International Myeloma Society

The International Myeloma Society

- Established as non-profit corporation in 2008
- Aims to promote research, education, clinical studies, and workshops to improve prevention, diagnosis, prognosis, and treatment of multiple myeloma and related disorders for patients worldwide.

PLEASE JOIN TODAY
if you are not a member

International Myeloma Society

- Promotes continued innovative collaborative research in myeloma
- Assures that resultant scientific advances are translated to improved diagnosis, prognosis, and treatment of myeloma for patients worldwide.
- Fosters training of the next generation of leaders in myeloma basic and translational research.

PLEASE JOIN TODAY
if you are not a member

Eligibility for Membership

- Any person who is, or has been, engaged in research, teaching or practice in connection with multiple myeloma or related disorders is eligible for election as an active member.

Membership Benefits

- Free online subscription to *Clinical Lymphoma and Myeloma*
- Access to the "updated summaries" and slides from the most relevant presentations at ASH, ASCO, EHA, and more
- Sponsor abstract at IMW
- Discounted registration at IMW and IMS sponsored events
- Eligible for Travel Award
- Eligible to be a candidate for Board of Directors, Subcommittee's, Awards, Travel Grants, Host the IMW
- An effective voice for myeloma advocacy

Waldenström Award

- Awarded to an individual in recognition of outstanding contributions to the field of multiple myeloma

Two young Investigator awards

Bart Barlogie (clinical and therapeutic research)
Ken Anderson (basic and transitional research)

Travel Grants

ASH/ ASCO/ EHA Updates

Multiple Myeloma: Clinical Updates from the American Society of Hematology Annual Meeting 2016
Evangelos Terpos

Slide collection of best of ASH 2016
Marivi Mateos

Educational Seminars in emerging countries

Grants for short training periods

2017-19 Officers IMS

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Salamanca, Spain
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Massachusetts General Hospital Cancer Center at Harvard Medical School
Boston, MA

Donna Reece, MD
Princess Margaret Hospital
Toronto, Canada

17th International Myeloma Workshop

September, 2019 - Boston, MA, USA

Co-Chairs:

• Steven Treon, M.D., Paul Richardson, M.D., Ken Anderson, M.D., Nikhil Munshi, M.D., Irene Ghobrial, M.D., Ruben Carrasco, M.D., Constanitne Mitsiades, M.D., David Avigan, M.D., Noopur Raje, M.D.

• http://imw2019boston.org/

Our website
https://www.myelomasociety.org/
provides information about IMS, its officers and programs, as well as an easy application for membership.

Scan and
Join Today

Thank you

International Myeloma Society

Educational Workshop

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Co-Chairs:

Bob Orlowski, MD Noopur Raje, MD Shaji Kumar, MD

Program Committee:

Ashraf Badros, MD David Vesole, MD

Two young Investigator awards: Bart Barlogie (clinical and therapeutic research) Ken Anderson (basic and transitional research)

- Established by IMS to honor the seminal contributions of Professor Bart Barlogie and Ken Anderson
- Awarded to an individual (< 45 years old) to both recognize and stimulate excellence in myeloma research
- The Awards Subcommittee elaborated the basis for a structured Document of Merit (CV).
- The members of the IMS Board and the Awards Subcommittee are the electors
- $25,000 USD to support the Award winner's research.

Travel Grants

- Age 35 years or younger
- Member of IMS
- Registered for IMW
- Have an abstract selected for oral or poster presentation at IMW
- $2,000 USD to support travel to IMW

The International Myeloma Society

Our website https://www.myelomasociety.org/ provides information about IMS, its officers and programs, as well as an easy application for membership.

Waldenström Award

The Awards Subcommittee:

The Awards Subcommittee elaborated the basis for a structured Document of Merit (CV) to be asked to the potential nominees and the selection process.

Composed of 10 recognized persons in the myeloma field and also representing different geographical areas.

The current composition is Douglas Joshua, Chair, Robert Kyle, Hirokazu Murakami, Gareth Morgan, Mario Boccadoro, Paul Richardson, Heinz Ludwig, Donna Reece, Michel Attal, and Vania Hungria.

Subcommittees

Financial Committee – Shaji Kumar
Sagar Lonial, Angela Dispenzieri, Angelo Maiolino

Membership Committee – Donna Reece & Giampaolo Merlini (co-chair)
Kazuyuki Shimizu, Vania Hungria, Sonja Zweegman

Education Committee – Nikhil Munshi
Philippe Moreau, Herman Einsele, Irene Ghobrial, Maria Victoria Matoes, Joy Ho, Donna Reece, Robert Orlowski, Sundar Jagannath

Awards Committee – Douglas Joshua & Robert Kyle (co-chair),
Hirokazu Murakami, Gareth Morgan, Mario Boccadoro, Paul Richardson, Heinz Ludwig, Michel Attal, Vania Hungria, Donna Reece

Workshop Committee- Sagar Lonial
Tierry Facon, Angela Dispenzieri, Giampaolo Merlini, Meletios-Athanassios Dimopoulos, Steve Treon, Vincent Rajkumar

Scientific Committee- Philippe Moreau
Michele Cavo, Herve Avet-Loiseau, Faith Davies, Keith Stewart, Pieter Sonneveld, Nikhil Munshi, Noopur Raje, Wee Joo Chng

Financial Committee

Chair: Shaji Kumar
Sagar Lonial
Angela Dispenzieri
Angeloa Majolino

Mission: Recommend financial policies, goals, and budgets that support the mission, values, and strategic goals of the organization.

Membership Committee

Chair: Donna Reece
Co-Chair: Giompaolo Merlini (co-chair)
Kazuyuki Shimizu
Vania Hungria
Sonja Zweegman

Mission: Develop new and innovative ways to attract new members as well as retain current membership via multiple mediums including the webpage of the Society.

Education Committee

Chair: Nikhil Munshi

Herman Einsele
Irene Ghobrial
Joy Ho
Robert Orlowski
Philippe Moreau
Maria Victoria Mateos-Manteca
Donna Reece
Sundar Jagannath, MD

Mission: The central role of the educational committee is to provide, through various means, myeloma related education to both healthcare providers as well as patients. This committee will develop and organize various printed, electronic, social media, and educational seminars to present state-of-the-art information on myeloma therapies and patient management. It will also support development of programs and various activities to promote basic laboratory research as well as translational applications. It will supervise various educational programs globally on a yearly basis following major hematologic and/or oncology meetings (ASCO, ASH, EHA and IMW) to inform the physicians about advances in myeloma as well as providing guidance in utilizing the novel diagnostic and therapeutic means available.

Awards Committee

Chair: Douglas Joshua

Co-Chair: Robert Kyle

Hirokazu Murakami
Gareth Morgan
Mario Boccadoro
Paul Richardson
Heinz Ludwig
Michel Attal
Vania Hungria
Donna Reece

Mission: To establish the application process for the three major awards, the Waldenström's award, the Bart Barlogie Clinical Therapeutic award and the Ken Anderson Translational Research award, given in recognition of the seminal contributions these physicians have made to the understanding and therapy of myeloma. In addition, we have established travel awards for young investigators to encourage attendance at the myeloma workshop, the premier myeloma meeting of our association.

Workshop Committee

Chair:

Sagar Lonial
Tierry Facon
Angela Dispenzieri
Giampaolo Merlini
Meletios-Athanassios Dimopoulos
Steve Treon
Vincent Rajkumar

Mission: To standardize and organize decision making around evaluation of IMW Organizing Committee and locations. This committee will solicit applications, evaluate applications, and score applications with the intent of objectively and transparently deciding which city and group will be awarded the opportunity to host the International Myeloma Workshop in odd calendar years.

Scientific Committee

Chair:

Phillippe Moreau
Michele Cavo
Herve Avet-Loiseau
Faith Davies
Keith Stewart
Pieter Sonneveld
Nikhil Munshi
Noopur Raje
Wee Joo Chng

Mission: The role of the scientific committee is to provide guidance for the scientific program for the meetings organized under the auspices of IMS including the biennial International Myeloma Workshop. The committee will review and approve the scientific program for the meetings. It will also lead the efforts to collate important presentations from major meetings and make them available for the members. It will play an active role in reviewing and providing necessary guidance to scientific studies and / or publications that are being planned by the IMS.

IMS and the International Myeloma Workshop

Workshop Venue

- Establishes an equitable process for solicitation of proposals and the selection of sites for our biennial International Myeloma Workshops.
- Assures that venues chosen for future workshops have appropriate meeting space, accommodations, and transportation, with a sponsoring institution and organizing committee.

IMS and the International Myeloma Workshop

Scientific Program

Provides assistance in defining the breadth and quality of content represented at the International Myeloma Workshops to include cutting-edge scientific and clinical advances, as well as all aspects of current diagnosis, prognosis, and treatment of myeloma.

Applying to Host IMW

- Deadline for proposals November 1, 2017 -There is no application form but we invite you to submit an outline proposal – no more than 6 pages – which addresses the areas identified below.

Criteria for hosting IMW meeting includes:

- Meeting Space - One should plan for up to 3,000 attendees.
- Accommodations - There should be approximately 2,500 sleeping rooms within easy commuting distance.
- Transportation - The host city should be within one hour from a major International airport.

Applying to Host IMW

- Please state the approximate proposed dates in your proposal, sponsoring institution and organizing committee.
- The call for proposals is sent out approximately four years in advance with a deadline of November 1.
- Proposals will be discussed at ASH IMS Board Meeting
- Final selection of the destination will be made by a transparent vote by the IMS Board and prior IMW Chairpersons, with notification of the winning site during January.

Applying to Host IMW

- Please send applications to IMS president for review to president@myelomasociety.org and copy adminassistant@myelomasociety.org

Waldenström Award

Nominations:

- Each member of the IMS Board and each member of the Awards Subcommittee *select two candidates, and the four with the most votes are nominated for the Waldenström Award*.

- All of the four nominees are then asked to complete the Document of Merit developed by the Awards Subcommittee, which is circulated among the electors.

Waldenström Award

Final Election:

- Members of the IMS Board and members of the Awards Subcommittee, each vote for one nominee, and the one who obtains the most votes becomes the awardee.
- Conflict of interest: Any member, either IMS or Awards Subcommittee, who are directly linked to the applicant will have access to the applications but will not be involved in the voting process

Bart Barlogie Young Investigator Award

- Established by IMS to honor the seminal contributions of Dr. Bart Barlogie to myeloma treatment
- Awarded to an individual (< 45 years old) to both recognize and stimulate excellence in myeloma research
- $25,000 USD to support the Award winner's research.

Bart Barlogie Young Investigator Award

- Personal data: Date of birth, institution, your current position and director of your research.
- Field of myeloma research: brief description of your clinical/lab/research activities.
- Research: original papers, reviews, book chapters, any consensus statements and abstracts at major meetings.
- Funded Research
- Honors and Prizes
- Teaching and Training activities
- Five top publications in which you are first or senior author
- Three top clinical and/or technology achievements/ innovations
- Maximum of 3 pages

Bart Barlogie Young Investigator Award

Application Evaluation

Each eligible application will be reviewed by the current members of the IMS Board and members of the Award Subcommittee. Applicants must be a member of IMS in good standing at the time the application is submitted and through the duration of the award funding period.

The members of the IMS Board and the Awards Subcommittee will be the electors by voting for only one applicant.

Conflict of interest: Any member, either IMS or Award Subcommittee, who are directly linked to the applicant will have access to the applications but will not be involved in the voting process.

Ken Anderson Young Investigator Award for basic and transitional research

- Established by IMS to honor the seminal contributions of Professor Ken Anderson to bench to bedside transitional research and myeloma treatment.
- Awarded to an individual (< 45 years old) to both recognize and stimulate excellence in myeloma research
- $25,000 USD to support the Award winner's research.

Ken Anderson Young Investigator Award for basic and transitional research

- Personal data: Date of birth, institution, your current position and director of your research.
- Field of myeloma research: brief description of your basis or bench to bedside transitional research activities.
- Research: original papers, reviews, book chapters, any consensus statements and abstracts at major meetings.
- Funded Research
- Honors and Prizes
- Teaching and Training activities
- Five top publications in which you are first or senior author
- Three top clinical and/or technology achievements/ innovations
- Maximum of 3 pages

Ken Anderson Young Investigator Award for basic and transitional research

Application Evaluation

Each eligible application will be reviewed by the current members of the IMS Board and members of the Award Subcommittee. Applicants must be a member of IMS in good standing at the time the application is submitted and through the duration of the award funding period.

The members of the IMS Board and the Awards Subcommittee will be the electors by voting for only one applicant.

Conflict of interest: Any member, either IMS or Award Subcommittee, who are directly linked to the applicant will have access to the applications but will not be involved in the voting process.

Clinical Lymphoma, Myeloma, & Leukemia

Senior Editor: Sundar Jagannath, MD

Editor, Myeloma: Sagar Lonial, MD

- Society: International Myeloma Society, Society of Hematologic Oncology
- Impact Factor: 2.02 (Increased from 1.6)
- Print Circulation: 10,000+
- Rejection Rate: 70%
- Article downloads per month: 5,222
- Will consider for publication: original research (including clinical trials), meta-analyses, reviews, current trial reports, case studies
- Open access publication opportunities: $1700.00 sponsorship fee
- Article submission: http://ees.elsevier.com/clml

ISSN: 2152-2650
Current Vol: 15
Frequency: Monthly

International Myeloma Society & Elsevier

- Elsevier provides free online access to CLML to IMS members (optional discounted print subscription rate of USD $95 (US) or USD $145 (International))
- Elsevier will publish “IMS Update” (limit 8,000 words print, unlimited online), which is provided by the IMS
- Elsevier provides IMS all publication schedules upon request
- Elsevier will publish one color advertising page in each issue of the Journal (non-covers). Ad provided by IMS
- Clinical Lymphoma, Myeloma & Leukemia carries "Official Journal of the International Myeloma Society” on its cover and all branded marketing communications
- Elsevier offers revenue-sharing supplement opportunities (print/online). IMS provides expertise on content

Thank you

Future Dates and Locations

Educational Workshop

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+Jd|orug#Qdwlrqdd#Krwho,

Co-Chairs:

Goal for the Educational Symposia Series

- Share with local hematologists the state of the art on diagnosis, monitoring and treatment of Plasma Cell malignancies paying special attention to the current practice in the local countries and the opportunities for improvement.
- Our purpose is also to offer the opportunity for social interaction in order to establish potential collaborations with the invited speakers including the possibility of visiting their institutions or establishing fellowship programs.

Program
Includes lectures plus roundtable discussions around the most hot and controversial topics.

- This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Mayo Clinic College of Medicine and Science and the International Myeloma Society. Mayo Clinic College of Medicine and Science is accredited by the ACCME to provide continuing medical education for physicians.
- The Mayo Clinic of College of Medicine and Science designates this live activity for a maximum of 10.75 AMA PRA Category 1 Credit(s) ™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Friday, August 11, 2017

07:45-8:00	Welcome and introduction
08:00-08:30	The myeloma pathogenesis with focus on the immune system *Ivan Borrelo, MD*
08:30-9:00	Genetics in MM patients *Rafael Fonseca, MD*
09:00-09:30	What are the optimal Imaging Techniques in MM? MRI, CT-scan and PET? *Marivi Mateos, MD*
09:30-10:00	Coffee
10:00-10:30	How to perform an appropriate protein screening and decisions on follow-up? *Joan Bladé MD*
10:30-11:00	Minimal residual Disease. How and when to do it? *Jesús San Miguel, MD*
11:00-12:00	**Roundtable:** How to do a correct diagnosis and follow-up, including the new diagnostic and response criteria *Moderator: Jesús San Miguel, MD:* ***2-3 clinical cases*** *Discussants: Guillermo Conte, MD, Dorotea Fantl, MD, Juan Navarro, MD, Joan Bladé, MD, Rafael Fonseca, MD, Marvi Mateos, MD*
12:00-13:00	Lunch
13:00-13:30	MGUS & Smouldering Myeloma. How to predict outcome & "To treat or not to treat" *Marivi Mateos, MD*

IMS Educational Workshop – Agenda

Santiago, Chile–August 11-12, 2017 (Crowne Plaza)

Friday, August 11, 2017 (continued)

13:30-15:00 How I treat newly diagnosed transplant candidate MM patients
Sergio Giralt, MD (30').
Roundtable on 6 controversial questions with emphasis in local practice (60') Moderator: *Rafael Fonseca, MD*
Discussants: *David Gómez-Almoguer, MD, Angelo Maiolino, MD, Natalia Schutz, MD, Joan Blade, MD, Sergio Giralt, MD, Jesus San Miguel, MD*

1. Best induction
2. Early vs. late transplant
3. One or two
4. Consolidation
5. Maintenance
6. Allotransplant

15:00-15:30 Coffee

15:30-17:00 How I treat newly diagnosed elderly patients?
Ruben Niesvizky, MD (30')
Roundtable on 5 controversial questions with emphasis in local practice (60')
Moderator: Marivi Mateos, MD
Discussants: Vania Hungria, MD, Jose Luis Lopez, MD, Eloisa Riva, MD, Sergio Giralt, MD, Rafael Fonseca, MD, Ruben Niesvizky, MD

1. Optimal combinations
2. Fixed versus continuous therapy
3. Do we need alkylators?
4. High risk
5. Frailty scales

IMS Educational Workshop – Agenda

Santiago, Chile–August 11-12, 2017 (Crowne Plaza)

Saturday, August 12, 2017

8:00-9:30 How to make the right choices in the relapsed patient
Enrique Ocio, MD
Roundtable on **5 clinical cases** with emphasis in local practice (60')
Moderator: Jesus San Miguel, MD
Discussants: Timoteo Anguita, MD, Edvan Crusoe, MD, Amado Karduss, MD, Enrique Ocio, MD, Ruben Niesvizky, MD, Rafael Fonseca, MD

1. Biological relapse versus aggressive relapse
2. Early and late relapse and ASCT
3. Triplet versus doublets: is it cost-effective?
4. Optimal sequence for new agents
5. Allotransplant

9:30-10:00 Amyloidosis: "Under-diagnosed disorder"
Joan Bladé, MD

10:00-10:30 Waldenstrom Macroglobulinemia
Enrique Ocio, MD

10:30-11:00 Coffee

11:00-11:30 Treatment of Disease Complications
Jesus Berdeja, MD

11:30-12:15 Keynote lecture: Present and future of MM
Nikhil Munshi, MD

12:15 Lunch

IMS Educational Workshop – Agenda

Santiago, Chile–August 11-12, 2017 (Crowne Plaza)


THANK YOU TO OUR SPONSORS
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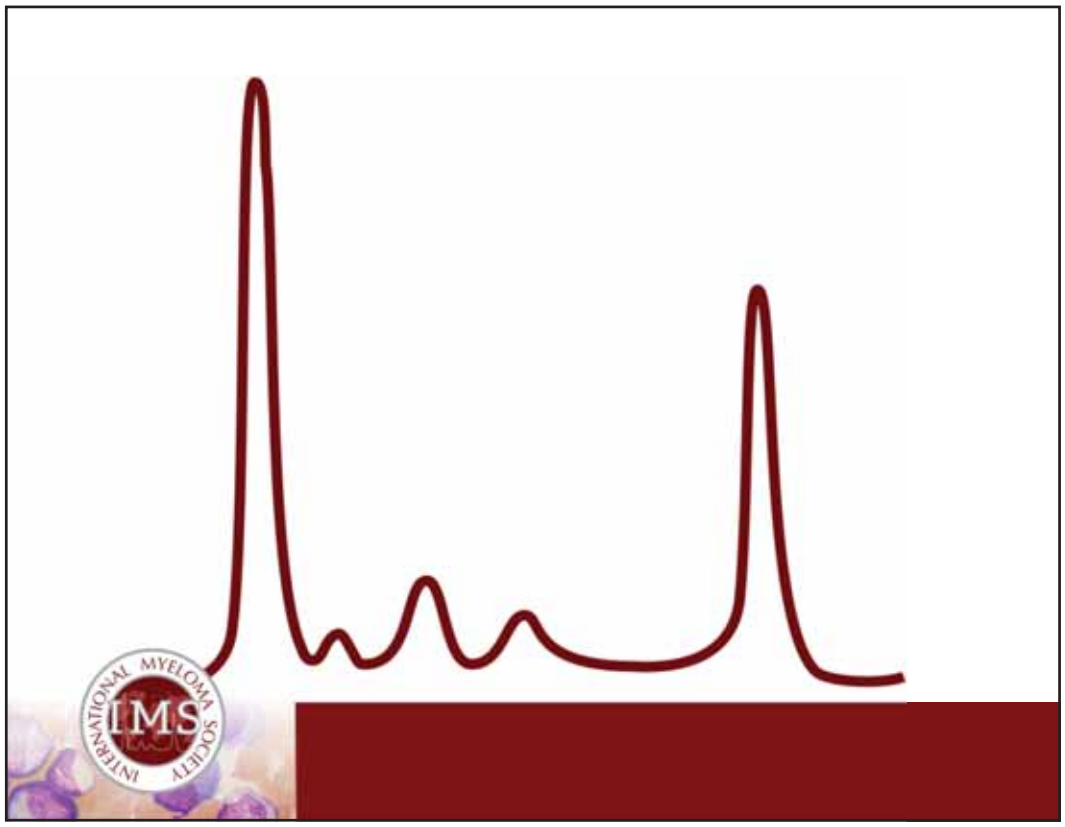
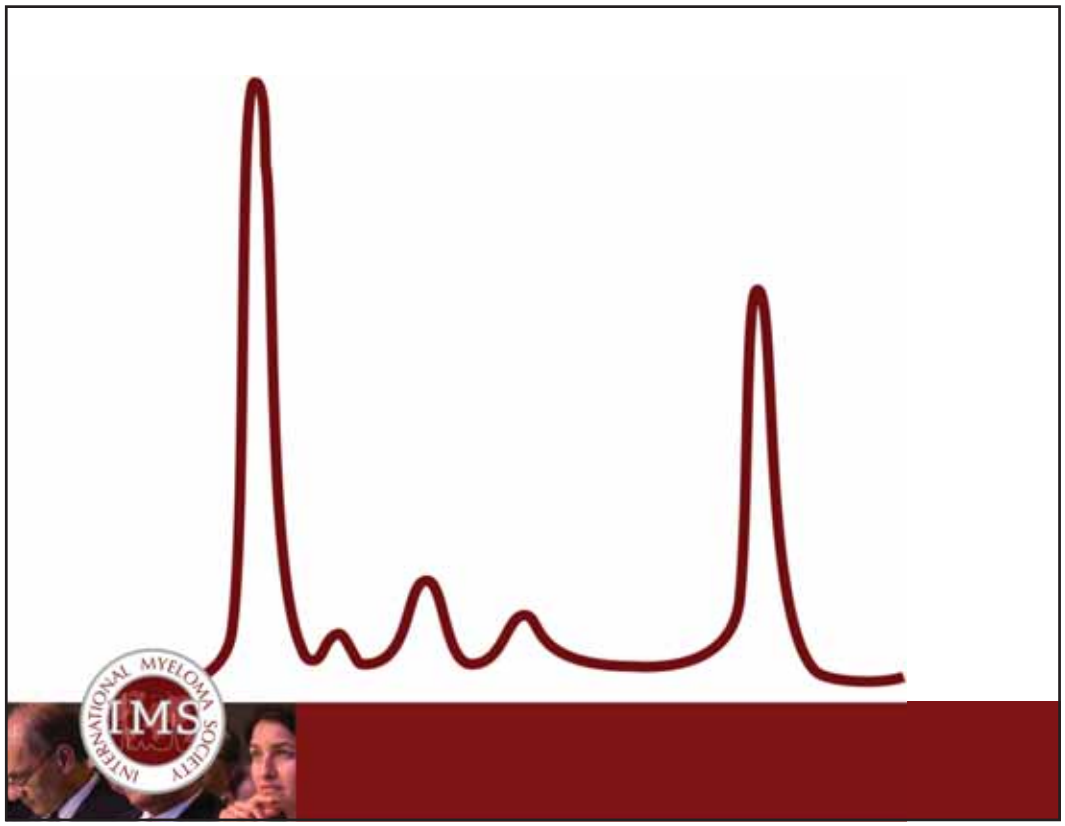
ONCOLOGY
This activity is supported by an educational grant from Celgene Corporation.
Additional support provided by:
Laboratorio Varifarma S.A.
INTERNATIONAL MYELOMA SOCIETY
IMS
IMS Educational Workshop – Agenda
Santiago, Chile–August 11-12, 2017 (Crowne Plaza)


