 prior ASCT and 1 had 2 previous ASCT. Median time from prior transplant was 1 year.

Method: This is a single center phase I/II dose escalating trial of Thal starting at 600 mg daily in cohorts of 3 patients with a planned maximum dose of 1000 mg on days -5 to -1. MelVel was administered as Mel 200mg/m2 on day -2 and Vel 1.6 mg/m2 IV on days -4 and -1. Stem cell infusion was on day 0. 9 patients were enrolled on the Phase I study: 3 patients in each cohort of thalidomide at 600 mg, 800 mg, 1000 mg. Due to somnolence associated with the increased doses of Thal in the initial 2 patients, dexamethasone (Dex) was added as 40 mg on day -5, 20 mg on day -4 and 10 mg on -2 for subsequent patients.

Results: Neutrophil and platelet engraftment occurred in all patients by 11 days post-ASCT. Grade 3 non hematologic toxicities included infections in 3 patients. 2 patients developed altered mental status following 800 mg of thalidomide. They responded to treatment with dexamethasone. No new emergent peripheral neuropathy was observed. Best response was determined at day + 100 post transplant: 2 of the 3 patients who received 600 mg of Thal showed progressive disease, one showed stable disease; 2 patients who received 800 mg of Thal showed a PR and one a VGPR. Of the patients who received 1000 mg, 1 had a VGPR, 1 had a PR and in 1 patient it was too early. Overall response rate for the 8 evaluable patients was 62% (5/8). The median PFS was 12 months. The median OS has not been reached.

Conclusion: The combination of Mel VelThal with ASCT has no added toxicities compared to ASCT with MelVel. We are currently completing the Phase II trial using Thal 1000 mg with MelVel.

P-34. Whole-Body Magnetic Resonance in the Diagnosis of Multiple Myeloma and MGUS

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Purpose of the study

The aim of the study was to assess the significance of the whole-body magnetic resonance (WB-MR) in monoclonal gammopathy of undetermined significance (MGUS) and initial form of multiple myeloma (MM).

Summarised description of the project

The analyzed cohort consisted of 28 MGUS individuals, 54 MM patients and 5 patients with solitary plasmocytoma (SP). Whole body coil with sequential acquisition – T2 STIR and T1 was used.

Results and conclusions

In the group of 28 MGUS individuals, there were 17 (61%) patients fulfilling the IMWG and/or WB-MR criteria of transformation into MM. In 4/17 (23%) patients, we found more advanced stage when comparing the D-S Plus to D-S stratification system. Nine out of 14 (64%) individuals with transforming MGUS with negative radiological assessment had positive WB-MR findings. The character of WB-MR findings led in 9/17 (53%) patients with MM to the initiation of treatment. The D-S Plus stratification divided the 54 newly diagnosed patients with MM into stages 1-3 (17%, 33% and 50%). In 22% there was a shift into a higher stage using D-S Plus in comparison with, D-S, in 9% the shift led to downstaging. In 13% we could trace extramedullary propagation. In 2 of the 5 SP patients we recognized a multifocal form using WB-MR. WB-MR is a very contributive imaging metod with substantially higher resolution than conventional radiography. It can evaluate the grade and the extent of myeloma bone disease, extramedullary propagation and the solitary form of plasmocytoma, and improves the differentiation of stable MGUS from the malignant transformation into MM.

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P-35. Analysis of Selected Biological Parameters Serum Levels in MGUS and Multiple Myeloma

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Purpose of the study

The aim of the study was to assess the benefit of 18 biological parameters in MGUS and multiple myeloma (MM) in differentiation of both conditions.

Summarised description of the project

The analyzed cohort consisted of 59 MGUS and 60 MM individuals. For the evaluation of the selected parameters we used radioenzyme assay, immunoradiometry, enzyme immunoassay, electrochemiluminiscence, quantitative sandwich enzyme immunoassay and Freelite™ system.

Result and conclusion

Statistically significant differences between MGUS and MM were found in the case of thymidinekinase (0,0002), ICTP (0,001), MIP-1alpha (0,002), osteopontin (<0,0001), HGF (<0,0001), syndecan-1 (<0,0001) and the κ/λ ratio of serum free light chains (0,0002). Lower significance was found in the case of angiogenin (0,031) and endostatin (0,011) whilst non-significant differences were within the IGF-1, osteocalcin, b-ALP, PINP, OPG, MIP-1beta, IL-17, VEGF and parathormon serum levels. Significant differences between MGUS vs MM were found in 9 of the 18 evaluated parameters, however, due to the overlaping of the measured values, non of the parameters is unabiquously able to distinguish between the compared units. A satisfactory contribution in the discrimination of MGUS from MM was found in markedly increased serum levels of thymidinekinase, MIP-1alpha, osteopontin, HGF and pathology of the κ/λ index.

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P-36. Nephelometric Measurements of κFLC and λFLC for Monitoring Light Chain Multiple Myeloma Patients

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Introduction: Serum free light chain (FLC) measurements have replaced urine electrophoresis in multiple myeloma (MM) diagnostic algorithms and are required to characterise a complete response (CR). However, with the exception of oligosecretory disease, their use is not recommended in current international guidelines for routine monitoring.

Purpose of the study: To investigate the use of serum FLC measurements for monitoring light chain MM (LCMM) patients.

Methods: Serum κFLC and λFLC levels were measured nephelometrically (The Binding Site Group Ltd) on serial samples from 25 LCMM patients (14 κFLC and 11 λFLC); specifically at presentation, after 2 and 4 cycles of therapy and post autologous stem cell transplantation (ASCT). The results were compared with historic urine protein electrophoresis (UPE) as well as urine and serum immunofixation electrophoresis (uIFE and sIFE).

Results: At presentation, all patients had a detectable band on uIFE and measurable disease using UPE (>200 mg/24h). 22/25 patients had a detectable monoclonal band by sIFE, with 1/25 patients having a monoclonal band quantifiable by SPE (11.5 g/L). In the κFLC patients, 14/14 patients had increased serum κFLC levels (median 3740 mg/L, range 689-13100 mg/L), and 14/14 patients had abnormal serum FLC κ/λ ratios (median 532, range 42-2400). In the λFLC subgroup, 11/11 patients had increased serum λFLC levels (median 3000 mg/L, range, 875-22000 mg/L) and abnormal serum FLC κ/λ ratios (median of 0.001, range 0.0001-0.02).

After treatment there were no patients with positive uIFE results and normal serum FLC ratios. After 2 cycles of therapy abnormal FLC ratios (18/20) correlated well to sIFE (17/20) results in the identification of residual disease (Pearson's r=0.7, p<0.001). The median involved FLC (iFLC) level in the 18 patients with abnormal FLC ratios was 152 mg/L (range 52-202 mg/L). uIFE underestimated the number of patients with residual disease (13/20) and moderately correlated with sIFE (Pearson's r=0.5, p=0.03). Post ASCT, uIFE and UPE indicated CR in 13/22 (59%) patients. However, serum FLC measurements detected residual disease in 5/13 (38%) of the patients achieving CR (median iFLC 23 mg/L, range, 15-32 mg/L).

Conclusion: Serum FLC measurements correlated well to sIFE results in the detection of residual disease, while urinalysis may over estimate therapeutic responses. Serum FLC measurements would provide a rapid and sensitive replacement to urinalysis for monitoring LCMM.

P-37. Multiple soft tissue lymphoplasmacytic lymphoma associated with Waldenstrom's macroglobulinemia

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We report a patient with Waldenstrom's macroglobulinemia (WM) who has developed multiple giant soft tissue masses, confirmed as lymphoplasmacytic lymphoma by biopsy. While lymphadenopathy, organomegaly and bone marrow involvement are common manifestations in WM, formation of distinct soft tissue masses has not been reported before.