INTERNATIONAL MYELOMA SOCIETY
IMS



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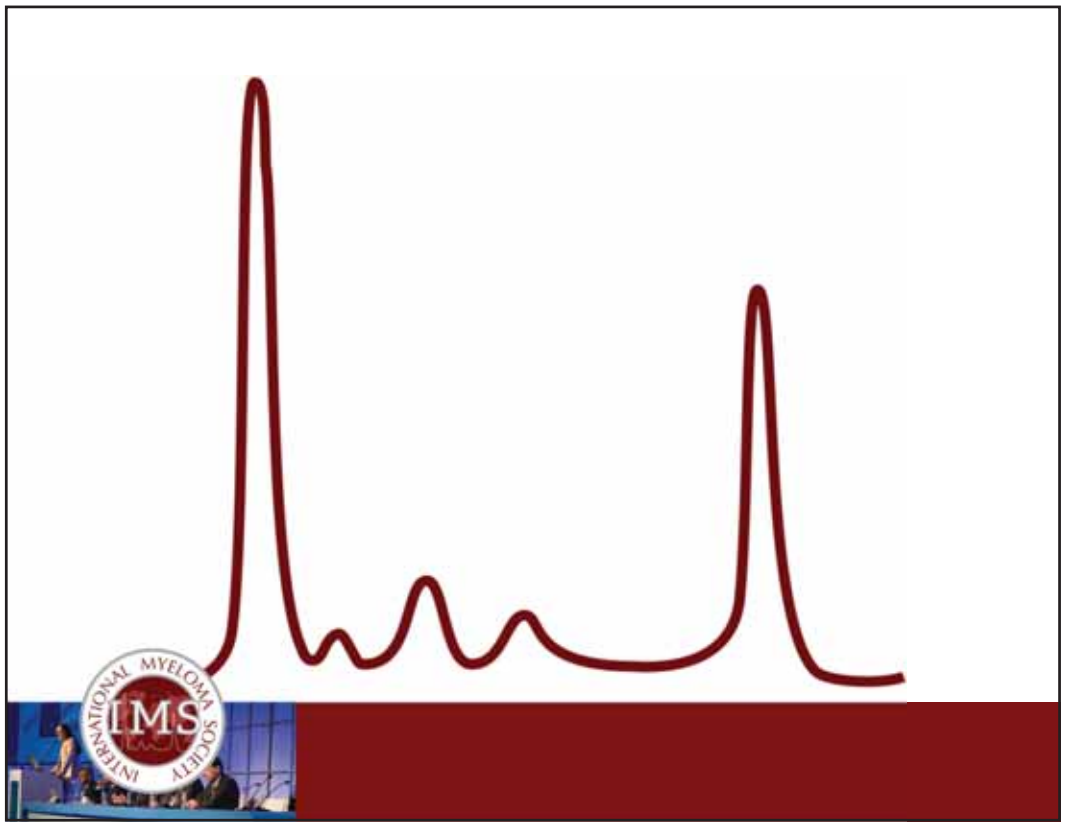

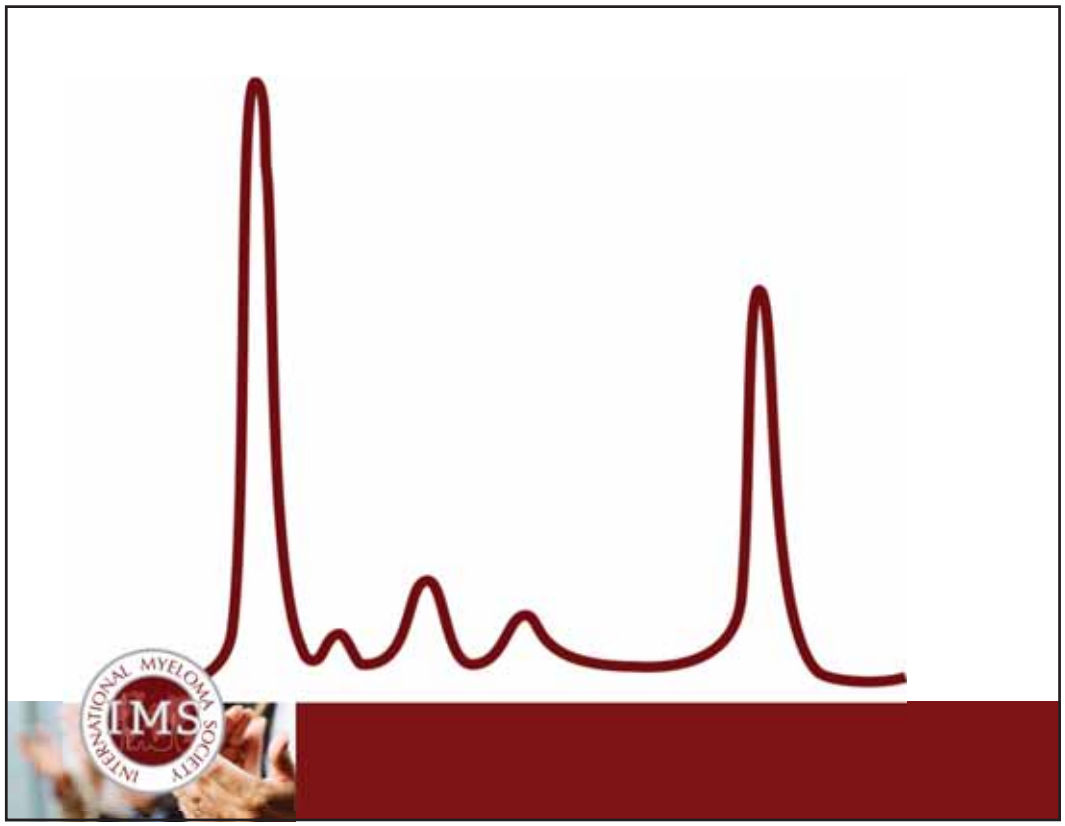

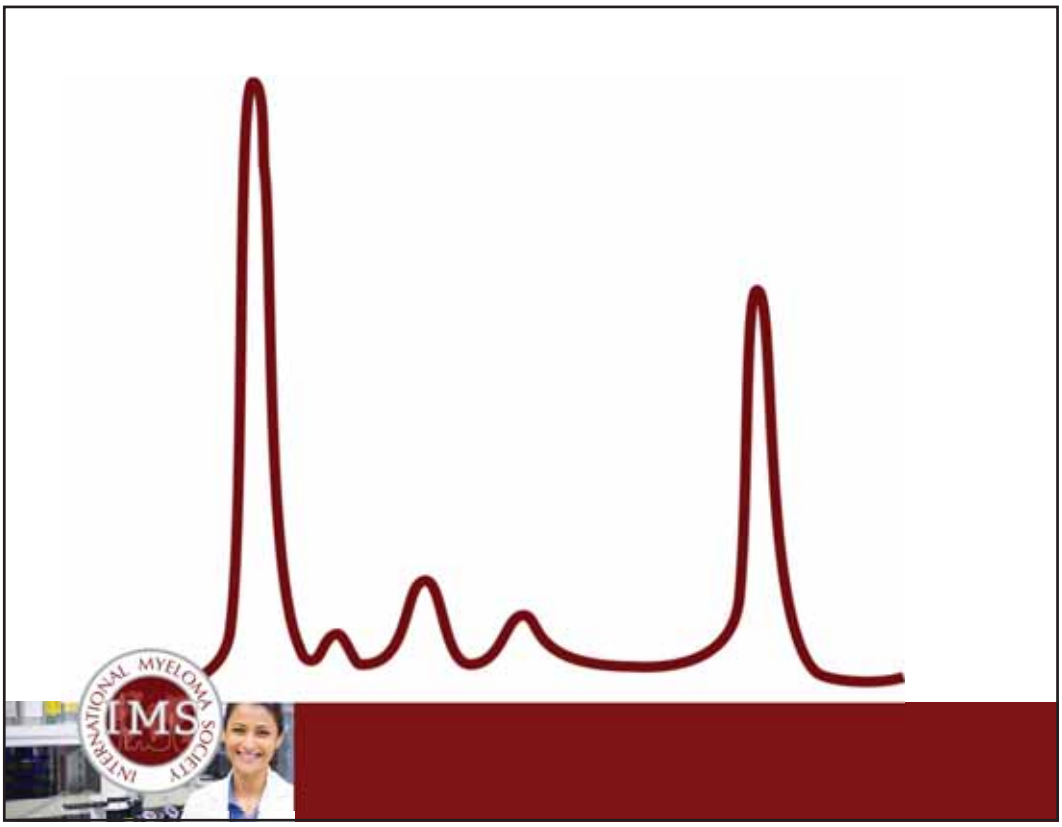

Multiple Myeloma: The Past, Present & Future

IMS Education Workshop
Washington, DC
October 27, 2017
Robert A. Kyle, MD
Mayo Clinic, Rochester, MN

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

Disclosures for Robert A. Kyle

Celgene	Disease Monitoring Committees
Bristol-Myers Squibb	Independent Monitoring Committee
Pharmacyclics	Data Safety Monitoring Board

My role for the Monitoring Committees is monitoring toxicity and efficacy of the tested drug. I do not participate in entering any patients on the above-listed activities.

All monitoring committees are compensated at an hourly rate.

I am not a member of a Speaker's Bureau.

Multiple Myeloma
Learning Objectives

- Gain an appreciation of progress in the past seven decades
- Introduction to the novel agents resulting in increased overall survival

MAYO CLINIC

Multiple Myeloma

Sarah Newbury, 39F

• 1840	Severe back pain
• April, 1842	Fractured femurs
• April 15, 1844	St. Thomas Hospital
• Rx	Orange peel, rhubarb pills & opiates
• April 20, 1844	Death

MAYO CLINIC

Solly S, Med Chir Trans Lond 27:435, 1844

MAYO CLINIC

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CASE OF

MOLLITIES AND FRAGILITAS OSSIUM,

ACCOMPANIED WITH URINE STRONGLY CHARGED WITH ANIMAL MATTER.

BY

WILLIAM MACINTYRE, M.D.

PHYSICIAN TO THE WESTERN GENERAL DISPENSARY.

Received February 4th.—Read April 9th, 1850.

Mr. M——, a highly respectable tradesman, aged 45, placed himself under my care on the 30th of October, 1845. He was then confined to the house by excruciating pains of the chest, back, and loins, from which he had been suffering, more or less, for upwards of twelve months. On

MAYO CLINIC

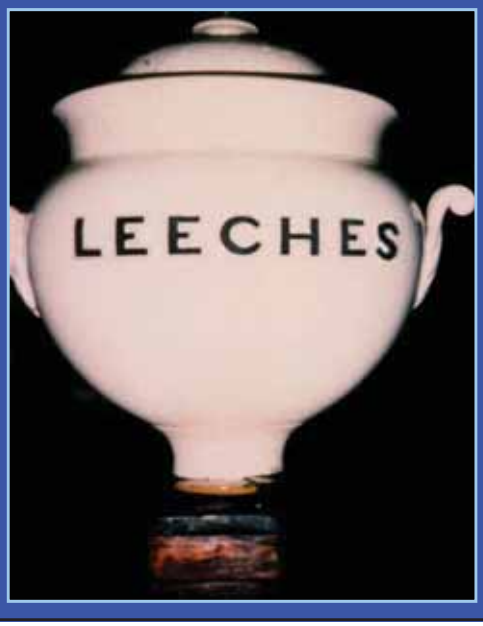
CP1143748-1

Treatment of Multiple Myeloma
Thomas Alexander McBean

- Strengthening plaster to chest
- Removal of a pound of blood
- Maintenance Therapy

MAYO CLINIC

Thomas Alexander McBean



MAYO CLINIC

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Thomas Alexander McBean

MAYO CLINIC

CP1143748-5

Treatment of Multiple Myeloma
Thomas Alexander McBean

- Cupping
- Steel and quinine
- Dover's powder
- Camphor julep
- Alum

MAYO CLINIC

CP1143748-8

Thomas Alexander McBean

CERTIFIED COPY OF AN ENTRY OF DEATH

Given at the GENERAL REGISTER OFFICE, SOMERSET HOUSE, LONDON

REGISTRATION DISTRICT Marylebone

1866 DEATH in the Sub-district of Cavendish Square in the County of Middlesex

DX 978854

1130 DISEASES OF THE BLOOD

Multiple Myeloma. *Definition.* Multiple myeloma is a malignant tumor arising in the bone marrow which tends to occur in persons after the fifth decade. It is usually characterized by pain in the back and weakness, skeletal involvement especially of the trunk, pathological fractures, a normocytic anemia of moderate degree, and the presence of a peculiar type of protein (Bence-Jones) in the urine.

Although it has not received general acceptance, the most satisfactory tentative view is to consider multiple myeloma as a neoplastic process in which the myeloid cells are derived from the hematopoietic system. If this is true, the condition bears a close relationship to leukemia. The cells making up the tumors have been most commonly regarded as plasma cells although their identification is by no means definite. Possibly myeloma cells are a distinctive type varying from all other forms.

Symptoms and Signs. The condition is observed twice as commonly in males as in females. Almost all cases occur after the age of forty years. Pain of a vague, intermittent, shifting type, often referable to the spine, is commonly the earliest evidence of the disease. As the condition progresses this frequently is a severe and dominant symptom. Tumors and pathologic fractures, usually in bones containing red marrow, are common. Changes in the spine causing compression of the spinal cord with its resultant neurological manifestations is not a rare complication.

Blood. A moderately severe normocytic or slight macrocytic normochromic anemia is almost always present. The leukocyte count is ordinarily normal, slightly elevated or diminished, and the differential formula is usually not disturbed or may reveal only an occasional abnormal white blood cell. Rarely have many plasma cells been observed in the blood stream but these, when present, have caused the condition to be regarded as a plasma cell leukemia.

A finding of great diagnostic importance is the presence of Bence-Jones protein in the urine, which appears in about two-thirds of the cases. It may occur occasionally in the urine of patients with leukemia and polycythemia. This protein precipitates at temperatures of 50° to 60° C.; further heating causes it to go into solution at about boiling, and on cooling it reappears. Its presence appears to be limited to pathologic conditions attacking the bone or bone marrow. There may be a pronounced hyperproteinemia, as indicated by plasma protein determinations, which are often found to be 10 Gm. per 100 cc. of plasma, or above; figures twice as high as this have been reported. This is due entirely to an increase in the globulin fraction. Autohemagglutination, or spontaneous clumping of the erythrocytes, occurs in some cases. This accounts for the tendency to striking rouleau formation and an accelerated sedimentation rate. Serum calcium is frequently elevated to levels of 18 to 20 mg. per cent, but the serum inorganic phosphates are usually normal.

In addition to those mentioned above, there are two diagnostic procedures which are of great importance: (1) sternal puncture, which usually reveals the presence of typical myeloma cells, and (2) roentgen ray examination which demonstrates the characteristic punched out areas, without evidence of bone regeneration, in the ribs, spine, clavicles, skull and the shoulder and pelvic girdles.

Prognosis and Treatment. The disease is uniformly fatal after an average duration of life of between two and three years. Occasionally the course is prolonged with remissions and exacerbations. Roentgen ray exposures should be employed in all cases, as it frequently gives worth-while symptomatic relief and may prolong life in some instances. This, with blood transfusions, is the only known therapeutic agent of recognized value. Otherwise the treatment is symptomatic.

PH965519_1

"Cyrus C. Sturgis"

Multiple Myeloma

Prognosis and Treatment. The disease is uniformly fatal after an average duration of life of between two and three years. Occasionally the course is prolonged with remissions and exacerbations. Roentgen ray exposures should be employed in all cases, as it frequently gives worth-while symptomatic relief and may prolong life in some instances. This, with blood transfusions, is the only known therapeutic agent of recognized value. Otherwise the treatment is symptomatic.

"Cyrus C. Sturgis"

PH965519_1.Dig

Cecil Textbook of Medicine 7th Ed., 1948

URETHANE AND STILBAMIDINE IN MULTIPLE MYELOMA*

REPORT ON TWO CASES

NILS ALWALL
M.D. Lund
From the Medical Clinic, Lund University, Sweden

Lancet 2:388, 1947

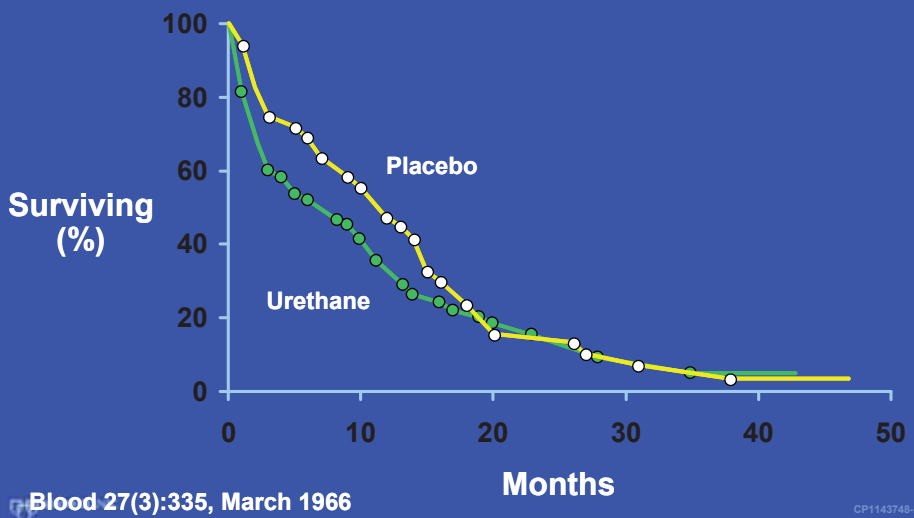
MAYO CLINIC

CP1143748-20

MAYO CLINIC

CP1143748-23

Survival from Onset of Treatment of Multiple Myeloma



Blood 27(3):335, March 1966

CP1143748-24

Treatment of Multiple Myeloma

L-sarcolysin (L-phenylalanine mustard) (Melphalan) (Alkeran)

Blokhin et al, 1958
Bergsagel et al, 1962

MAYO CLINIC

CP1143748-22

MULTIPLE MYELOMA AND ACUTE MYELOMONOCYTIC LEUKEMIA

Report of Four Cases Possibly Related to Melphalan

ROBERT A. KYLE, M.D., ROBERT V. PIERRE, M.D., AND EDWIN D. BAYRD, M.D.

NEJM 283:1121, 1970

MAYO CLINIC

CP1143748-31

Multiple Myeloma
Single (M/P) vs Combination Chemotherapy (CCT)

n=4,930 (20 trials)

Therapy	Response (%)
M/P	53
CCT	60

P<0.00001

No difference in survival

No subsets with benefit

MAYO CLINIC

J. Clin Oncol. 16:3823, 1998.

CP1123175-33

Autologous Stem Cell Transplant

- Plasma cell leukemia
- Melphalan 140 mg/m^2 IV with good response
- Collected stem cells
- Relapsed and given Melphalan 140 mg/m^2 IV plus stem cells
- Treated 8 myeloma patients

MAYO CLINIC

McElwain TJ, Powles RL. Lancet 1983 Oct 8;2(8354):822-4.

Multiple Myeloma
Autologous Stem Cell Transplantation
N=700

			PFS Mos	CR %	MRD Absent %	OS 5 yr %
RVD x 3	Autologous transplant + RVD x 2	lenalidomide 1 year	50	59	79	81
	RVD x 5	lenalidomide 1 year	36	48	65	82

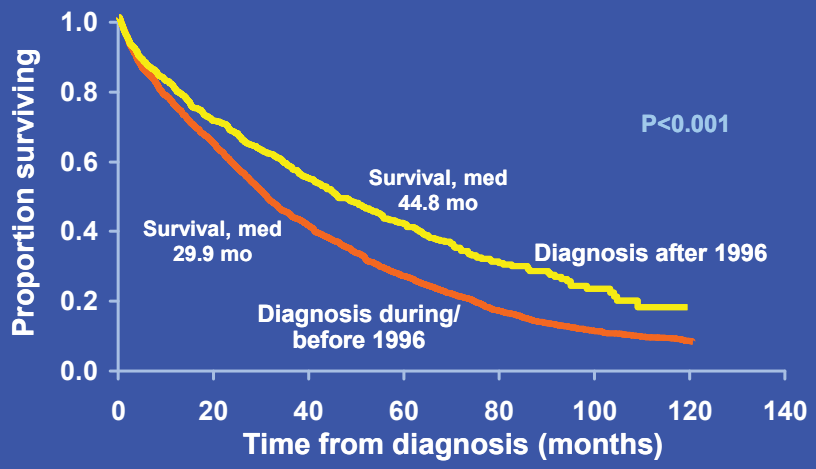
Attal M et al., N Engl J Med 376:14, 2017

Multiple Myeloma

Novel Agents

- Thalidomide
- Bortezomib (Velcade)
- Lenalidomide (Revlimid)

Multiple Myeloma 1971-2006 n=2,981



Kumar et al: Blood 111:2516, 2008

MAYO CLINIC

CP1315995-1

Multiple Myeloma

Novel Agents

- Pomalidomide (Pomalyst)
- Carfilzomib (Kyprolis)

MAYO CLINIC

Multiple Myeloma

Newer Approved Agents

- Ixazomib (Ninlaro)
- Elotuzumab (Empliciti)
- Daratumumab (Darzalex)

Multiple Myeloma
Relapsed, Refractory

Castor Trial
N=474

	N	Response	PFS 12 mos	PFS* Median (mos)
Daratumumab + Bortezomib + Dexamethasone	240	83%	77.5%	9.3
Bortezomib + Dexamethasone	234	63%	29%	6.5

*Received 2 or 3 previous lines of therapy

Palumbo A, et al., N. Engl J. Med 375:754, 2016

Multiple Myeloma
Relapsed, Refractory

Castor Trial – Side Effects

	Grade 3/4	Thrombocytopenia	Anemia	Neutropenia	Infusion reaction
Daratumumab + Bortezomib + Dexamethasone	76%	45%	14%	13%	45%
Bortezomib + Dexamethasone	62%	44%	31%	9%	-------

Palumbo A, et al., N. Engl J. Med 375:754, 2016

Multiple Myeloma
Relapsed, Refractory

POLLUX Trial

	CR	≥ PR	PFS (12 mos)
Daratumumab + Lenalidomide + Dexamethasone (DRd)	43%	93%	83%
Lenalidomide + Dexamethasone (Rd)	19%	76%	60%

Dimopolous MA et al., New Engl J. Med 375:1319, 2016

Multiple Myeloma
Relapsed, Refractory

POLLUX Trial

	Gr 3-4	Thrombocytopenia	Anemia	Neutropenia	Infusion
Daratumumab + Lenalidomide + Dexamethasone (DRd)	43%	13%	12%	52%	48%
Lenalidomide + Dexamethasone (Rd)	19%	14%	20%	37%	

Dimopolous MA et al., New Engl J. Med 375:1319, 2016

Multiple Myeloma
Relapsed Myeloma

Trial	Regimen	CR (%)	PFS (Median in months)	HR (95% CI) for progression free survival; P value
Lenalidomide-Based Regimens				
ASPIRE Carfilzomib (Selective proteasome inhibitor)	Rd	14	17.6	0.69 (0.57-0.83) P=0.0001
	KRd	32	26.3	
POLLUX Daratumumab (monoclonal antibody targeting CD 38)	Rd	19	18.4	0.37 (0.27-0.52) P<0.001
	DRd	43	NR	
Bortezomib-Based Regimens				
CASTOR Daratumumab (monoclonal antibody targeting CD 38)	Vd	19	7.2	0.39 (0.28-0.53) P<0.001
	DVd	**9**	**NR**	

Rajkumar SV, Kyle RA, N Engl. J Med 375:1390, 2016

kyle.robert@mayo.edu

MAYO CLINIC

Genomics to predict disease outcomes: Are we there yet?

Hervé AVET-LOISEAU, MD, PhD
IUC-Oncopole
Toulouse, France

Why Evaluate Genetics

- To evaluate risk – prognosis
- To select therapy
  - Induction
  - Consolidation/maintenance
  - Therapy for relapse
- To consider targeted agents
- Identify new targets and agents
- Understand biology -prevention

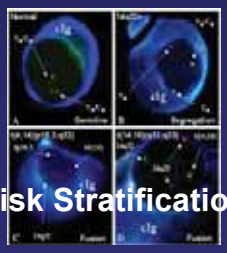
What Are the Methods Used to Evaluate Genetics

- FISH and ~~Cytogenetics~~
- Copy number Changes
  - SNP array
  - CGH array
- Expression Profile
  - array-based
  - RNA-sequencing

Multiple Myeloma – Genomic Studies

Gene Expression Profile

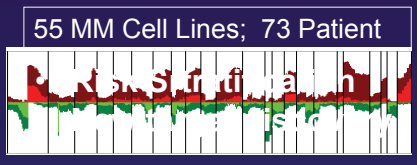
- Risk Stratification
- New target discovery
- Drug selection
- Personalized medicine



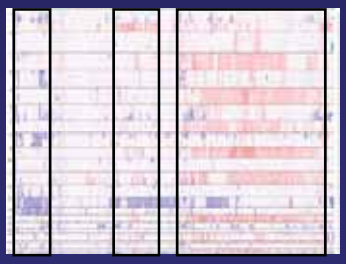
- Risk Stratification

Cytogenetics/FISH

aCGH

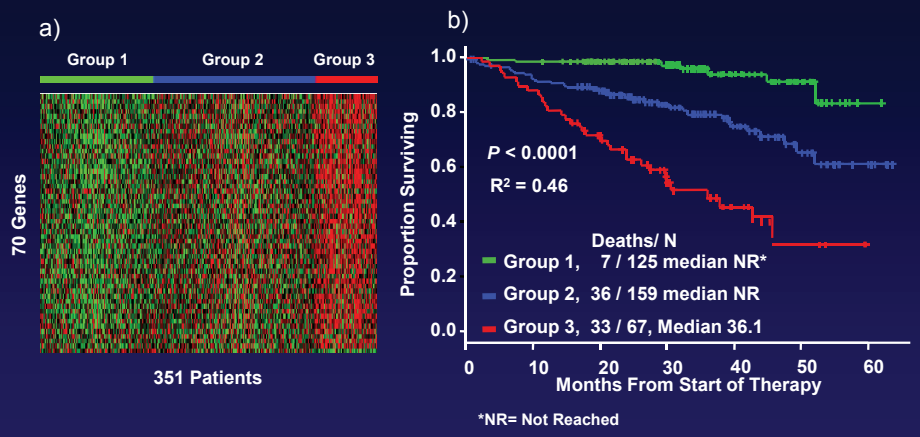


192 Newly Dx patients - HDT



SNP Array
Copy Number Alteration

Gene Expression Profiling Predicts Outcome

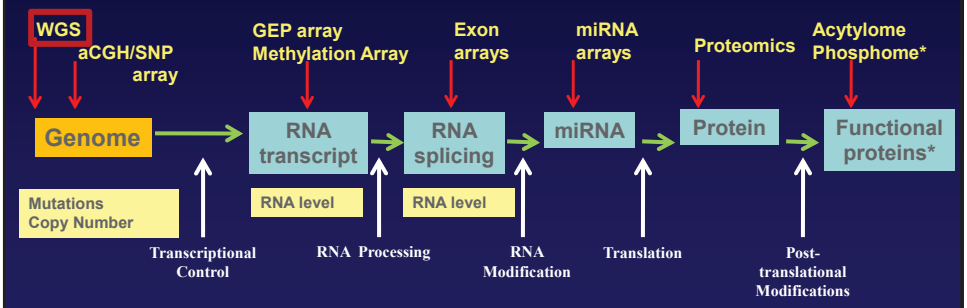


Overall survival of MM patients from the start of therapy based on 70 highly overexpressed or underexpressed genes distinguished 3 groups of patients: good, intermediate or poor prognosis

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

	Signature	No of genes	No of Genes common with 70 Gene Signature	No of Genes common with 92 Gene Signature
1	UAMS	70 genes	--	2 genes (BIRC5, LTBP1)
2	HOVON-65/GMMG-HD4 (EMC92)	92 genes	2 genes (BIRC5, LTBP1)	--
3	IFM	15 genes	None	1 gene (FAM49A)
4	Chromosome instability signature	214 genes	7 genes	15 genes
5	Centrosome index signature (CNTI)	4 genes	None	None
6	Cell death signature implicated by homozygous deletion (HZDCD)	6 genes	None	None
7	7-gene prognostic signature HMCL MM cell lines study	7 genes 6 genes	None None	None None
8	Proliferation signature	50 genes	3 genes (BIRC5, ASPM, CKS1B)	6 genes (ESPL1, MCM6, NCAPG, SPAG5, ZWINT, BIRC5)

High-throughput genomic analysis spanning all regulatory checkpoints

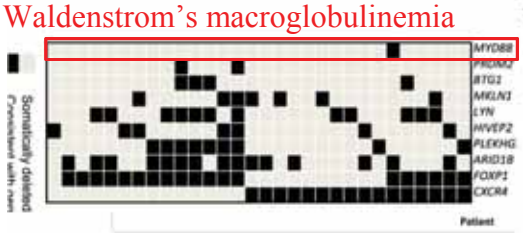


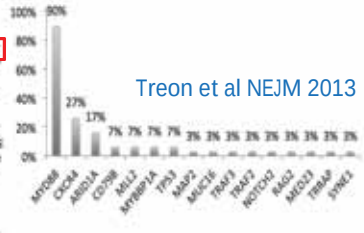
What Are the Methods Used to Evaluate Genetics

- FISH and ~~Cytogenetics~~
- Copy number Changes
  - SNP array
  - CGH array
- Expression Profile
  - array-based
  - RNA-sequencing
- DNA Sequencing
  - Whole exome, whole genome
  - Targeted sequencing

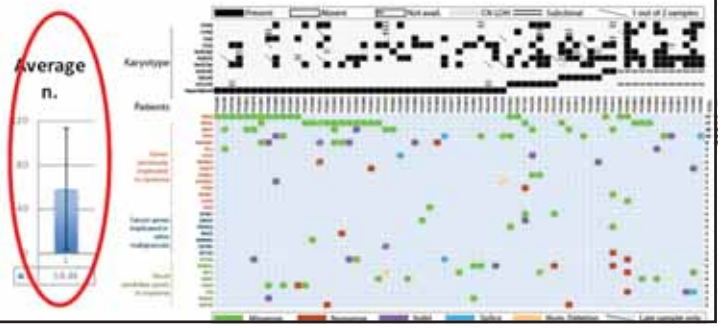
Somatic variants in Multiple Myeloma

Waldenstrom's macroglobulinemia



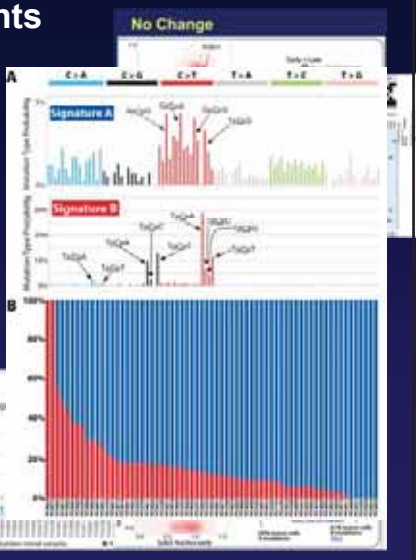


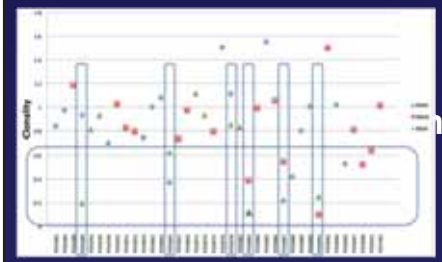
Treon et al NEJM 2013



Genomic studies

- Description of Somatic variants in Multiple Myeloma
- Heterogeneity of Somatic Variants
- Clonal Diversity and driver mutations
- Patterns of Clonal Evolution

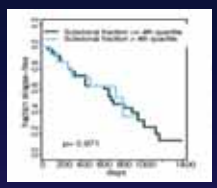


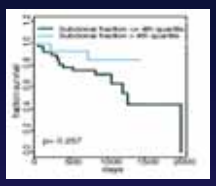


Bolli et al *Nature* Comm 2014

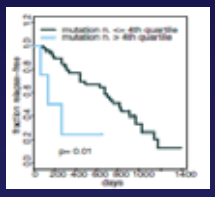
Prognostic Implications of Mutations in Myeloma

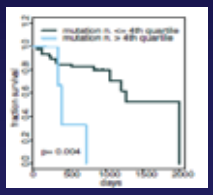
Subclonal Fraction





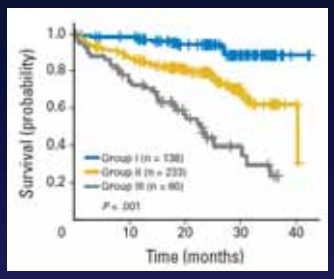
Frequency of Mutation





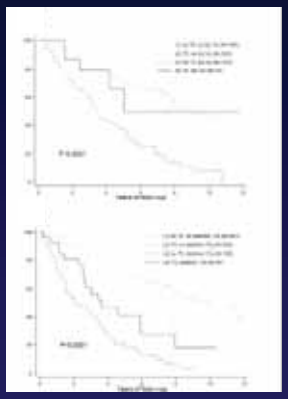
Bolli et al. Nature Comms 2014

Next generation sequencing improve risk stratification

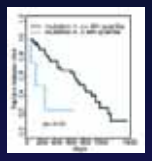


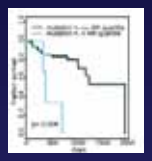
Group 1: ISS I and II with no copy number and structural abnormality [CNSA] or mutation
Group 2: ISS III with no CNSA or mutation or ISS I, II, and III with one CNSA or mutation
Group 3: two CNSAs or mutations regardless of their ISS

Combination of ISS/CNSA and mutations



Impact of trisomie 5 in *t*(4;14) and *del*(17p) myeloma





Mutation load

Walker et al, *J Clin Oncol.* 2015 Nov 20;33(33):3911-20

Avet-Loiseau et al, *Blood.* 2015 Dec 17;126(25):2713-9

Why Evalute Genetics

- To evaluate risk – prognosis
- To select therapy
  - Induction
  - Consolidation/maintenance
  - Therapy for relapse
- To consider targeted agents
- Identify new targets and agents
- Understand biology -prevention

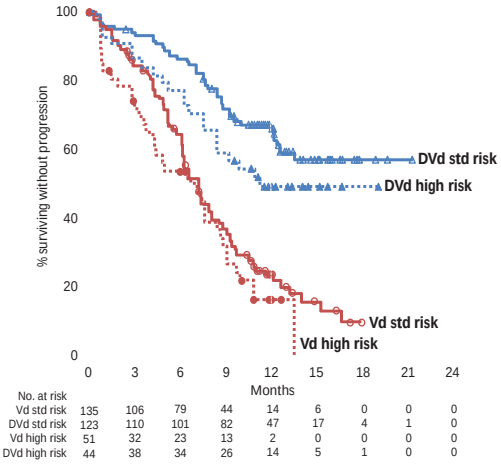
Triplets with an Rd backbone will become standard of Care for elderly patients with high risk disease ?

Median PFS

Regimen	All high risk	del17p	T(4:14)
KRD[1]	23.1 vs 13.9 months (HR=0.70)	24.5 vs.11.1 months (HR=NA)	23.1 vs 16.7 months (HR=NA)
Elo-RD[3]		21.2 vs 14.9 months (HR=0.70)	15.8 vs 5.5 months (HR=0.52)
IRD[4]	21.4 vs 9.7 months (HR=0.543)	21.4 vs 9.7 months (HR=0.596)	18.5 vs 12 months (HR=0.645)
DRd[5]	NR vs 10.2 (HR=0.44)		

1 Avet-Loiseau H et al, oral presentation ASH 2015, Abstract 731
2 Dimopoulos MA et al, Lancet Oncology 2016
3 Dimopoulos MA et al, oral presentation ASH 2015, Abstract 28
4 Moreau P et al, oral presentation ASH 2015, Abstract 727
5 Usmani S et al, ASH 2016

Castor: PFS: Cytogenetic Risk in All Evaluable Patients[a]



High risk[b]	DVd n = 44	Vd n = 51
Median PFS, mo	**11.2**	**7.2**
HR (95% CI)	0.49 (0.27-0.89)	
P value	0.0167	
	n = 44	n = 47
ORR, %	**82**	**62**
P value	0.039	

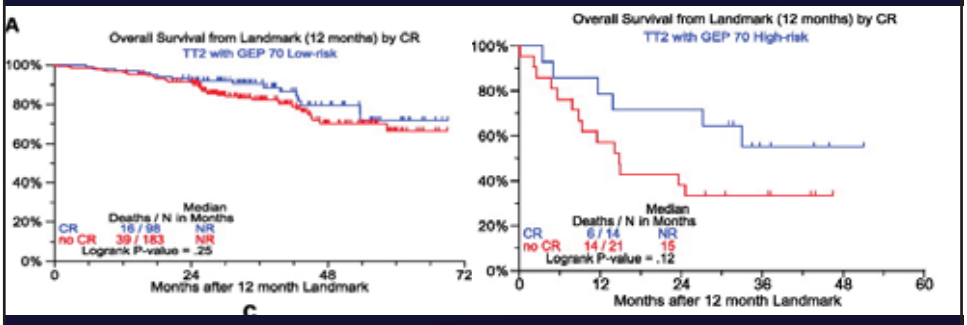
Standard risk	DVd n = 123	Vd n = 135
Median PFS, mo	**NR**	**7.0**
HR (95% CI)	0.29 (0.20-0.43)	
P value	<0.0001	
	n = 118	n = 131
ORR, %	**85**	**64**
P value	0.0003	

- DVd improves outcomes regardless of cytogenetic risk

NR, not reached.
[a]ITT/Biomarker risk–evaluable analysis set.
[b]Central next-generation sequencing. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

Mateos M, et al, ASH 2016 (Abstract 1150), oral presentation

CR is particularly important for HR MM



Leukemia (2011) 25, 1195–1197

Why Evalute Genetics

- To evaluate risk – prognosis
- To select therapy
  - Induction
  - Consolidation/maintenance
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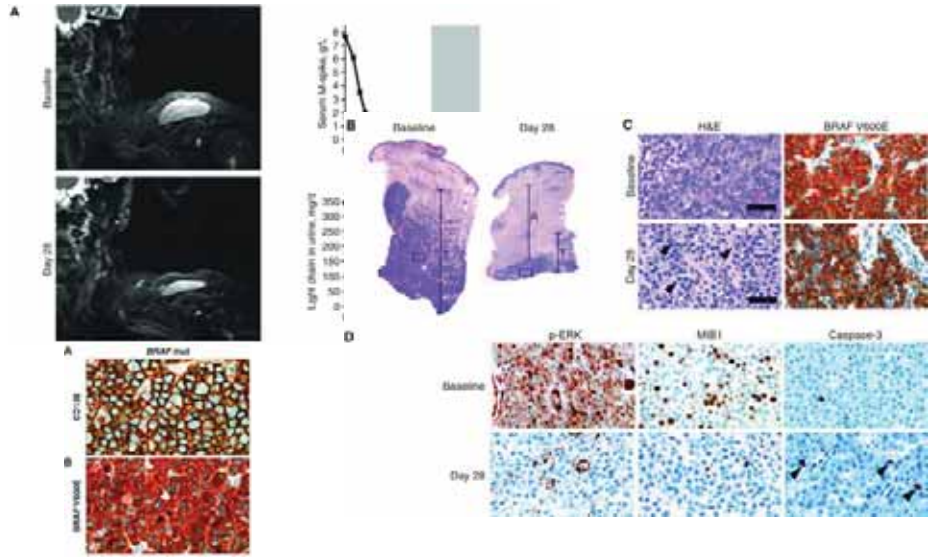
Heterogeneity of Somatic Variants

Gene	Bolli et al. (n=84 pts)	Lohr et al. (n=203 pts)	Walker et al (n=463)
NRAS	25%	20%	22%
KRAS	25%	23%	20
TP53	15%	8%	3.5%
DIS3*	1.5 %	11%	10%
FAM46C	12%	11%	5.4%
BRAF	15% V600E in 3/10	6%	8%
SF3B1	3%	1.5%	<2%
CYLD	3%	2.5 %	3%
TRAF3	3%	5.5%	4.1%
ROBO1	7%	2%	<2%
EGR1	6%	3.5%	3.6%
SP140	7%	4.4%	<2%
LTB	4.5%	1%	3%
RASA2	3%	3%	<2%
FAT3	7%	4.4%	3.9%
CCND1	3%	3%	3.5%%

Bolli et al Nat Comm 2014

Patient With BRAF V600E - Response to Vemurafenib



Andrulis M et al. Cancer Discovery 2013;3:862-869

American Association for Cancer Research

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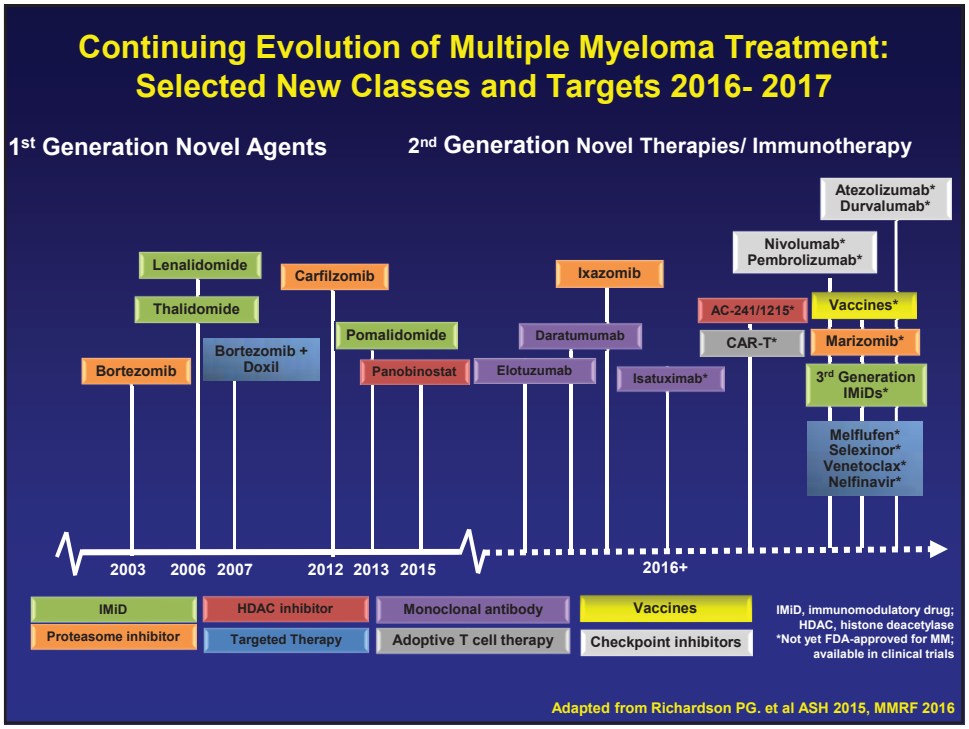
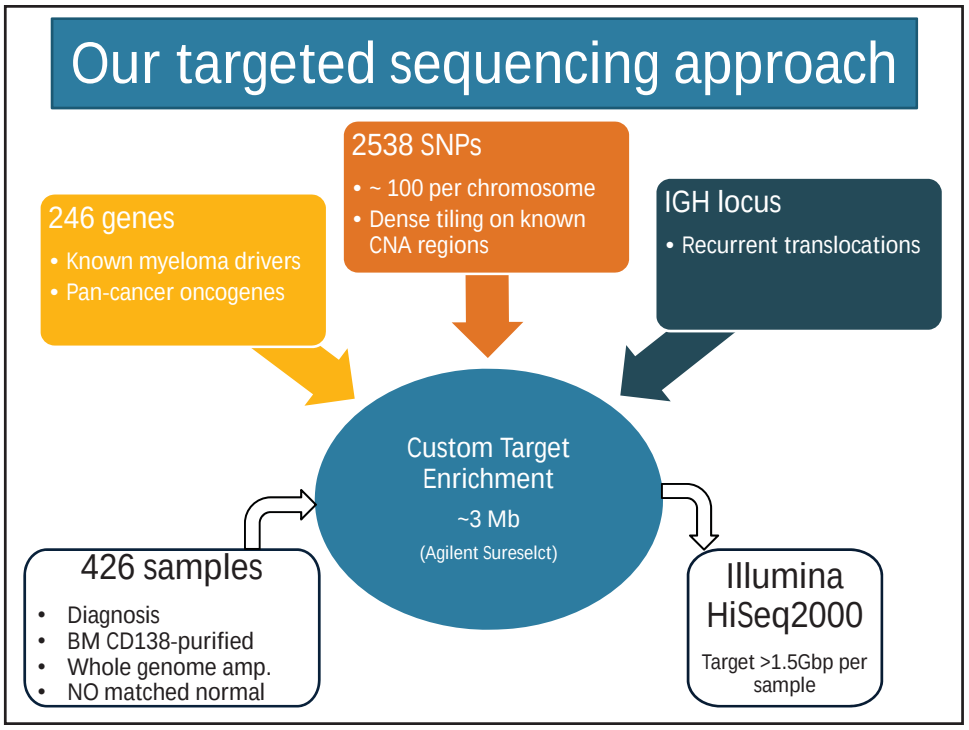
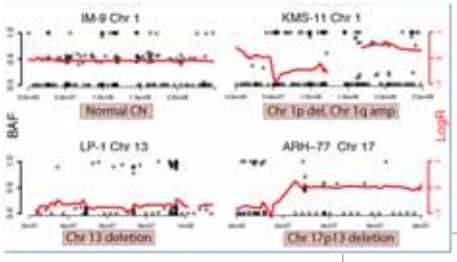
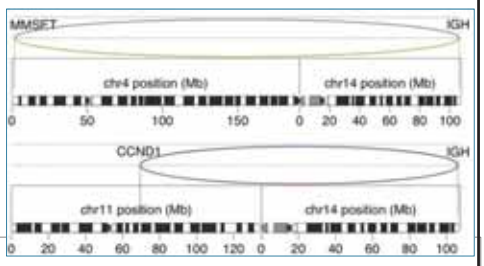
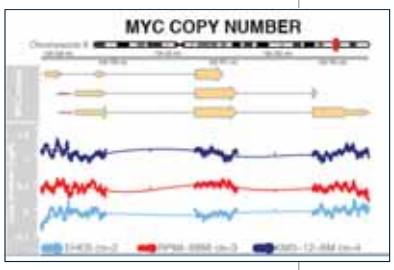