P-38. Spindle like morphology of the KSHV- LANA interacting protein one (KLIP1) is necessary for proper mitotic cell division

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Kaposi's sarcoma-associated herpesvirus (KSHV) causes Kaposi's sarcoma (KS), primary effusion lymphoma (PEL) and some types of multicentric Castleman's disease (MCD). After infection, the virus enters into lymphocytes where it remains in a latent ("quiet") state expressing the viral latency-associated nuclear antigen, LANA. It (LANA) is a multifunctional protein and plays a crucial role in modulating viral and cellular gene expression. It is also necessary for the maintenance and proper segregation of the KSHV episome. KSHV – LANA interacting protein one (KLIP1) is a cellular protein discovered in our lab through its interaction with KSHV LANA. It is shown that KLIP1 is a ubiquitous nuclear protein with potent transcriptional repression capability. Besides, KLIP1 is also known as MLF1IP, CENP-50, CENP-U, ICEN24, and PBIP1. The KLIP1 gene locus is at chromosome 4q35.1 and is composed of 14 exons spanning 75.8 kb of genomic DNA. The KLIP1 cDNA encodes a 46 kDa protein that contains two bipartite and two classical nuclear localization signals, two nuclear receptor-binding motifs (LXXLL), two leucine zippers, two PEST residues and several potential phosporylation sites. There are different reports demonstrate the function of KLIP1 such as its requirement in recovery from spindle damage or proper chromosome segregation or behaves as a transcriptional factor that represses herpesvirus thymidine kinase. However, the specific function (s) of the KLIP1 is still a matter of speculation. In this present study we have determined the KLIP1 sub cellular localization along with morphological variations through immuno-fluorescence analysis at different phase of the cell cycle. Data from both ImageStreamX® cytometry and immuno-fluorescence staining followed by confocal microscopy analysis of KILP1 with different cell cycle markers revel that the expression and sub-cellular localization of KILP1 is modulated in a cell cycle dependent manner. Data also suggests the level of KLIP1 content is tightly regulated in cell cycle progression. The protein level is low in G0/G1, accumulate during S/G2, and reduce rapidly after mitosis. It has also observed that KLIP1 mainly localizes with centromere, however, it also localizes at nucleolus during S-phase. The most striking observation is that KLIP1 forms spindles similar to beta-tubulin during mitotic cell division. Both over-expression and micro-RNA mediated knockdown of KLIP1 show reduction of mitotic phase. This is the first observation which confirmed the spindle like morphology of the KLIP1 during mitotic cell division. Along with the previous findings and the present results strongly suggest that KLIP1 plays an important role in forming mitotic spindles leading to proper mitotic cell division and chromosome segregation.



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What is your occupation (mark one only)?

○ Physician ○ Academic Physician ○ Fellow or Resident
○ Nurse ○ Pharmacist ○ Other _____

Please indicate your practice type:

○ Solo ○ Academic Institution ○ Group Practice ○ Other _____
○ Hospital ○ NCI-Designated Cancer Center

What is your primary specialty (mark one only)?

○ Hematology ○ Medical Oncology ○ Radiation Oncology ○ Internal Medicine
○ Nursing ○ Pharmacology ○ Other _____

How many patients with lymphoma, myeloma, or other plasma cell disorders do you see during a typical week?

○ 1-20 patients ○ 21-40 patients ○ 41-60 patients ○ N/A – I do not see patients

How often do you <u>CURRENTLY</u> use (prior to participating in this activity) each of the following clinical management strategies for your patients with lymphoma, myeloma, or other plasma cell disorders?

	Never	Infrequently	Sometimes	Frequently	Always
Use immunomodulatory agents as frontline therapy in transplant-ineligible myeloma patients	○	○	○	○	○
Recommend transplantation only at relapse for myeloma patients	○	○	○	○	○
Use radiation therapy for Hodgkin's disease	○	○	○	○	○
Use prognostic factors to determine timing of CLL treatment	○	○	○	○	○
Use epigenetic inhibitors as a potential treatment strategy in lymphoma therapy	○	○	○	○	○
Use consolidation radiation for advanced Hodgkin's disease	○	○	○	○	○
Continue to recommend R-CHOP-21 as the standard therapy for lymphoma	○	○	○	○	○
Avoid use of purine analogs for CLL therapy	○	○	○	○	○
Recommend maintenance therapy in myeloma	○	○	○	○	○
Use targeted therapy in HL	○	○	○	○	○
Monitor for second primary malignancies for patients receiving IMiD maintenance therapy	○	○	○	○	○

After participating in this activity, how often do you <u>NOW PLAN</u> to use each of the following clinical management strategies for your patients with lymphoma, myeloma, or other plasma cell disorders?