Continuing Evolution of Multiple Myeloma Treatment: Selected New Classes and Targets 2016- 2017
1st Generation Novel Agents
2nd Generation Novel Therapies/ Immunotherapy
Lenalidomide
Thalidomide
Bortezomib
Bortezomib + Doxil
Carfilzomib
Pomalidomide
Panobinostat
Ixazomib
Daratumumab
Elotuzumab
Isatuximab*
Atezolizumab* Durvalumab*
Nivolumab* Pembrolizumab*
AC-241/1215*
CAR-T*
Vaccines*
Marizomib*
3rd Generation IMiDs*
Melflufen* Selexinor* Venetoclax* Nelfinavir*
2003
2006
2007
2012
2013
2015
2016+
IMiD
Proteasome inhibitor
HDAC inhibitor
Targeted Therapy
Monoclonal antibody
Adoptive T cell therapy
Vaccines
Checkpoint inhibitors
IMiD, immunomodulatory drug; HDAC, histone deacetylase
*Not yet FDA-approved for MM; available in clinical trials
Adapted from Richardson PG. et al ASH 2015, MMRF 2016

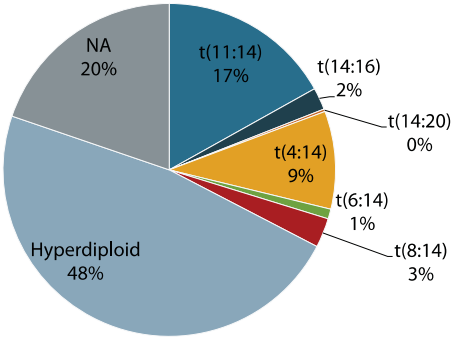

Our targeted sequencing approach
246 genes
• Known myeloma drivers
• Pan-cancer oncogenes
2538 SNPs
• ~ 100 per chromosome
• Dense tiling on known CNA regions
IGH locus
• Recurrent translocations
Custom Target Enrichment
~3 Mb
(Agilent SureselCt)
426 samples
• Diagnosis
• BM CD138-purified
• Whole genome amp.
• NO matched normal
Illumina HiSeq2000
Target >1.5Gbp per sample

Copy number and IGH translocations are called with good accuracy



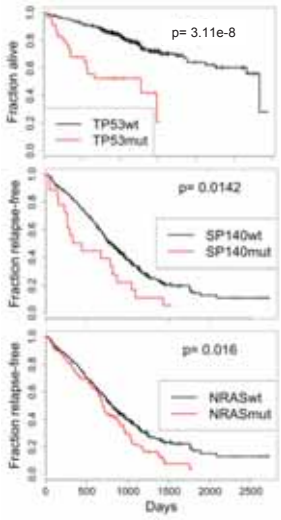


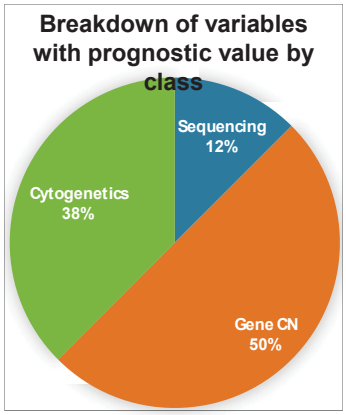




CN and karyotype dominate the landscape of (negative) prognostic variables

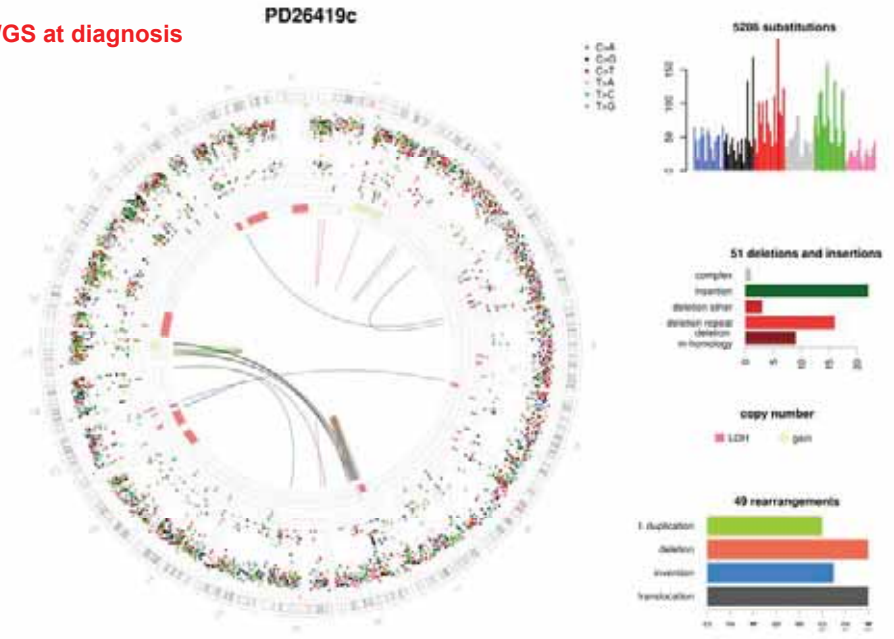
	PFS	OS
TP53	✓	✓
NRAS	✓	×
SP140	✓	×
APC_del	×	✓
CYLD_del	✓	✓
FAM46C_del	×	✓
FAT1_del	✓	✓
FAT3_del	✓	✓
SNX7_del	✓	✓
TP53_del	✓	✓
CDKN2C_del	✓	×
MYC_amp	✓	×
PRDM1_del	✓	×
SP140_del	✓	×
del1p	✓	✓
amp1q	✓	✓
del12p13.31	×	✓
del13	✓	✓
del16q	✓	✓
del17p13	✓	✓
t(14:20)	✓	✓
t(4:14)	✓	✓
t(8:14)	✓	×





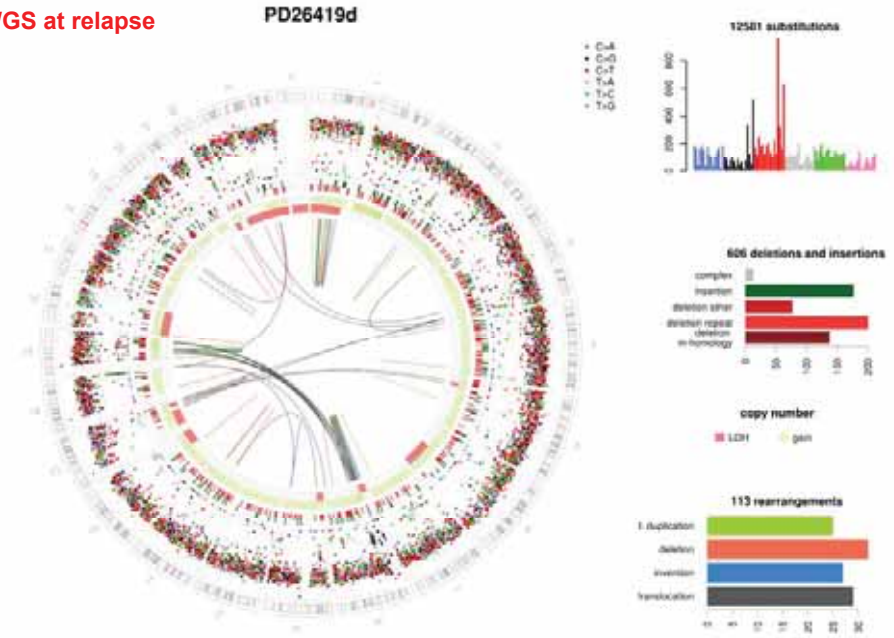
✓ = p < 0.05 on univariate analysis

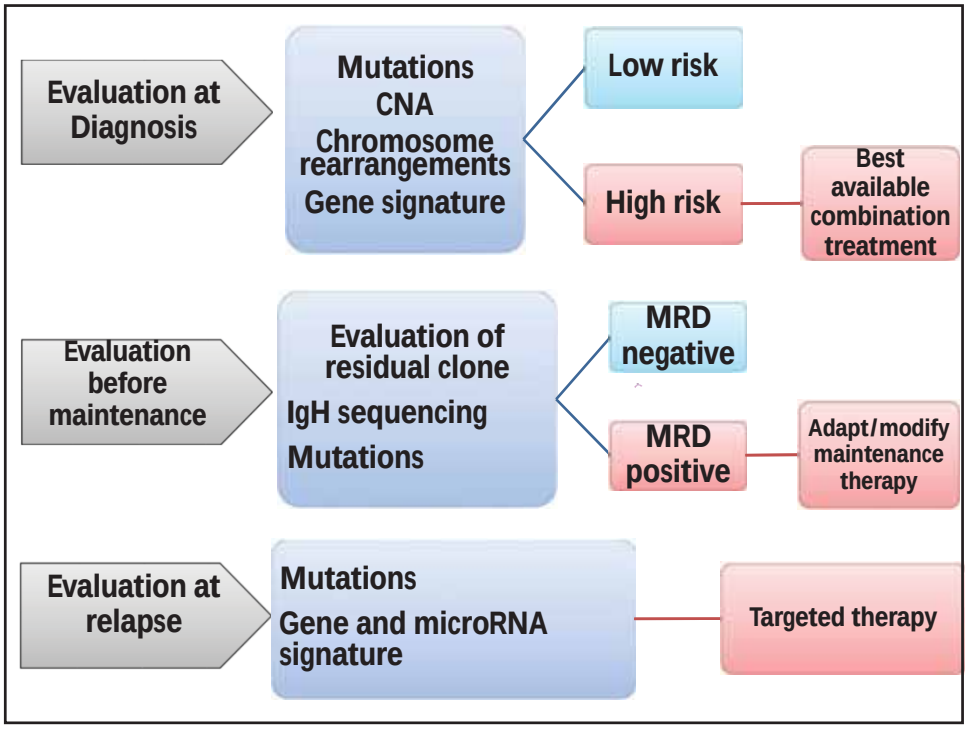
WGS at diagnosis



Courtesy of Nikhil Munshi MD, DFCI

WGS at relapse





What is Beyond 2017

- Gene Splicing
- Cell free DNA
- Circulating Single myeloma cell genomics
- Linc RNA
- Epigenomic profile – super enhancers
- Proteomics

What are the Optimal Imaging Techniques in Multiple Myeloma?

Noopur Raje, MD

Director, Center for Multiple Myeloma
MGH Cancer Center
Professor of Medicine
Harvard Medical School

MASSACHUSETTS GENERAL HOSPITAL

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

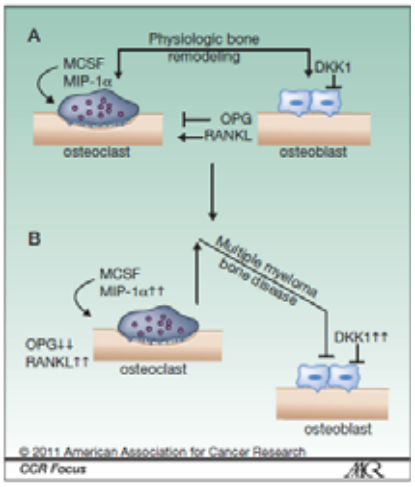
Disclosures

•Consultant /Advisory Board: Celgene, Millenium Takeda, Amgen-Onyx, Novartis, Janssen, BMS

•Research Funding: Astra Zeneca

•Steering Committee: Amgen, Roche

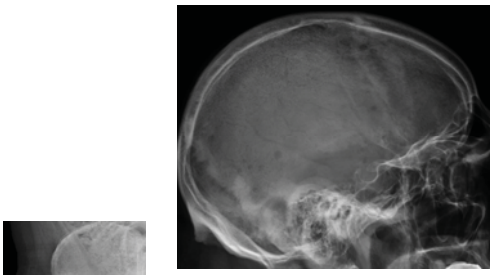
Pathophysiology of Myeloma Bone Disease

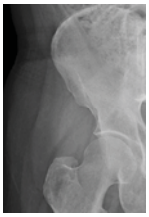


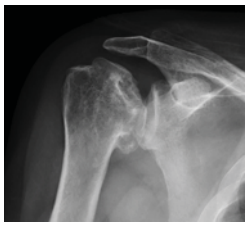
Raje and Roodman CCR 2011

IMAGING FOR BONE DISEASE

SKELETAL SURVEY: GOLD STANDARD FOR DECADES





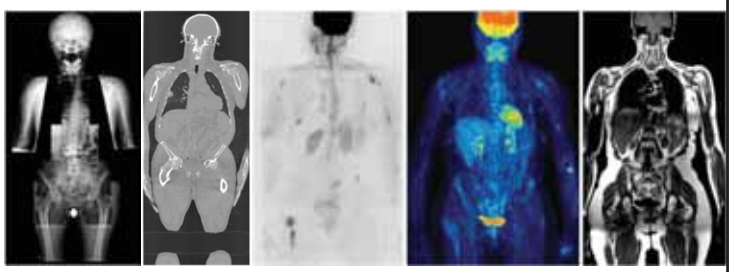


Imaging for Bone Disease

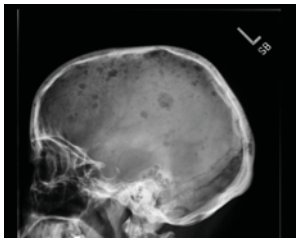
- What is New?
- What is Recommended?

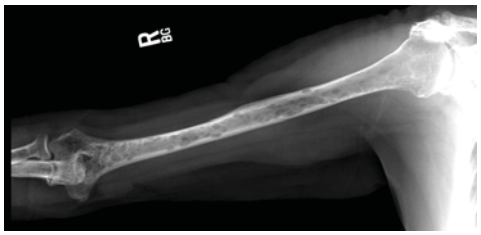
What we will cover

- **Benefits** and **Limitations** of different Imaging Techniques
- **Bone** versus **Bone Marrow** Imaging
- **Early** versus **Advanced** Stages
- **Initial Diagnosis** versus **Monitoring (treatment and surveillance)**



Skeletal survey





% have lytic lesions

- Vertebrae, 65%
- Ribs, 45%
- Skull, 40%
- Shoulders, 40%
- Pelvis, 30%
- Long bones, 25%

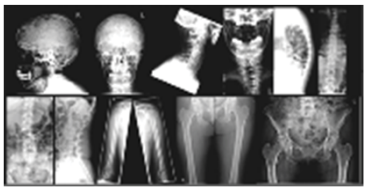
Uncommonly, lesions distal to elbows and knees

Dimopoulos et al., *Leukemia* 2009

Skeletal Surveys

Advantages

- Widely **available**
- Basis for Durie/ Salmon staging system and old **CRAB** criteria
- **Low** irradiation dose



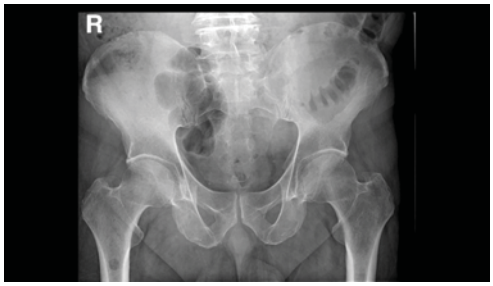
Disadvantages

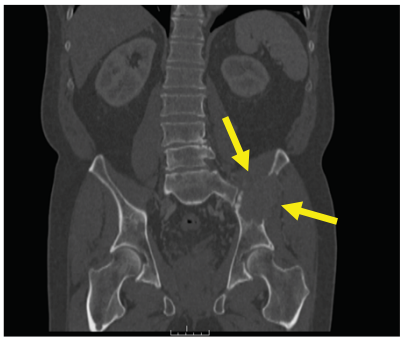
- **Low** sensitivity
- **Low** specificity (e.g. gas in colon)
- Several **regions** not easily evaluable (Sternum, Ribs)
- **Long** examination time
- **Uncomfortable** for patients

Dimopoulos 2011 Blood

Limitations of conventional radiographs

Lytic lesions seen on plain films only after 30-50% of bone mass destroyed





Large lytic lesion not readily appreciated on skeletal survey

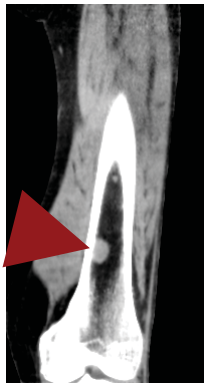
Computed Tomography (CT)

Advantages

- **Superior** to **x-ray** for detection of **bone** defects1
- whole body **low-dose** protocol for patients available
- evaluation of stability because of **3D information**
- **follow-up** evaluation feasible2
- patient **convenience**
- New **standard** imaging technique1

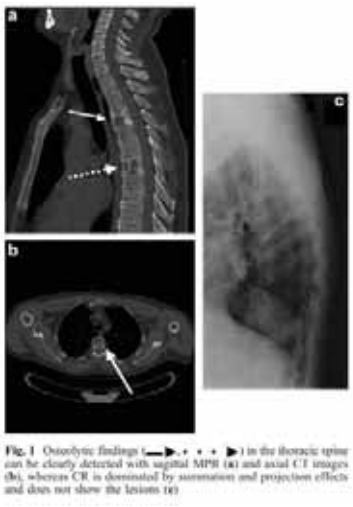
Disadvantages

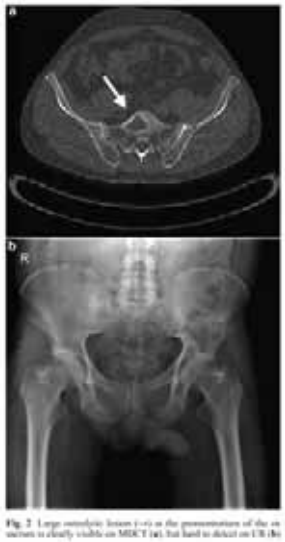
- **higher** radiation dose even in „low-dose"-technique (4.1 mSv => approx. 2x skeletal survey)
- **lower** sensitivity than MRI for PC infiltration



[1]Hillengass 2017 BCJ
[2]Horger 2007 Cancer

Whole body low dose CT





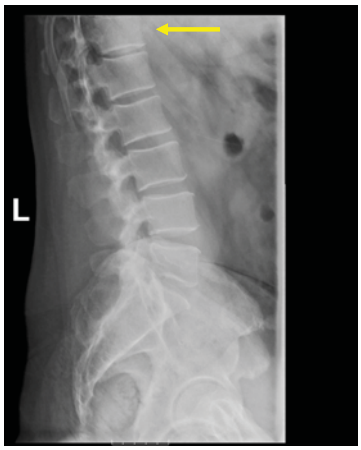
Minimal radiation exposure with WBLDCT

- Skeletal survey, 1.7 mSV
- WBLDCT, 4.8 mSV
- Chest/ab/pelvic CT 2

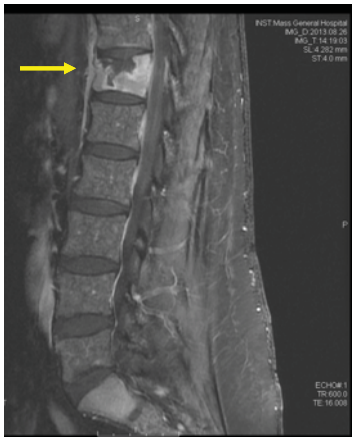
Whole body low dose CT can detect lytic lesions in an additional 23% of patients compared to plain films (Wolf et al., *Eur J Radiol* 2014)

Limitations of conventional radiographs: role for MRI

53M with kappa light chain MGUS with new back pain at work

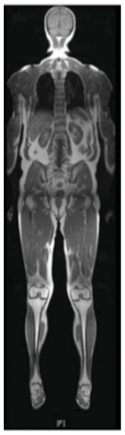


No fracture seen on plain film



Pathologic compression fracture at T12

Magnetic Resonance Imaging (MRI)



Advantages

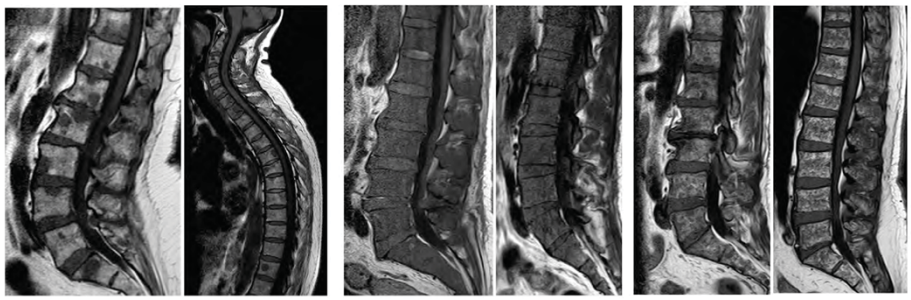
- Shows infiltration **before** bone has been destroyed
- **Highest** resolution for soft tissue and bone marrow
- Differentiation between **benign** and **malignant** fractures[1]
- **Follow-up** relevant[2]
- Basis of the new **definition of MM**[3]

Disadvantages

- **Inferior** to CT for assessment of **bone** disease/ stability
- Not applicable in patients with some **metallic implants**/ claustrophobia
- Inferior to PET-CT for **residual disease** diagnostic

[1]Baur 1998 Radiology
[2]Hillengass 2012 Haematologica
[3]Rajkumar 2014 Lancet Oncol
[4]Moreau 2017 JCO

MRI patterns: normal, variegated, diffuse, focal



Focal

Diffuse
(worse prognosis)

Variegated

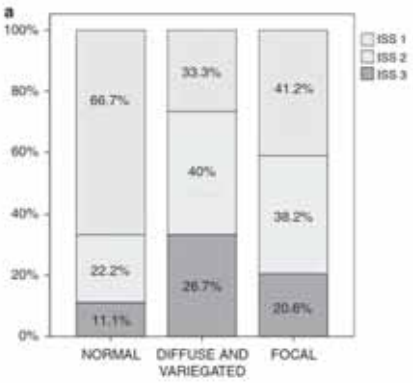
MRI ideal method for detecting marrow involvement

MRI more sensitive than plain films: 52% of MM patients with normal skeletal survey had focal lesions on MRI (Walker et al, *J Clin Oncol* 2007)

In **smoldering multiple myeloma** (according to older criteria), more than 1 focal lesion detected by MRI associated with 70% risk of progression in 2 years (Hillengass et al, *J Clin Oncol* 2010)

Terpos et al., ASCO 2016 Educational Book

MRI patterns and prognosis



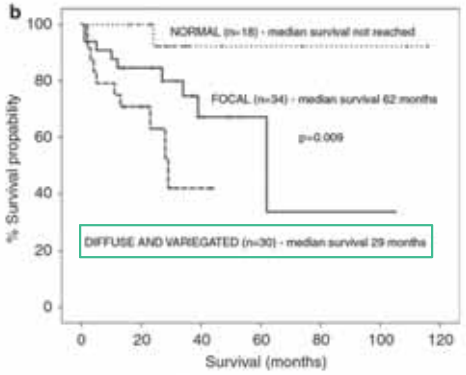


Figure 1 Patients with diffuse and variegated patterns correlated with advanced ISS stage (analysis of variance $P = 0.018$; **a**) and had inferior survival compared with focal and normal MRI patterns ($P = 0.009$; **b**).

Focal	41%
Diffuse	31%
Normal	22%
Variegated	`4%

Moulopoulos et al., *Leukemia* 2010

Spinal versus Whole Body MRI

N = 100

Results

- **whole body-MRI** significantly better than **spinal MRI**

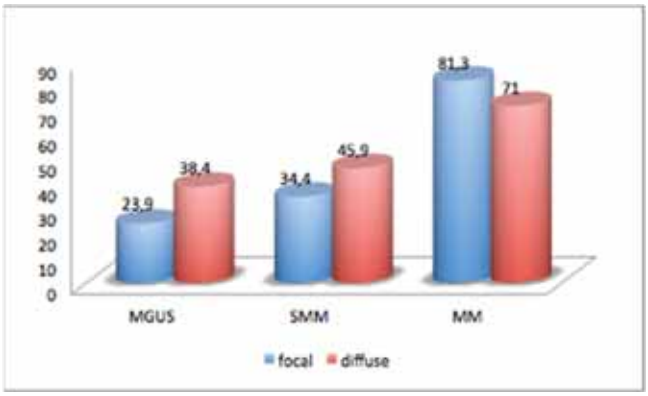
axial			**extra-axial**		
intra-osseous	exceeding cortical bone	mixed	intra-osseous	exceeding cortical bone	mixed
24	2	14	24	0	15

exclusively axial lesions	exclusively **extra-axial** lesions
11	**10**

Bäuerle 2009 Radiology

Patterns in different stages of disease

Heidelberg whole body MRI cohort
N = 138 MGUS
157 SMM
252 MM



Kloth 2014 Int J Cancer

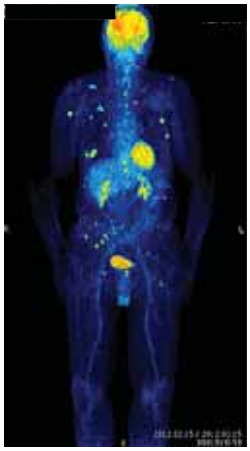
Positron Emission Tomography

Advantages

- Assessment of **Metabolism**
- **Prognostic** significance
- Disease **activity**
- **Significance** for **residual disease** diagnostic

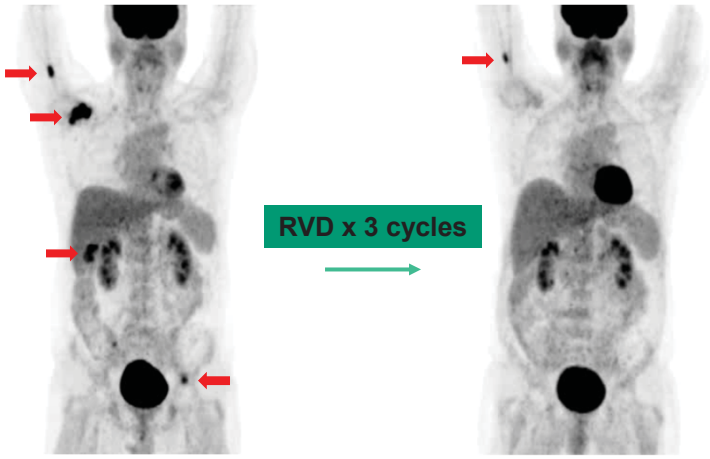
Disadvantages

- **False positive** results (inflammation)
- **Costs**
- **Radiation** dose

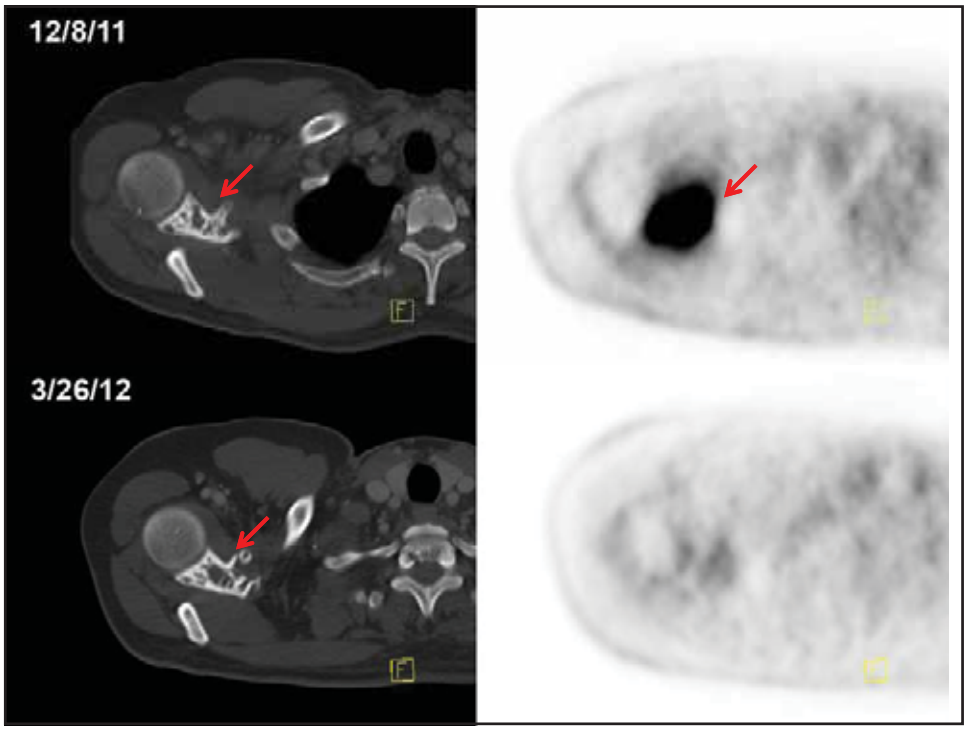


Bartel 2009 Blood

^{18}F-FDG PET CT demonstrates response



December 9, 2011 March 28, 2012

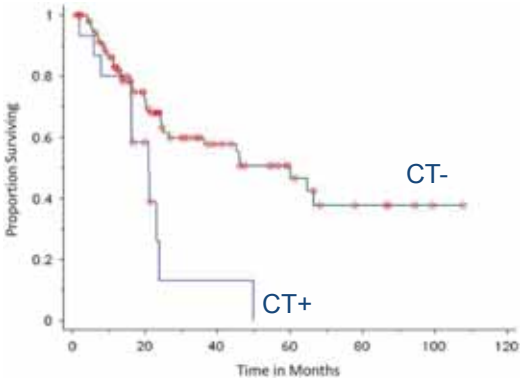


Role of ^{18}F-FDG PET CT

Role of ^{18}F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group

- Solitary plasmacytoma v. multiple myeloma
- Detecting disease outside of field of view of MRI
- Detecting extramedullary disease
- In IFM 2009, response on PET CT more prognostic than MRI (Moreau et al., ASH 2015)

Prognostic Significance of Bone Lesions



N = 188 pts. with SMM prognostic significance of osteolyses in CT

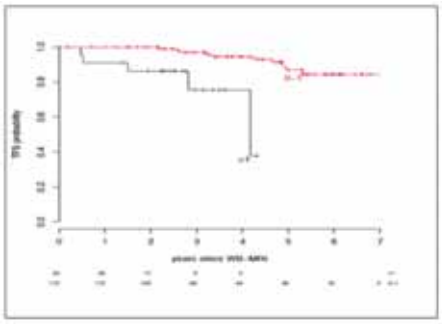
PET-CT+ in 74 pts
PET-CT- in 114 pts

Of PET-CT+
25 considered to be SMM
49 treated

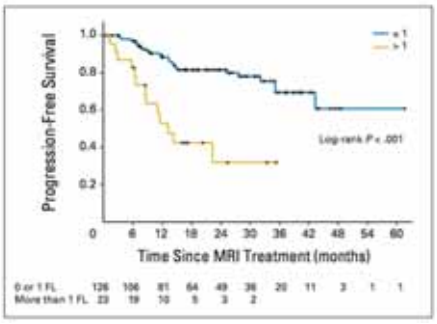
Siontis 2015 BCJ

Prognostic Significance of Focal Lesions in MRI

MGUS



SMM



Hillengass 2013 Leukemia, Hillengass 2010 JCO

Prognostic Significance of Focal Lesions in PET-CT in SMM

N = 120 patients with SMM

Results:

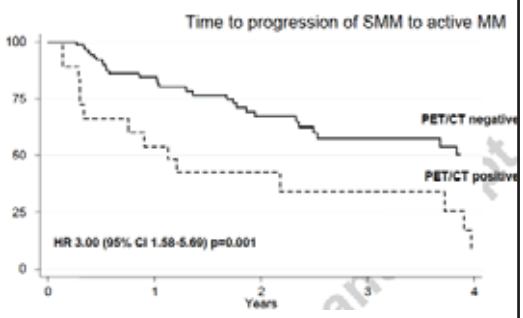
16% PET-positive

1 FL: 8 pts.

2 FL: 3 pts.

≧3 FL: 6 pts.

diffuse: 2 pts



median TTP 1.1 versus 4.5 years

2 year progression: 58% versus 33%

Zamagni 2015 Leukema

Updated IMWG Criteria for Diagnosis of Multiple Myeloma

MGUS	Smoldering	Multiple Myeloma
▪ M protein < 3 g/dL ▪ Clonal plasma cells in BM < 10% ▪ No myeloma defining events	▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) ▪ Clonal plasma cells in BM ≥ 10% to 60% ▪ No myeloma defining events	▪ Underlying plasma cell proliferative disorder ▪ AND 1 or more myeloma defining events ▪ ≥ 1 CRAB* feature ▪ Clonal plasma cells in BM ≥ 60% ▪ Serum free light chain ratio ≥ 100 ▪ > 1 MRI focal lesion

C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT

Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548

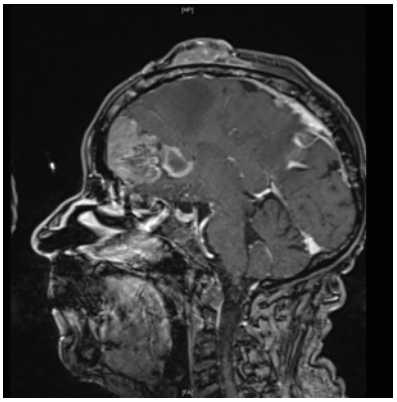
Imaging Studies

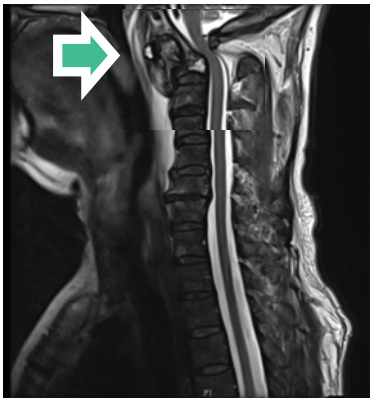
- In a patient with diagnosis of SMM, a whole body low dose CT or PET/CT) should be done and if negative a spine MRI →rule out myeloma requiring therapy.
- In a patient with MGUS, a low dose whole body CT (or skeletal survey if WBLDT is not available) can provide a baseline assessment for comparison for future assessments
- In all patients, a DEXA scan should be considered to rule out osteoporosis out of proportion to that expected for age.
- Symptom guided assessments should be considered in all patients.

Follow up testing

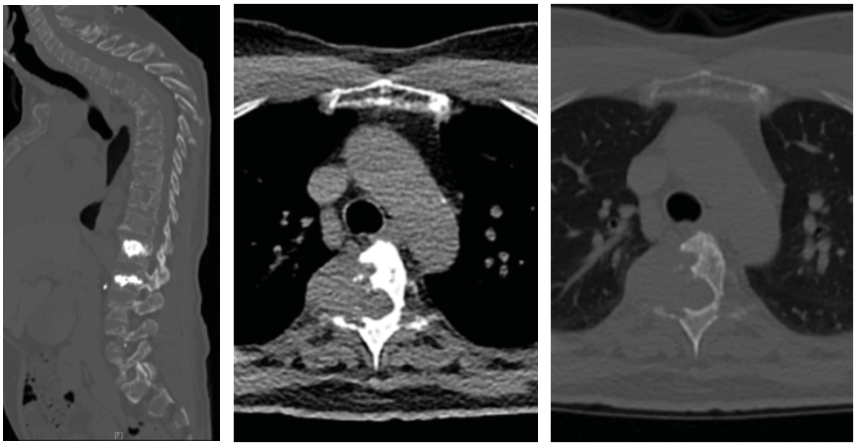
- In patients with 1 focal lesion on MRI or equivocal lesions, a repeat MRI should be considered in 6 months
- In patients with SMM, a whole body low dose CT can be considered, if cost constraints are not present, annually at least for the first 5 years from diagnosis

Advanced Stage: Cord Compression/ EMD

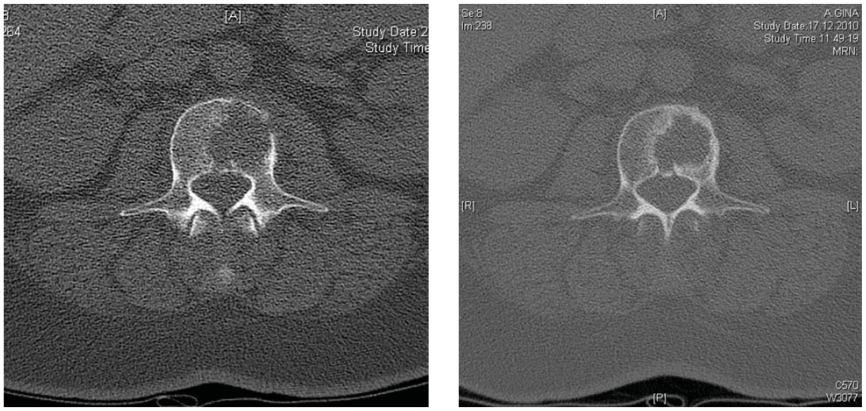




Advanced Stage: Stability

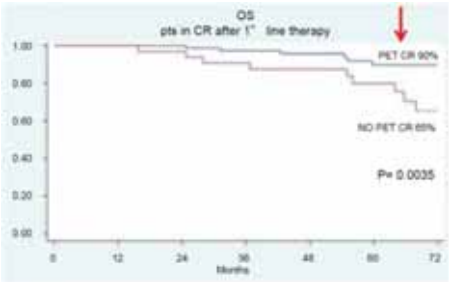


Monitoring Therapy: Role of CT?

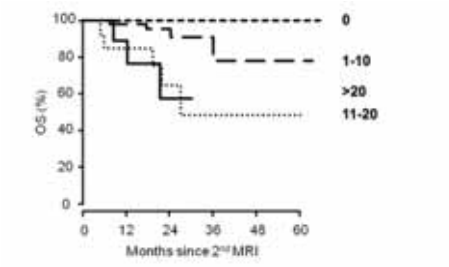


Prognostic Significance of Imaging CR

PET-CT



MRI



Zamagni 2013 ASH, Hillengass 2012 Haematologica

Prognostic significance of residual lesions in PET-CT

N = 189 PET-CT after therapy

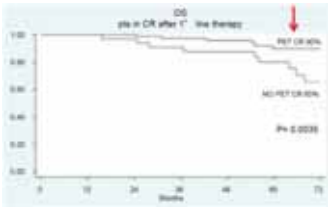
88% ≧ VGPR

55% CR

=> 29% of pts. in CR had residual lesions in PET-CT

Median PFS of PET + 44 months

Median PFS of PET - 84 months



Zamagni 2015 Clin Cancer Res

Prognostic significance of residual lesions in PET-CT

At diagnosis:

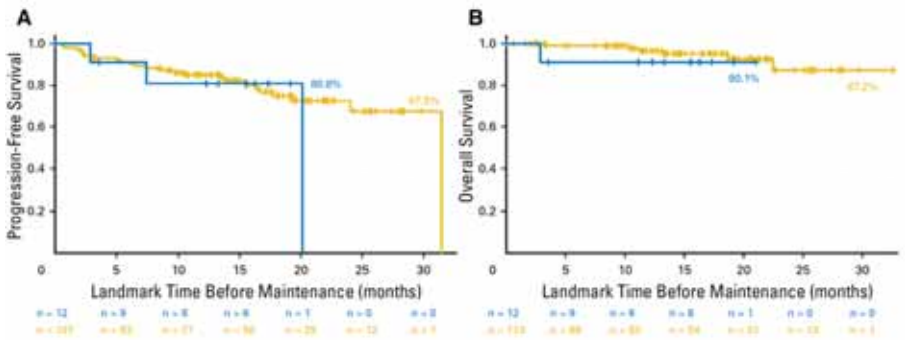
MRI positive in 127/134 (95%),

PET-CT positive in 122/134 (91%)

(McNemar test = 0.94, p-value = 0.33).

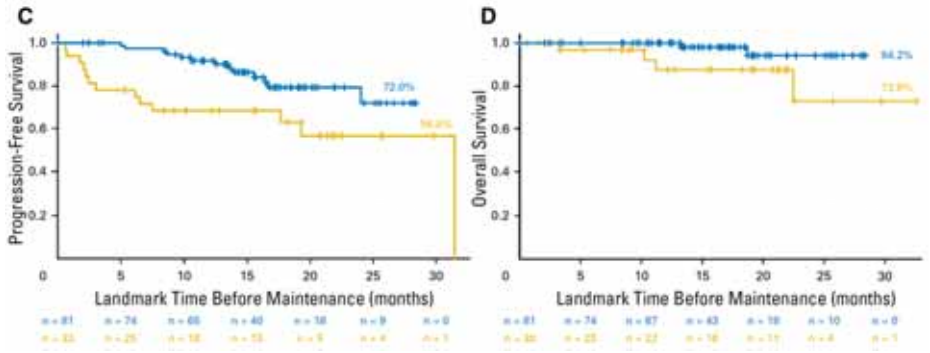
Moreau 2017 JCO

Prognostic Significance of Residual Lesions in MRI before Maintenance



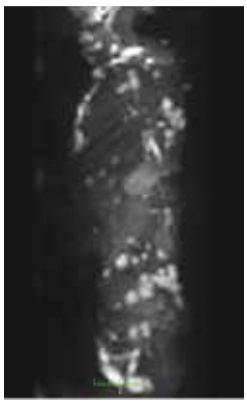
Moreau 2017 JCO

Prognostic Significance of Residual Lesions in PET-CT before Maintenance

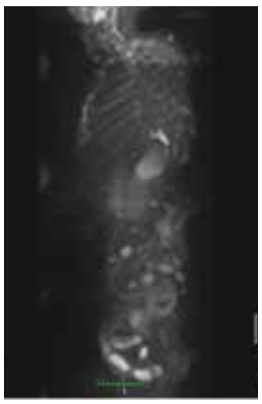


Moreau 2017 JCO

Whole body DWI



First Diagnosis



in CR

Jens Hillengass University of Heidelberg S.D.G.

PET-CT versus Functional MRI

N = 17 patients with 20 pairs of scans

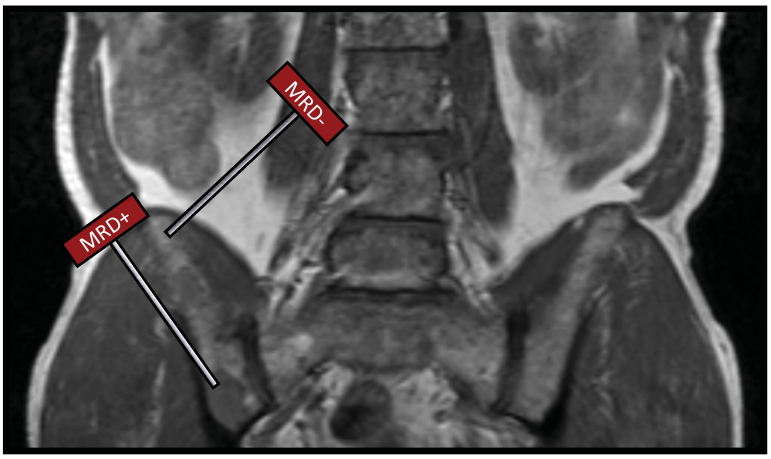
Table 1. Observer scores for whole-body diffusion-weighted imaging (WB-DWI) are higher than for FDG PET–CT for the whole body and in all body regions

	Score mean (± s.d.)		P-value[a]
	FDG PET–CT	WB-DWI	
Whole body	8.45 (±8.70)	17.65 (±12.24)	0.002
Region			
C spine	0.47 (±1.17)	1.68 (±1.92)	0.016
T spine	1.20 (±1.64)	2.60 (±2.04)	0.011
L spine	1.00 (±1.62)	2.50 (±2.04)	0.007
Pelvis	2.40 (±2.54)	3.30 (±1.95)	NS, 0.13
Long bones	1.85 (±2.35)	2.80 (±2.71)	NS, 0.19
Skull	0.21 (±0.63)	1.95 (±1.96)	0.004
Ribs/other	1.35 (±1.90)	3.00 (±1.97)	0.006

Abbreviations: FDG PET–CT, ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography; NS, not significant. [a]Wilcoxon matched-pairs signed rank test.

Pawlyn 2016 Leukemia

Magnetic Resonance Imaging (MRI)



Jens Hillengass University of Heidelberg S.D.G.

MRD- and PET-Negativity

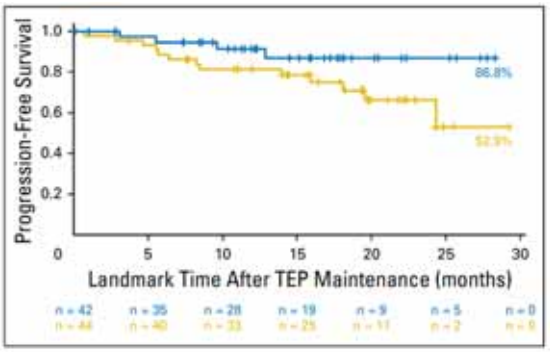


Fig 5. Progression-free survival for patients with negative positron emission tomography-computed tomography and negative minimal residual disease by flow cytometry before maintenance (41 of 86; 48%) versus others (45 of 86; 52%; $P = .05$).