	Never	Infrequently	Sometimes	Frequently	Always
Use immunomodulatory agents as frontline therapy in transplant-ineligible myeloma patients	○	○	○	○	○
Recommend transplantation only at relapse for myeloma patients	○	○	○	○	○
Use radiation therapy for Hodgkin's disease	○	○	○	○	○
Use prognostic factors to determine timing of CLL treatment	○	○	○	○	○
Use epigenetic inhibitors as a potential treatment strategy in lymphoma therapy	○	○	○	○	○
Use consolidation radiation for advanced Hodgkin's disease	○	○	○	○	○
Continue to recommend R-CHOP-21 as the standard therapy for lymphoma	○	○	○	○	○
Avoid use of purine analogs for CLL therapy	○	○	○	○	○
Recommend maintenance therapy in myeloma	○	○	○	○	○
Use targeted therapy in HL	○	○	○	○	○
Monitor for second primary malignancies for patients receiving IMiD maintenance therapy	○	○	○	○	○

Please rate your agreement with the following statements (use the last column of each row for any comments):

	Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree	Comments
The content of this activity was relevant to my practice	○	○	○	○	○	
The educational objectives of this activity were met	○	○	○	○	○	
The speakers were appropriate for this content	○	○	○	○	○	
Participating in this activity will influence my practice of medicine	○	○	○	○	○	
The activity addressed competencies identified by my specialty	○	○	○	○	○	

Please identify any practice changes you will consider as a result of attending this educational activity:

_____

_____

Please rate the organizational aspects of this activity (use the last column of each row for any comments):

	Excellent	Above Average	Average	Below Average	Extremely Poor	Comments
Overall quality	○	○	○	○	○	
Usefulness of the printed materials	○	○	○	○	○	
Audio-Visual aspects	○	○	○	○	○	
Quality of venue	○	○	○	○	○	
Convenience of location	○	○	○	○	○	
Registration process	○	○	○	○	○	
Clarity of the registration confirmation	○	○	○	○	○	

Commercial Bias:

	Yes	No	If yes, please elaborate
Were any aspects of the OVERALL CONTENT of this activity in any way inappropriately influenced by a commercial interest and, therefore, impacted your educational experience?	○	○	
Were any aspects of the INDIVIDUAL SPEAKER PRESENTATIONS of this activity in any way inappropriately influenced by a commercial interest and, therefore, impacted your educational experience?	○	○	

What is (are) the most important point(s) you learned from this activity?

_____

_____

If you have any comments regarding this activity, including how it might be improved, please add them here:

_____

_____

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities: _____

_____

If there are any other topics you would like to see addressed in future educational activities, please identify them here: _____

_____

_____

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A premier forum for discussion on the latest advances in lymphoma and myeloma, Lymphoma & Myeloma uses an interdisciplinary approach, featuring clinical controversies, debates, and examinations of current treatment regimens. Guided by the expertise of leaders in the fields of molecular biology, pathology, immunology, and translational and clinical research, attendees will receive a thorough understanding of the evolution of thought and therapy of lymphoma and myeloma, as well as any significant developments which may lead to improved results in patient outcomes.

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- Risk adapted approaches
- Optimal frontline regimens
- Treatment of relapsed/refractory disease
- Response criteria and monitoring
- Emerging agents and combination regimens in clinical development
- Role of maintenance therapy
- Timing and aggressiveness of treatment

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Wonderful conference; continue to bring in the world's experts and address [these] difficult topics

All presentations were excellent; it is a privilege to attend

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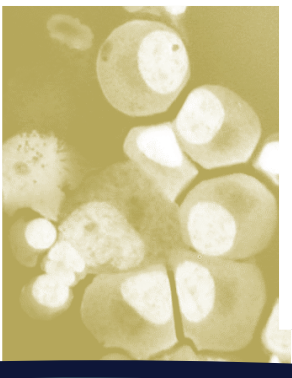
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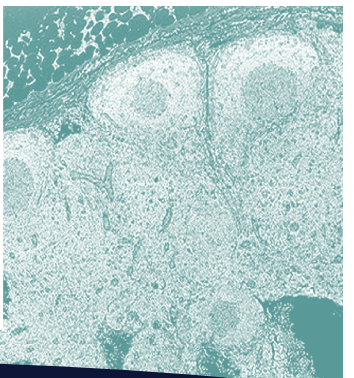
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