Moreau 2017 JCO

Summary

(suspected) stage	first diagnosis	follow up
MGUS	Osteolyse CT (MRI) MRI (PET-CT) (PET)-**CT** (MRI) MRI ((PET)-CT)	Osteolyse CT (MRI) MRI (PET-CT) (PET)-**CT** (MRI) MRI ((PET)-CT)

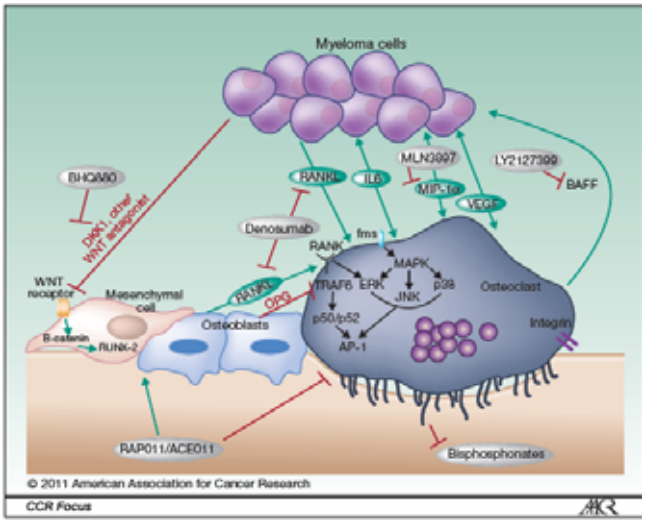
Jens Hillengass University of Heidelberg S.D.G.

Key points for imaging

- Whole-body LDCT is superior to conventional radiography for the detection of osteolytic lesions, and it is suggested to replace it in the work-up of patients with myeloma.
- MRI is the best imaging method for the depiction of marrow infiltration by myeloma cells.
- Whole-body MRI (or at least MRI of the spine and pelvis if whole-body MRI is not available) should be performed for all patients with smoldering multiple myeloma with no lytic lesions to look for occult disease, which may justify treatment.
- PET/CT allows better definition of complete response and minimal residual disease.
- PET/CT has an independent prognostic value both at diagnosis and after treatment.

Terpos et al, ASCO Educational Book 2016

Targeting Myeloma Bone Disease



Raje and Roodman CCR 2011

Future Directions and Issues

- Better imaging to determine bone anabolic effects
- Clear guidance on monitoring
- Clinical trial still rely on skeletal surveys:
- Therefore difficult to CHANGE standard for monitoring

Implementing the New Diagnostic Criteria in Daily Practice and Appropriate Tests for Follow Up and Treatment Decisions

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Mount Sinai

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Grant or research support	Amgen, Array Biopharma, Celgene, Millenium/Takeda, Novartis Pharmaceuticals, Janssen, Pharmacyclics
Paid consultant	Celgene, Millenium/Takeda, Novartis Pharmaceuticals, Janssen

2

Implementing New Diagnostic Myeloma Criteria

- Differential Diagnoses – Rule out other clonal plasma cell and non plasma cell disorders
- Freelite
  - Diagnosis
  - Monitoring
  - Prognosis
- Hevylite
  - Diagnosis
  - Monitoring

Plasma Cell Disorders

- Multiple Myeloma
- Solitary Plasmacytoma (Bone vs. Extramedullary)
- Primary Amyloidosis (AL)
- POEMS syndrome / osteosclerotic myeloma
- Monoclonal gammopathy of renal significance
  - Light chain deposition disease
  - Heavy chain deposition disease
  - Acquired Fanconi's syndrome
- TEMPI syndrome
- Schnitzler's syndrome
- *Smoldering Multiple Myeloma and
- *Monoclonal gammopathy of undetermined significance (MGUS)

*Diagnoses of exclusion

Other D/o w/Monoclonal Gammopathy

- B cell lymphoproliferative d/o
  - NHL, CLL, WM, PTLD
- Cold hemagluttinin - IgM
- Autoimmune/Connective Tissue d/o
  - Scleromyxedema IgG lambda
- Cryoglobulinemia
  - type 1 monoclonal vs 2 mixed and 3 polyclonal
- Other heme d/o – MDS, CNL
  - Likely epi-phenomonon due to median age of onset

Amyloidosis - classification

Class		Precursor protein	Clinical association
primary	AL	Ig light chain	Plasma cell dyscrasias
	AH	Ig heavy chain	
secondary	AA	Amyloid A protein	Secondary to infection, RCCa, FMF
	ATTR	Transthyretin	Senile systemic amyloidosis
	AFib	Fibrinogen Aα	Hereditary renal amyloid
	A Apo I	Apolipoprotein A	Cardiomyopathy, neuropathy
	Aβ2 M	β_2-microglobulin	Dialysis amyloid

Paraffin embedded tissue (NOT FIXED) to Mayo Labs for laser microdissection + tandem mass spectrometry based proteomic analysis of amyloid subtype

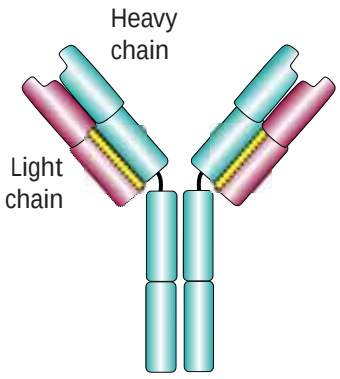
Paraproteinemias and Neuropathy

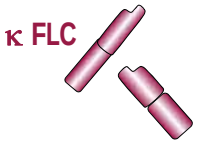
DISORDER	NEUROPATHY	SYSTEMIC FEATURES	PARAPROTEIN	ELECTROMYO-GRAPHIC CHANGES
Multiple Myeloma	Symmetric, distal sensory or sensorimotor; usually mild	Bone pain, fatigue, anemia, hypercalcemia, renal insufficiency	IgM-κ or IgG-κ (>3 g/dl)	Axonal
Waldenström's macroglobulinemia	Symmetric, distal sensory or sensorimotor, progressive; may simulate CIDP	Fatigue, weight loss, oronasal bleeding, visual blurring, encephalopathy	IgM-κ	Demyelinating
Osteosclerotic myeloma	Symmetric, proximal and distal sensorimotor, progressive areflexia; simulates CIDP	POEMS syndrome – elevated VEGF, Castleman's disease	IgG-λ or IgA-λ	Demyelinating
Amyloidosis	Symmetric, distal, progressive, painful, sensory, and autonomic symptoms	Congestive heart failure, Renal failure, hepatosplenomegaly, macroglossia, weight loss	IgG-λ or IgA-λ	Axonal
Cryoglobulinemia	Symmetric or multifocal, distal, painful, sensory or sensorimotor; multiple mononeuritis	Hepatosplenomegaly, purpura, arthralgias, leg ulcers, Raynaud's phenomenon	IgM or IgG	Axonal
Lymphoma (Castleman's disease, hypersensitivity adenopathy, and chronic leukemia)	Variable: pure sensory or pure motor, sensorimotor, motor neuron disease; may simulate CIDP or Guillain–Barré syndrome	Lymphadenopathy, fatigue, weight loss, POEMS syndrome	IgM or IgG	Axonal demyelinating; Motor neuronopathy
MGUS	Tremor, sensory loss, ataxia (anti MAG/SGPG)	None	IgM (60%); k>1 IgG (30%), A(10%)	Demyelinating Axonal

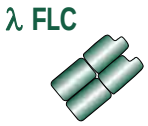
Implementing New Diagnostic Myeloma Criteria

- Differential Diagnoses
- Freelite
  - Diagnosis
  - Monitoring
  - Prognosis
- Hevylite
  - Diagnosis
  - Monitoring

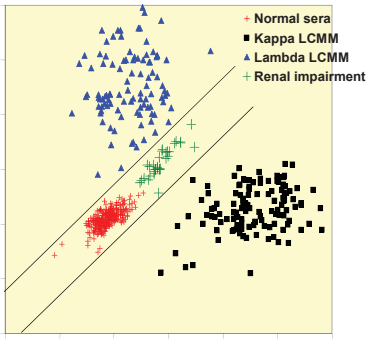
Detecting Cancer/Clonality of Plasma Cells: Heavy Chains and Light Chains







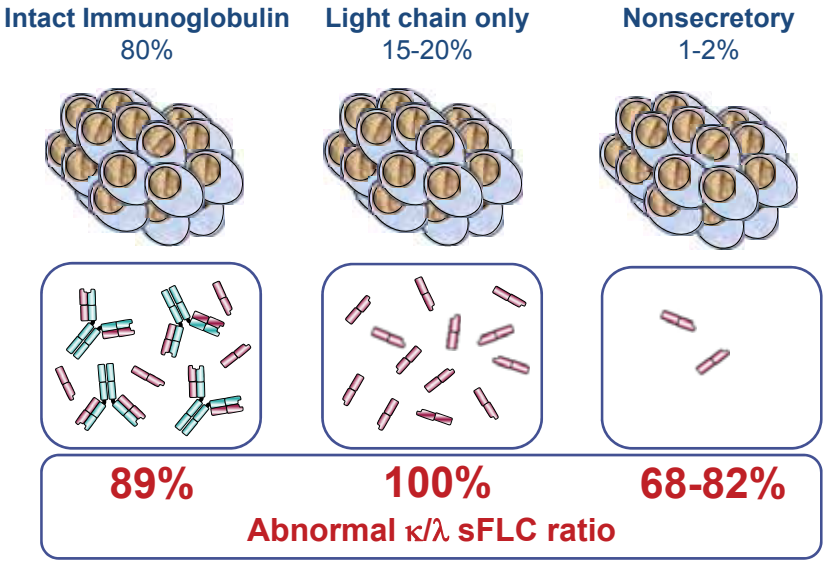
Serum Free Light Chains



- FLC determined by production and clearance
  - Normally, κ producing cells 2* λ so KLR 1.8
  - However, κ a small monomer, is cleared by kidney faster (ie shorter half life) than λ dimer so median KLR 0.6
  - In renal insufficiency, FLC cleared more by RES rather than kidney, so κ and λ half-lives comparable so FLCr reflects FLC production and hence ratios are higher

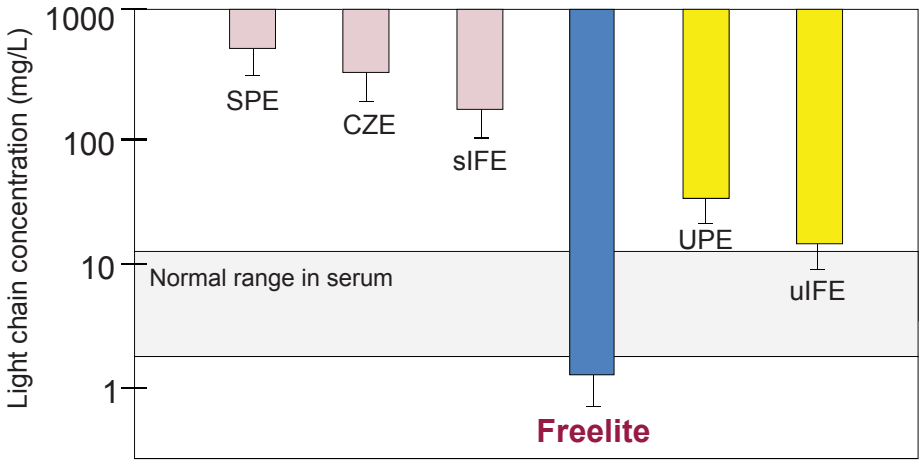
Bradwell, AR et al. Lancet 361:489-491, 2003.
Drayson, M et al. Blood 97:2900-2902, 2001. Katzmann et al *Clin Chem* 2002

Any type of Multiple Myeloma can express free light chains



Analytical sensitivity

Freelite ~10X more sensitive than uIFE and quantiative



Serum Monoclonal Protein Studies in MM: Summary

Study	Sensitivity
SPEP	~81%
Serum IFE	~94%
UPEP + urine IFE	~100%*
Serum free light chains	~86%
Serum IFE + SFLC	~99%

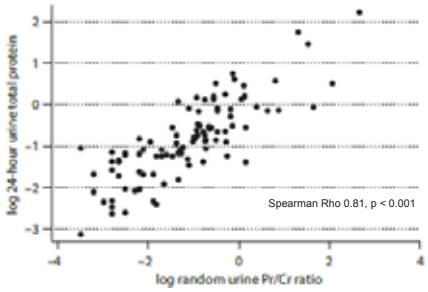
* 100% of samples were considered abnormal by urine IFE based on the definition of the cohort, but not all 428 urine samples in this study had a urine M-spike on PE.

FLC, free light chain; IFE, immunofixation electrophoresis; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

Katzmann et al Mayo Clin Proc. 2006; 81(12): 1575-1578
Dispenzieri A et al. Leukemia 2009; 23, 215-224.

Protein:Creatinine Ratio

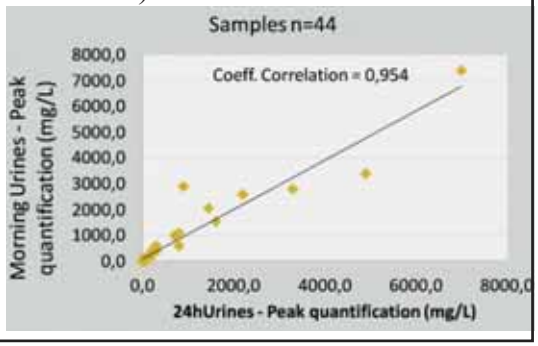
- Random urine total protein:creatinine ratio correlates well with 24-hour urine total protein
- National Kidney Foundation recommends random protein:creatinine ratio over 24-hour urine
- Validated in myeloma patients for estimating 24 hr urine total protein



Levey AS, et al. Ann Intern Med. 2003 Jul 15;139(2):137-47.
Wozney, et al. Acta Haematol. 2010;123(4):226-9.

Morning Urine Correlates with 24-hour Sample

- 284 patients morning UPEP was compared to 24-hr UPEP (not all with MM)
- Excellent correlation between morning M-spike and 24-hr M-spike by concentration (not total)
- Excellent correlation also seen with the pattern of proteinuria (glomerular vs tubular)



Boulard P. Clinical Lymphoma, Myeloma and Leukemia 15:e88

Freelite Use in Cerebrospinal and Pleural Fluid

- Extramedullary MM is difficult to diagnose and monitor
- CNS MM (n=8) cytology positive only in 3/8 but abnormal FLCR in 7/8; also 3 without detectable CNS disease had abn FLCR and later went on develop CNS MM; useful for monitoring as well

- Unlike CNS, pleural space not separated from systemic circulation so 4 variables: iFLCs in serum & pleural fluid and uFLCs in both
- MM pts with pleural effusion (n=15), dFLC **ratio** across the compartments were more concordant with initial detection of a clonal excess of FLCs in the pleural effusion (~Light's criteria tp & LDH of > 0.5 and > 0.6)
  - However, ? **difference in dFLCs** across compartments is better suited for monitoring the response to therapy

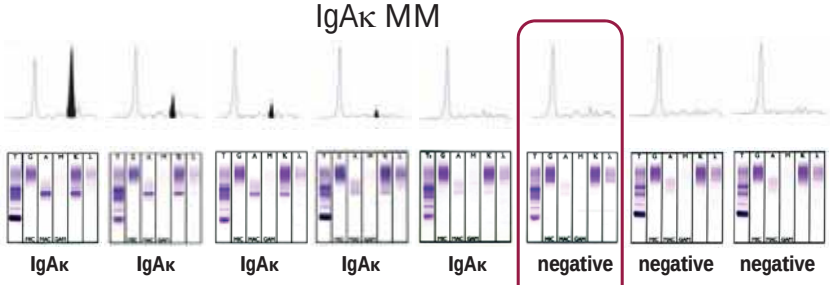
Marron et al Chari. Clin Lymphoma Myeloma '15.
Marron et al. Chari. Clin Lymphoma Myeloma '16.

Implementing New Diagnostic Myeloma Criteria

- Differential Diagnoses
- Freelite
  - Diagnosis
  - Monitoring
    - FLCR for intial diagnosis or evaluation of residual disease
    - dFLC for response assessment
  - Prognosis
- Hevylite
  - Diagnosis
  - Monitoring

Detection of residual disease

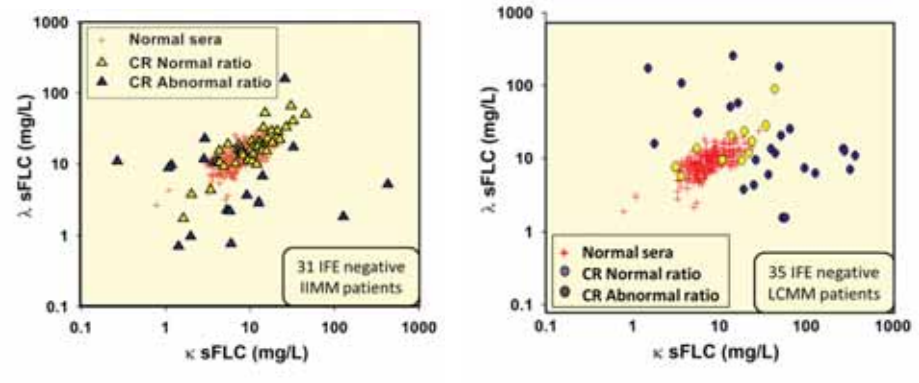
IgAκ MM



Freelite								
κ sFLC mg/L	230	31.6	23.1	17.7	16.4	5.3	0.9	0.6
λ sFLC mg/L	0.8	0.7	0.9	0.7	2.6	0.4	2.2	1.4
κ/λ ratio	287.5	45.1	25.7	25.3	6.31	**13.3**	0.4	0.4

Ludwig Leukemia 2013;27:213-9

Abnormal FLC ratios indicate residual disease in Intact Ig MM and Light Chain MM



Reid Bone Marrow Transplant 2004;33:623a
Reid Clin Chem 2004;50:C34a

Monitoring Response: using difference in FLC (versus FLCR)

	κ sFLC (mg/L)	λ sFLC (mg/L)	κ/λ sFLC ratio	dFLC (mg/L)
Normal range	3.3 – 19.4	5.7 - 26.3	0.26 – 1.65	
Baseline	240	10	24	230
Post Treatment	24	1	24	23

κ/λ sFLC ratio

The same pre- and post-therapy
Therapy failure?

iFLC *or* **dFLC**

90% reduction
Therapy successful

Leukemia (2009) 23, 215–224

www.nature.com/leu

SPOTLIGHT REVIEW

International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders

A Dispenzieri[1], R Kyle[1], G Merlini[2], JS Miguel[3], H Ludwig[4], R Hajek[5], A Palumbo[6], S Jagannath[7], J Blade[8], S Lonial[9], M Dimopoulos[10], R Comenzo[11], H Einsele[12], B Barlogie[13], K Anderson[14], M Gertz[1], JL Harousseau[15], M Attal[16], P Tosi[17], P Sonneveld[18], M Boccadoro[6], G Morgan[19], P Richardson[14], O Sezer[20], MV Mateos[3], M Cavo[17], D Joshua[21], I Turesson[22], W Chen[23], K Shimizu[24], R Powles[25], SV Rajkumar[1] and BGM Durie[26] on behalf of the International Myeloma Working Group[27]

[1]Departments of Hematology/Laboratory Medicine/Pathology, Mayo Clinic, Rochester, MN, USA; [2]Department of Biochemistry, Universit… Vienna, Austria; [5] …ision… Ematolog… …ehensive Cancer C… …tology/ Medical … …reece; [11]Depart… …Internal Medicine… …tle Rock, AR, USA; Hematol… …oulouse, France; [1]… …atology, Rotterdar… …lon, UK; [20]Depart… …Alfred Hospital, …eden; [23]Department of Hematology/Oncology/Beijing Chaoyang Hospital, Beijing, China; [24]Department of Internal Medicine, Nagoya City Higashi General Hospital, Nagoya, Japan; [25]Department of Hematology/Oncology, Parkside Cancer Centre, London, UK and [26]Aptium Oncology Inc., Cedars-Sinai Outpatient Cancer Center at the Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA, USA

"for serial measurements, either the involved FLC or the difference between the involved and uninvolved (dFLC) should be used."

Dispenzieri Leukemia 2009;23:215-224

Response Depth: Conventional IMWG Criteria

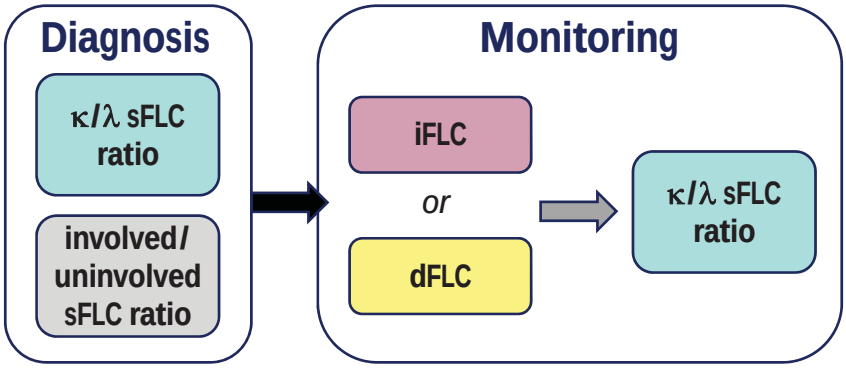
Response	M protein	% Plasma Cells in BM	Skeletal Disease
Stringent CR (sCR)	normal FLC ratio AND PEP/IFE negative	No clonal PC AND< 5%	Stable
Complete Response (CR)	PEP negative IFE negative	< 5%	Stable
Very Good PR (VGPR)	PEP negative but IFE positive	< 5%	Stable
Partial Response (PR)	> 50% reduction in SPEP > 90% reduction in UPEP ≥ 50% dec Inv -Uninv FLC	N/A	Stable
Stable Disease (SD)	Not meeting criteria for sCR, CR, VGPR, PR nor PD		
Progressive Disease (PD)	> 25% increase (SPEP by 0.5, UPEP by 0.2, Inv- Uninv FLC by 10)	25% increase	New bone lesions or increased size

Updated International Society of Amyloidosis Criteria for Staging and Response

Standard staging system [37]	The system is based on NT-proBNP (cutoff 332 ng/L) and cTnT (cutoff 0.035 ng/mL). Stage I, II, and III, patients have none, one or two markers above the cutoffs, respectively.
Revised staging system [38]	The revised staging system is based on NT-proBNP (cutoff 1800 ng/L), cTnT (cutoff 0.025 ng/mL), and dFLC (cutoff 180 mg/L). Stage I, II, III, and IV patients have none, one, two or three markers above the cutoffs, respectively.

Type of response [143]	Definition
Complete response	Negative serum and urine immunofixation and normal FLC κ/λ ratio
Very good partial response	dFLC <40 mg/L
Partial response	dFLC decrease >50%
No response	other
NT-proBNP response*	>30% and >300 ng/L reduction in subjects with baseline NT-proBNP≥650 ng/L

Summary of IMWG recommendations



Define clonality

Define biomarker of malignancy

Assess response

Define sCR

Dispenzieri Leukemia 2009;23:215–224
Rajkumar Lancet Oncology 2014;15:e538-e548

Taking Advantage of Short Half-Life of sFLC - Early After Stem Cell Transplantation as a Prognostic Factor in Multiple Myeloma

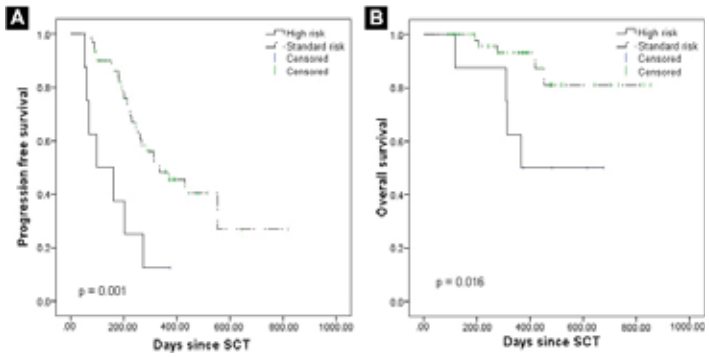


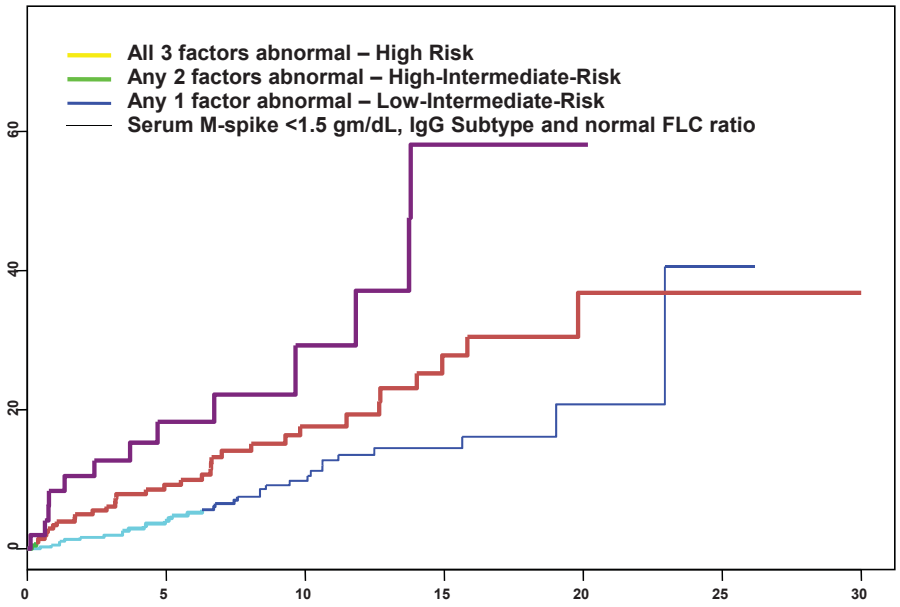
Figure 1. PFS and OS for Patients Considered High Risk by Early FLC Response Compared to Standard-Risk Patients by Kaplan-Meier Analysis and Log Rank Test. (A) PFS for High-Risk Patients Who Did Not Experience Partial Response by FLC Criteria Versus Standard-R...

Kevin Barley, Sharon Tindle, Emilia Bagiella, Sundar Jagannath, Ajai Chari. Clinical Lymphoma Myeloma and Leukemia, Volume 15, Issue 9, 2015, 541–545

Implementing New Diagnostic Myeloma Criteria

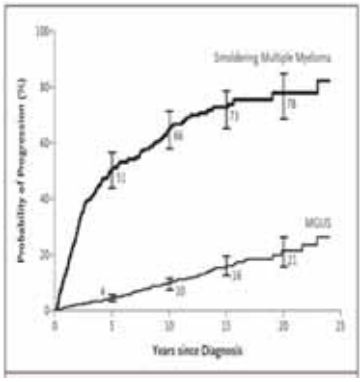
- Differential Diagnoses
- Freelite
  - Diagnosis
  - Monitoring
  - Prognosis
    - Baseline characteristics versus evolving features
- Hevylite
  - Diagnosis
  - Monitoring

Risk Stratification Model for MGUS



Rajkumar SV et al. Blood 2005;106:812-817

Mayo and Pethema Risk Stratification of Smoldering Multiple Myeloma



Risk factor	Progression at 5 years
Mayo Risk Factors (> 10% PC, m > 3/gl, FLCR < 0.125 or > 8)	
0	25%
1	51%
2	76%
Pethema Risk Factors (≥95% abn PC, immunoparesis)	
0	4%
1	46%
2	72%

Kyle RA, et al. *N Engl J Med.* **2007;356:2582-2590;** . Perez-Persona E, et al. Blood. 2007;110:2586-92

Risk Factors for Non-CRAB SMM Progression at 2 Years

Risk group	Probability of progression to myeloma or related disorder in first 2 years from initial diagnosis of SMM (%)
Bone marrow clonal plasma cells ≥60%	90
Serum involved/uninvolved free light chain ratio ≥100	80
Abnormalities on MRI (>1 focal lesion)	70
Abnormal plasma cell immunophenotype ≥95%	50
Evolving type of SMM*	65
t(4;14) or del 17p	50
M protein ≥30 g/l and bone marrow clonal plasma cells ≥10%	50
Serum involved/uninvolved free light chain ratio ≥8 and <100	40
No high-risk factors	10–20

*Increase in serum monoclonal protein by ≥10% on each of two successive evaluations within a 6-month period. †Further efforts to refine cut-off values are ongoing to identify a patient population with ≥80% risk of progression in the first 2 years. Abbreviation: SMM, smoldering multiple myeloma.

Rajkumar, S. V. & Kyle, R. A. (2013) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.160

Current Definitions of MGUS, SMM and MM

	MGUS	SMM	MM
(1) Serum M-protein	< 3 g/dL	≥ 3 g/dL or BJP > 500 mg/d	Any paraprotein
(2) Bone marrow plasma cell %	< 10%	10-60%	≥ 10% or biopsy-proven plasmacytoma
(3) CRAB*	None	None	At least one
(4) Myeloma Defining Events**	None	None	Possible
For diagnosis	All 4 criteria must be met	Either (1) OR (2), WITHOUT (3) OR (4)	Either (2) + (3), OR (2) + (4)

*CRAB criteria:
(1) Serum calcium > 11 mg/dL or > 1 mg/dL above ULN,
(2) renal insufficiency (serum Cr > 2 mg/dL or Cr Cl < 40 mL/min),
(3) anemia (hemoglobin > 2 g/dL below the LLN, or < 10 g/dL), and
(4) bone lesions (one or more osteolytic lesions revealed by skeletal radiography, CT, or PET)

** Myeloma defining events:
(1) clonal bone marrow plasma cell % ≥60
(2) involved to uninvolved serum free light chain ratio ≥ 100
(3) > 1 focal lesions (each ≥ 5 mm in size) on MRI

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Smoldering Multiple Myeloma (SMM): Predictive Value of Free Light Chains and Group Based Trajectory Modeling (GBTM)

Vernon Wu, Erin Moshier, Ajai Chari ASCO 2017

Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Comparison of high risk SMM at various institutions

	Mayo Clinic	University of Athens	University of Pennsylvania	Denmark	MMGIMEMA-Latium Working Group	Mount Sinai
Years of investigation	1970-2010 (FLCR), 1996-2010 (BMPC)	-	2008-2012	2005-2013	1980-2010	2010-2015
Number of Centers	single	-	single	multi	multi	single
Inclusion Criteria†	yes	-	-	yes	yes	yes
FLCR						
n	586	96	118	209	-	185
FLCR ≥ 100 (n/%)	90(15%)	-	11(9%)	23(11%)	-	27(15%)
median TTP (mo)	15mo	13mo	20mo	-*	-	40mo
2 year progression (%)	72%	98%**	64%	30%	-	44%
Overall progression†† (%)	98%	100%	-	-	-	56%
BMPC						
n	655	96	121	-	397	273
BMPC ≥ 60 (n/%)	21(3.2%)	8(8%)	6(5%)	-	10(2.5%)***	22(8%)
median TTP (mo)	7mo	15mo	-	-	-	31mo
2 year progression (%)	95%	95.5%****	100%	-	100%	41%
Overall Progression†† (%)	-	100%	100%	-	100%	73%

Abbreviations: † stipulation that lab data be obtained within 3mo of diagnosis. †† progression during study follow up period which is median of 77mo for N=273 and median of 60mo for N=185. - data not available. *data at 14mo. ** data at 18mo. *** not enough patients progressed to calculate median TTP. ****in 7 by bone marrow biopsy core, N=10 by bone

1. Larsen JT et al. Leukemia 2013;27:941-6.
2. Kastritis E et al. Leukemia 2013;27:947-53.
3. Waxman AJ et al. Leukemia 2015;29:751-3.
4. Sorrig R et al. Eur J of Haematology 2015.

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Predictive Value of Group-Based Trajectory Modeling Factors

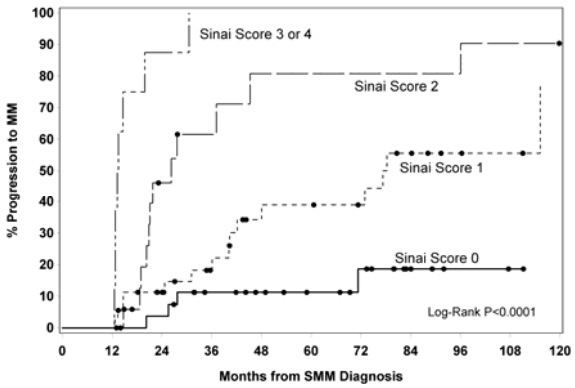
	n (%)	median TTP (mo)	Log-Rank P-value	2y PD %	overall PD %	Specificity %	Sensitivity %	Diagnostic Accuracy
eHB								
No eHb	180 (68%)	115.2	<0.0001	14%	35%			
eHb	35 (13%)	**26.3**		**43%**	66%	89%	37%	79%
Not Evaluable	58 (21%)							
eMP								
No eMP	112 (41%)	115.2	0.0230	14%	38%			
eMP	33 (12%)	**39.8**		**36%**	58%	82%	43%	74%
Not Evaluable	128 (47%)							
eFLCr								
No eFLCr	108 (40%)	Not Reached	0.0028	14%	31%			
eFLCr	19 (7%)	**37.2**		**32%**	63%	88%	29%	78%
Not Evaluable	146 (53%)							
edFLC								
No edFLC	104 (38%)	115.2	0.0586	13%	33%			
edFLC	23 (9%)	**45.3**		**30%**	48%	85%	33%	76%
Not Evaluable	146 (53%)							

Over 1 year
- eHb patients decrease of 1.57 g/dL (95% CI: 1.29, 1.84)
- eMP patients experienced either a 64% [95% CI: 44%, 83%] increase in M-protein
- eFLCr patients on average experienced either a 188% [95% CI: 183%, 193%] increase in FLCr
- edFLC patients on average experienced a 169% [95%CI: 143%, 195%] increase in dFLC

Multivariable Modeling to predict 2y PD

n=90†	Univariable		Multivariable	
	HR [95%CI]	P-value	HR [95%CI]	P-value
Age	1.002 [0.97-1.03]	0.9007		
Male Sex	0.88 [0.47-1.65]	0.6824		
BMPC ≥ 20%	3.29 [1.45-7.49]	0.0046		
BMPC ≥ 60%	0.98 [0.30-3.25]	0.9790		
M-Protein ≥ 3g/dl	3.59 [1.80-7.17]	0.0003		
IgA SMM	0.72 [0.30-1.73]	0.4645		
Immunoparesis	2.90 [1.46-5.77]	0.0025	**3.90 [1.80-8.44]**	**0.0006**
FLCr ≥ 100 and dFLC≥100	1.53 [0.59-3.99]	0.3827		
dFLC≥100	1.36 [0.70-2.64]	0.3658		
eMP	3.64 [1.89-6.99]	0.0001	**3.98 [1.80-8.44]**	**<0.0001**
eHb	4.54 [2.22-9.29]	<0.0001	**8.05 [3.53-18.35]**	**<0.0001**
eFLCr	2.09 [1.04-4.21]	0.0395		
edFLC	3.02 [1.45-6.27]	0.0031	**2.84 [1.28-6.29]**	**0.0100**

Time to progression to symptomatic myeloma stratified based on risk factors (immunoparesis, eHb GBTM, eMP GBTM, edFLC GBTM).



The median times to progression for 0, 1, 2, or >3 risk factors are not reached, 77, 26, and 13mo respectively (p <0.0001).

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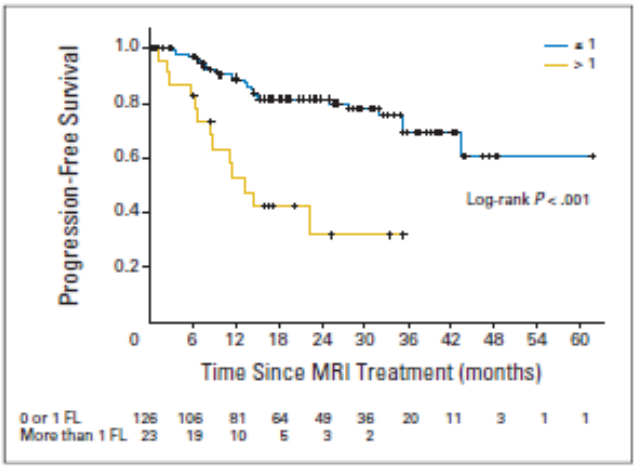
More than 1 Focal MRI Lesion Increases Risk of SMM PD (13 months vs. Not Reached)



Hilenglass et al JCO 2010. 28:1606-1610.

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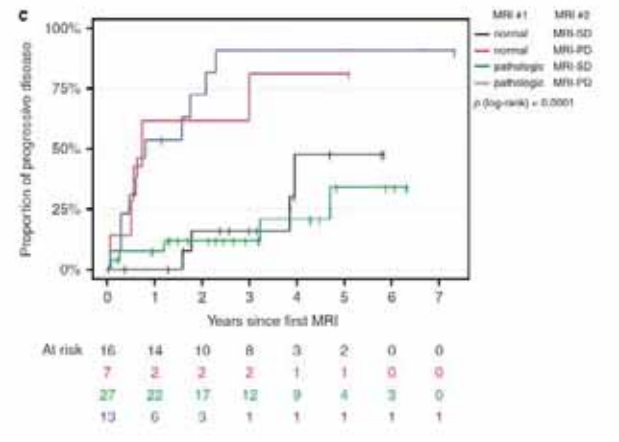
Patients with MRI-Stable Disease at 2nd MRI No Higher Risk of Progression Even with Focal/diffuse Lesions on 1st MRI



Merz et al. Leukemia 2014;28:1902-1908.

37

Early SMM Treatment vs Symptomatic Treatment - Considerations for Future Therapeutic Studies

	Early treatment	Treatment @ Symptoms
Clinical	- Deep responses in SMM possible now - Prevention/reduction of end-organ damage and infections - Potential for increased OS and ? cure	- Insufficient data re improved OS and PFS - Treatment toxicity- Grade 3 /4 or chronic Grade 1/2; QOL impairment/PROs - # needed to treat vs harm
Patho-physiologic	- Potential for increased curability due to presence of less genomic complexity - Ability to target significant mutations	- Unclear impact on PFS2 - Driver mutations have yet to be identified - Disease heterogeneity
Risk stratification	- Truly high-risk SMM very high probability of early progression - Kinetic risk stratification may mitigate some biases	- Lack of global concordance, consensus regarding high-risk status - Need to incorporate additional phenotypic and genomics features
Trial design	- Randomized early vs late treatment using same regimen ethical & feasible - Stratify by time from diagnosis - Standardized sensitive osseous screening (WBLDCT, PET-CT, or MRI) - Fix duration of treatment	- Inability to specifically target significant/driver mutations - Lead & length time biases can make benefits difficult to discern
Economic	- Less end-organ damage costs - Potential for increased OS - ? Cure	- Likely prolonged therapy if not fixed duration - Need for stem cell harvest if IMIDs used

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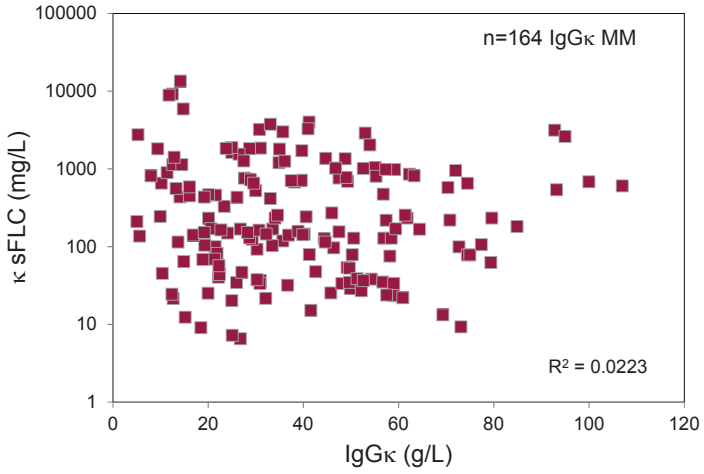
Implementing New Diagnostic Myeloma Criteria

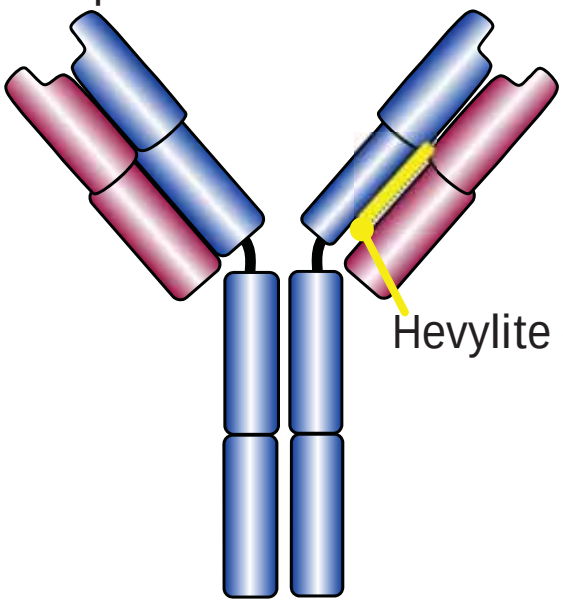
- Differential Diagnoses
- Freelite
  - Diagnosis
  - Monitoring
  - Prognosis
- Hevylite - Quantitative assessment of heavy/light chain pairs
  - Diagnosis
  - Monitoring

sFLCs and intact Igs are independent tumor markers

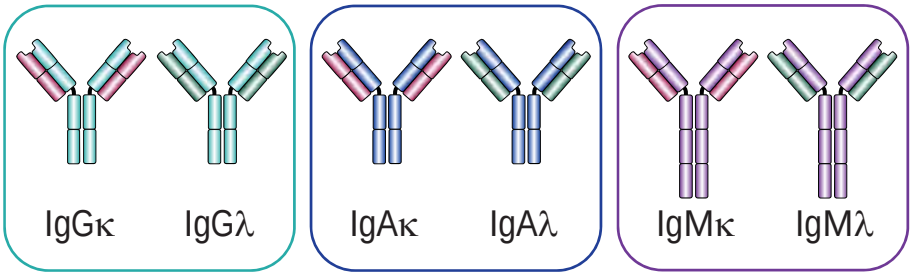


IFM 2005-01 data courtesy of H. Avet-Loiseau
κFLC measured using Freelite
IgGκ measured using Hevylite

Hevylite specificities



Hevylite specificities



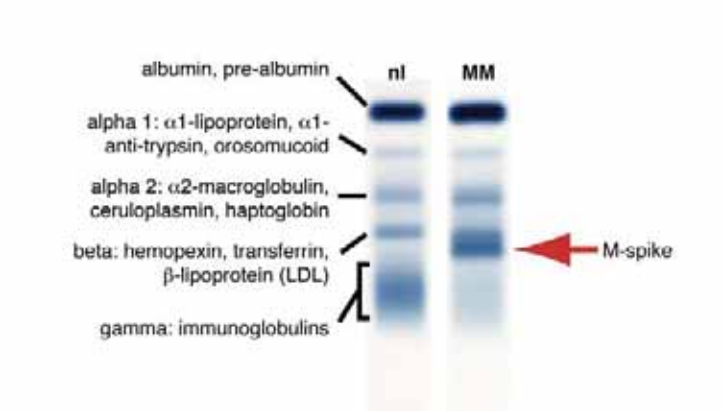
medians and 95% ranges provided by the manufacturer, and like FLCR, abnormal HLCr can result from elevated involved HLC as well as suppressed uninvolved HLC

IgGκ (3.84 – 12.07 g/L)
IgGλ (1.91 – 6.74 g/L)
IgGκ/λ ratio (1.12 – 3.21)

IgAκ (0.57- 2.08 g/L)
IgAλ (0.44 – 2.04 g/L)
IgAκ/λ ratio (0.78 – 1.94)

IgMκ (0.19 – 1.63 g/L),
IgMλ (0.12 – 1.01 g/L),
IgMκ/λ ratio (1.18 -2.74)

Monoclonal proteins may co-migrate with other serum proteins

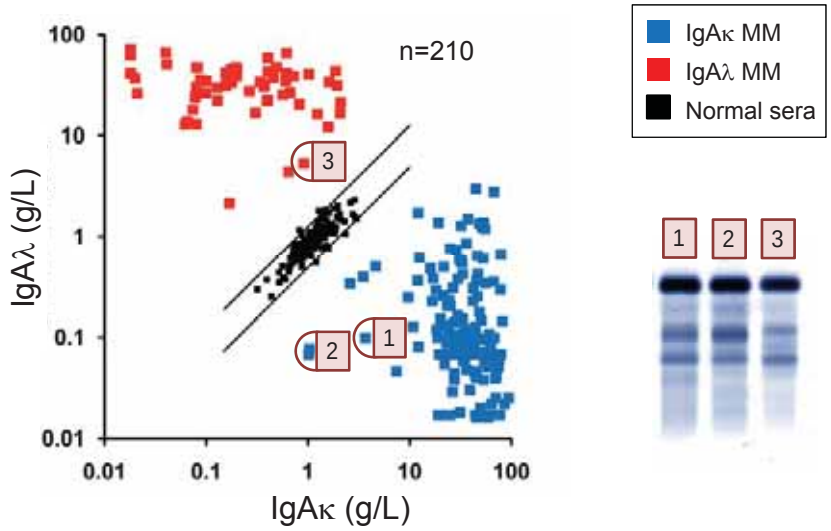


M-spike Position by M-protein Type

M-protein type	M-spike position on SPEP (n)			
	%, Alpha	% Beta	% NOT Gamma	N
IgG	0	5	6	866
IgA	0	58	58	425
IgM	0	0	0	65
IgD	0	0	0	65
Free K	0	50	50	111
Free L	6	33	39	177
				1807

Wang *et al*. Cell Mol Immunol. 2008

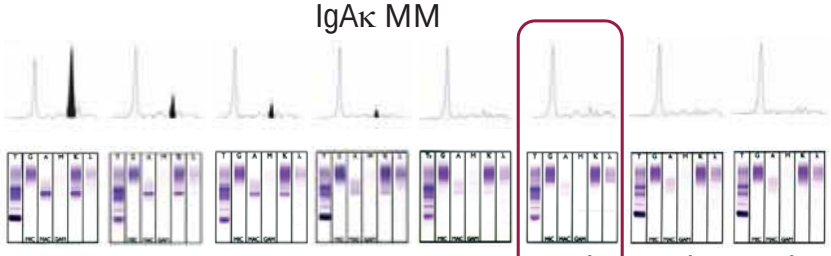
IgA Hevylite in multiple myeloma



Courtesy of L. Mirbahai
Clin Chem 2011;57:C64a

Detection of residual disease

IgAκ MM



Hevylite	IgAκ	IgAκ	IgAκ	IgAκ	IgAκ	negative	negative	negative
IgAκ g/L	18.53	5.20	2.39	1.50	1.77	0.67	0.53	0.90
IgAλ g/L	0.02	0.08	0.17	0.23	0.36	0.30	0.31	0.52
IgAκ/IgAλ	805.7	61.9	14.06	6.52	4.92	**2.23**	1.71	1.73
Freelite								
κ sFLC mg/L	230	31.6	23.1	17.7	16.4	5.3	0.9	0.6
λ sFLC mg/L	0.8	0.7	0.9	0.7	2.6	0.4	2.2	1.4
κ/λ ratio	287.5	45.1	25.7	25.3	6.31	**13.3**	0.4	0.4

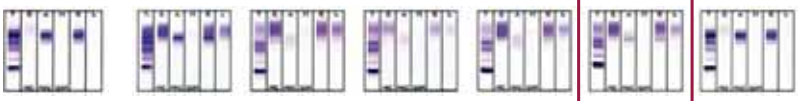
Ludwig Leukemia 2013;27:213-9

HLC provides early indication of relapse

IgAκ MM

SPE

IFE



	IgAκ	IgAκ	negative	negative	negative	IgAκ	IgAκ
Hevylite							
IgAκ	45.55	25.42	0.51	0.68	1.25	4.25	78.23
IgAλ	0.11	0.23	0.38	0.46	0.41	0.29	0.01
IgAκ/IgAλ	421.3	110.5	1.36	1.48	**3.05**	**14.66**	**7823**

5.5 months

Ludwig Leukemia 2013;27:213-9

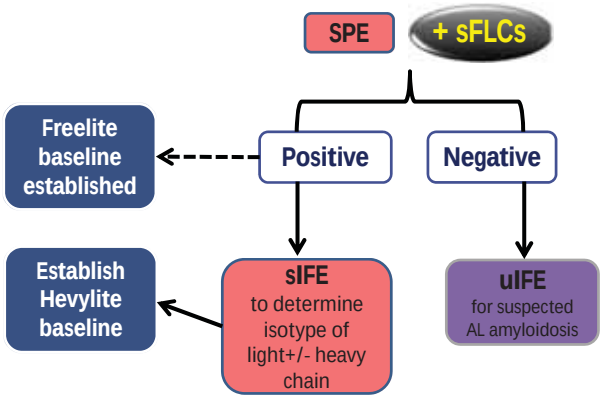
A comparison of heavy/light chain analysis to conventional serologic measurements

	Complicated IgA n=46		Non-measurable n=92	
	HLCr normal	HLCr abnormal	HLCr normal	HLCr abnormal
qIgs normal	3 (6.5%)	10 (21.7%)	45 (49%)	47 (51%)
qIgs abnormal	1 (2.2%)	32 (69.6%)	n/a	n/a
SPEP normal	2 (4.4%)	5 (10.8%)	27 (29.3%)	11 (12.0%)
SPEP abnormal	2 (4.4%)	37 (80.4%)	18 (19.6%)	36 (39.1%)
FLCr normal	2 (4.4%)	10 (22.2%)	36 (39.1%)	19 (20.7%)
FLCr abnormal	2 (4.4%)	31 (68.9%)*	9 (9.8%)	28 (30.4%)
IFE -	1 (2.2%)	0 (0%)	7 (7.6%)	4 (4.3%)
IFE +	3 (6.5%)	42 (91.3%)	38 (41.3%)	43 (46.7%)
Serological CR	1 (2.2%)	0 (0%)	7 (7.6%)	2 (2.2%)
Serological non-CR	3 (6.5%)	42 (91.3%)	38 (41.3%)	45 (48.9%)

Hevylite® Summary

- Hevylite recognizes unique conformational epitopes which can distinguish heavy chain - light chain pairs
- Allows quantitation of involved and uninvolved intact immunoglobulin in myeloma and related PCD
- HLC ratio can quantify disease (involved:uninvolved Ig) in ways in which total Ig isotype measurements cannot
- HLC ratio can be measured at levels below detectable range of SPE or IFE

Screening for monoclonal gammopathy



Conclusions

- SMM & MGUS are diagnoses of exclusion– r/o other clonal PCD and non PCDs
- sFLC is sensitive test for PCDs and with SPEP/SIFE - 99% sensitivity
  - may be helpful in CSF as well
- sFLCR for initial diagnosis vs dFLC (difference inv-uninv) for monitoring
  - Shorter half life of FLCs can be helpful for earlier disease evaluation
- Baseline FLCR can be helpful in risk stratification of MGUS (<0.125 or > 8) and SMM vs MM (>100); similarly > 1 focal MRI Lesion (SMM vs MM)
  - however, kinetics of increase of FLC and MRI lesion may be helpful
  - no prospective data for treating FLCR> 100 and study design challenging
- Abnormal HLCR may be useful for detecting residual disease, earlier relapse particularly in nongamma migrating/IgA patients

Minimal Residual Disease (MRD) in Multiple Myeloma: How and When to Do it?

Nikhil C. Munshi, MD

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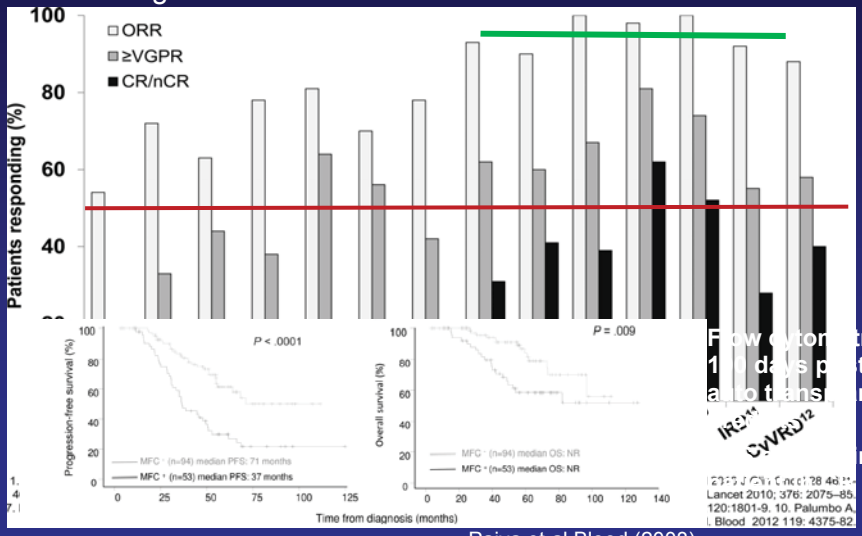
Dana-Farber Cancer Institute

DANA-FARBER CANCER INSTITUTE

BACKGROUND

- Treatment advances have increased the likelihood of achieving CR.



Paiva et al Blood (2008)

Clinical utility of immunoglobulin heavy chain gene rearrangement identification for tumour cell detection in multiple myeloma

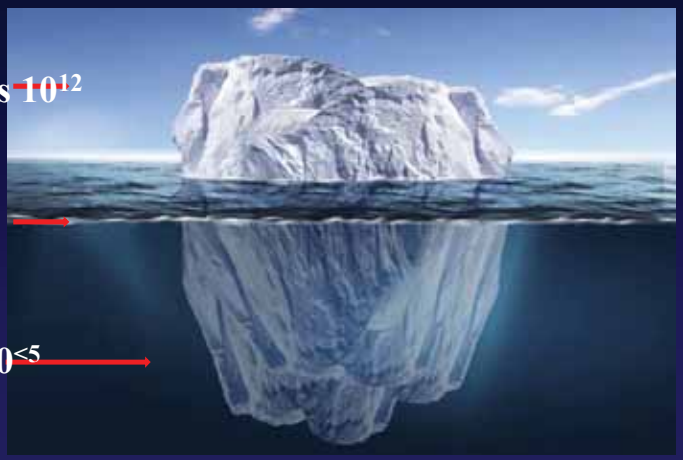
BLOOD, 19 JANUARY 2012 - VOLUME 119, NUMBER 3

High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Major Tumor Shrinking and Persistent Molecular Remissions After Consolidation With Bortezomib, Thalidomide, and Dexamethasone in Patients With Autografted Myeloma

ssess MRD in Myeloma?

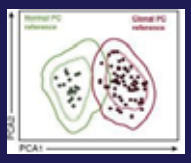


Depth matters !

MRD: What are the techniques?

Multiparametric Flow Cytometry

MRD MONITORING USING 2ND GENERATION FLOW IMPROVES DISCRIMINATION BETWEEN NORMAL VS. CLONAL PCS



MARKER	SIGNIFICANCE
CD56	21.71
CD19	19.67
CD81	14.38
CD27	12.07
CD117	8.47
CD45	6.56
CD38	4.40

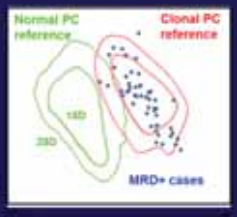
50 randomly selected MRD-positive patients

Performance

4-color

- ✓ CD38
- ✗ CD138
- ✓ CD19
- ✓ CD56
- ✗ CD27
- ✗ CD81
- ✗ CD117
- ✓ CD45

8-color



82% accuracy (41/50 patients) → *96% accuracy (48/50 patients)*

GEM2010MAS65

Paiva et al. Blood, 2016

NGF reaches 10^{-6} sensitivity in the vast majority of MM patients (GEM2012MENOS65)

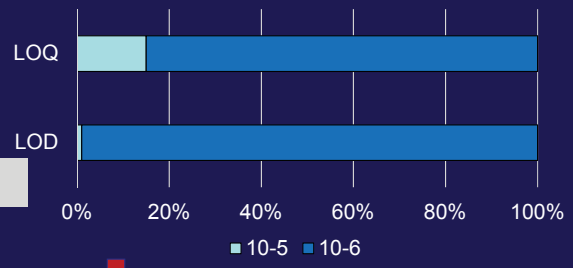
8-COLOR PANEL 12 TOTAL MARKERS

	TUBE-1	TUBE-2
PE-Cy7	CD19	CD19
PerCP-Cy5	CD45	CD45
PE	CD56	CD56
APC-C750	CD81	CyIgl
BV510	CD27	CD27
APC	CD117	CyIgk
FITC	CD38	CD38
V450	CD138	CD138

LOQ: 50 cells / total nucleated viable cells
LOD: 20 cells / total nucleated viable cells

Bulk lyse protocol

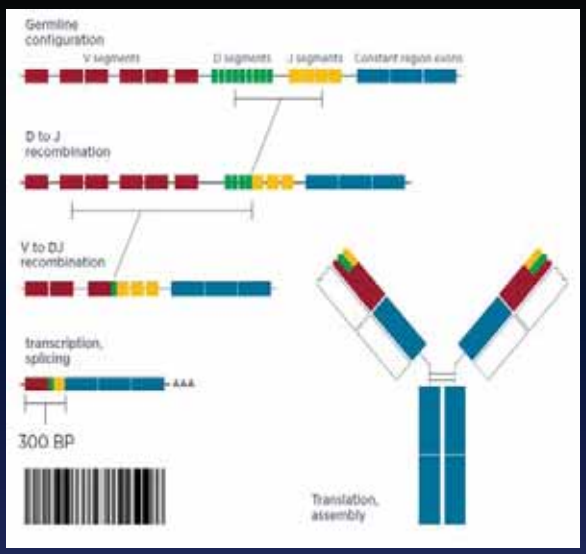
Measure **>5 x 10^6 cells/tube** in the FCM



IMPROVED PREDICTION OF PATIENT OUTCOME

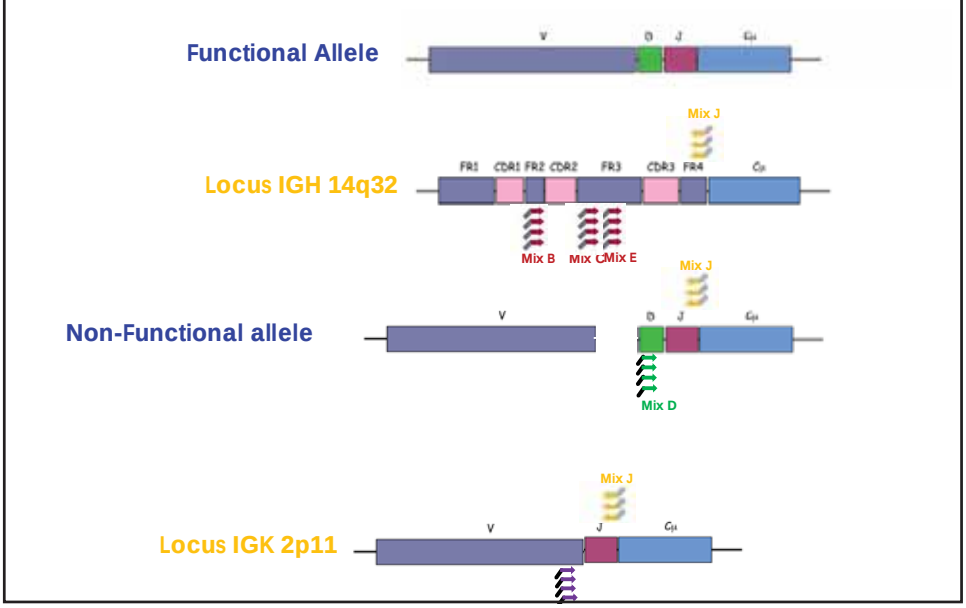
Flores-Montero J, et al. Leukemia. 2017

Studying Clone content by Immunoglobulin VDJ Rearrangement



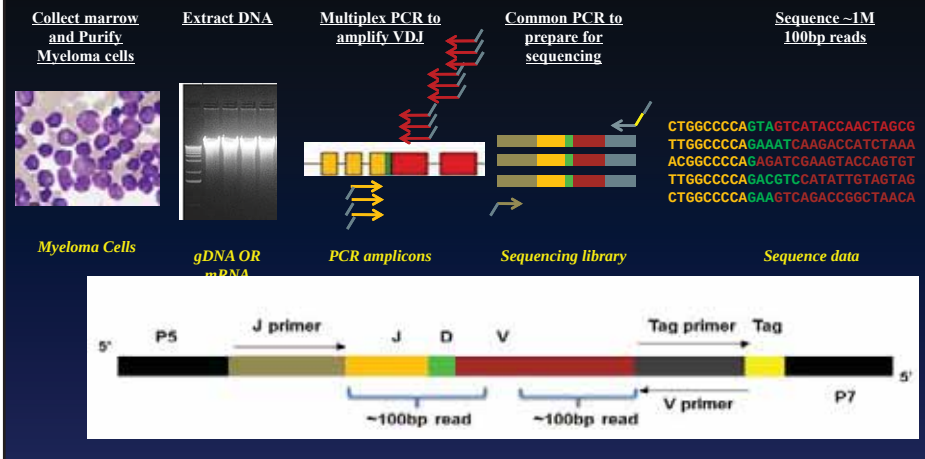
- Immunoglobulin loci
  - Somatic hypermutation occurs frequently
- Enables identification of myeloma cells and analysis of phylogenetic relationship between different myeloma subclones

NGS: Technical principles

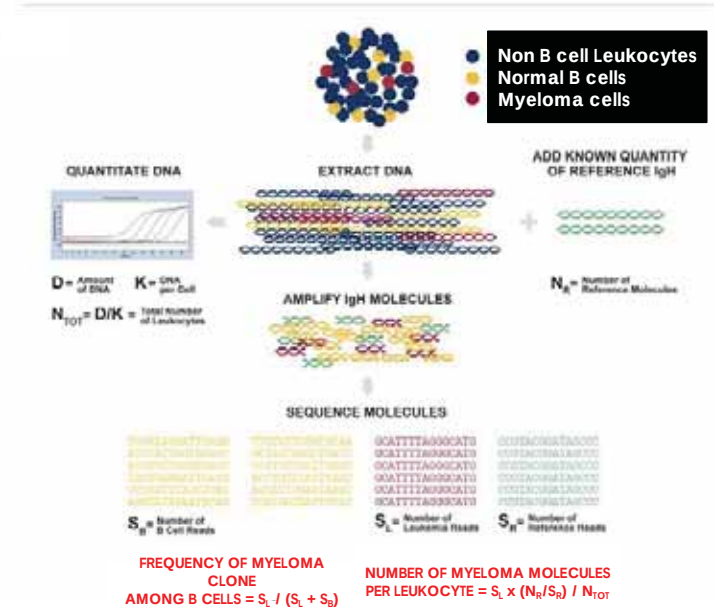


Next-Generation Sequencing Method

LymphoSIGHT™ platform: *Sequencing of Immunoglobulin gene*

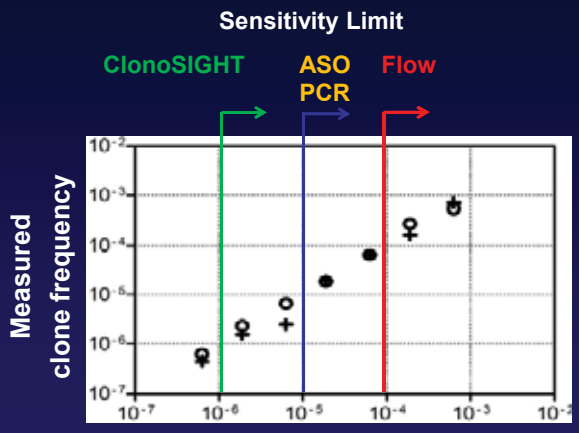


NGS: Technical principles



Sequencing-based method has higher technical performance

- 12 tumors diluted into healthy blood in duplicate
- 2 orders of magnitude more sensitivity than flow cytometry

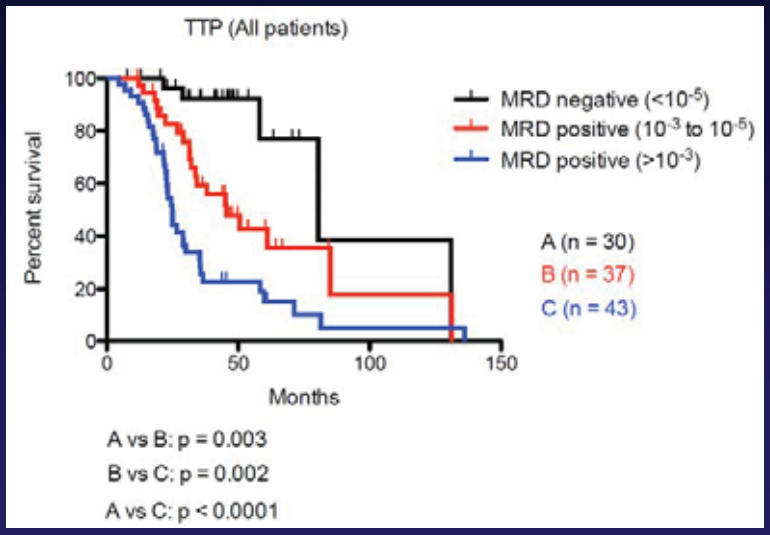


Faham et al Blood 2012

Comparison with flow cytometry and ASO PCR

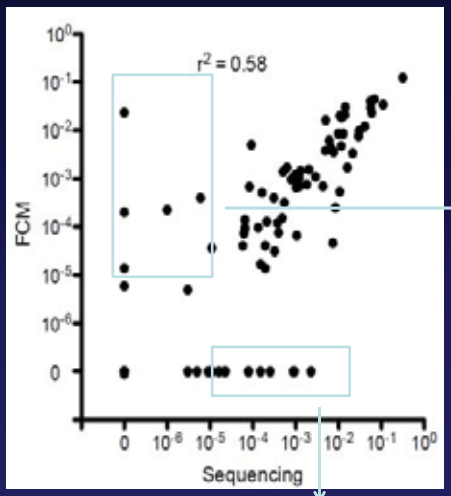
	Flow cytometry	ASO PCR	Sequencing
Universal reagents	Yes		Yes 3 validated universal assays
Applicability	~98% of patients		>90% of patients (multiple receptors)
Sensitivity	1 cell in 100,000		1 cell in 1,000,000
Evolution	Cannot be measured		Can be measured at diagnosis and during follow-up using algorithmic methods
Turnaround time	In 1-2 Days		Clone ID: 7 days MRD: 7 days

Higher levels of sensitivity translate into improved prediction of time to tumor progression (TTP)



Martinez-Lopez J, et al. 2014;123(20):3073-9.

Correlation between sequencing and MFC MRD results



B curve next slide

- Concordance between sequencing and FCM method ($r^2 = 0.58$)
- MRD positivity threshold: 10^{-5}

Discordances (Sequencing negative, MFC positive)

Pt	Seq	Flow	Clinical Outcome
1	0	1.40E-05	Alive, No relapse
2	0	2.00E-04	Alive, No relapse
3	0	2.33E-02	Alive, No relapse
4	1.40E-06	2.25E-04	Alive, relapse
5	5.65E-06	4.00E-04	Alive, No relapse

Martinez-Lopez J, et al. 2014;123(20):3073-9.

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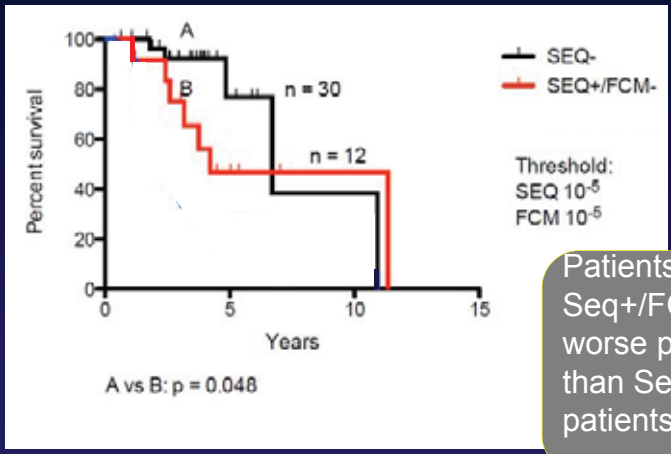
Sequencing method provides improved prognostic value compared to MFC

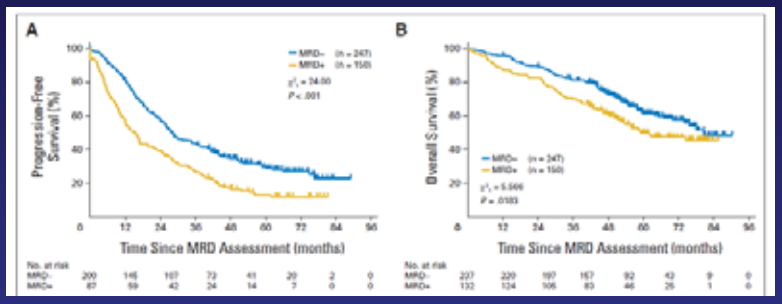


Patients who are Seq+/FCM- have worse prognosis than Seq- patients (A vs B)

Martinez-Lopez J, et al. 2014;123(20):3073-9.

Where does MRD Assessment Play a Role?

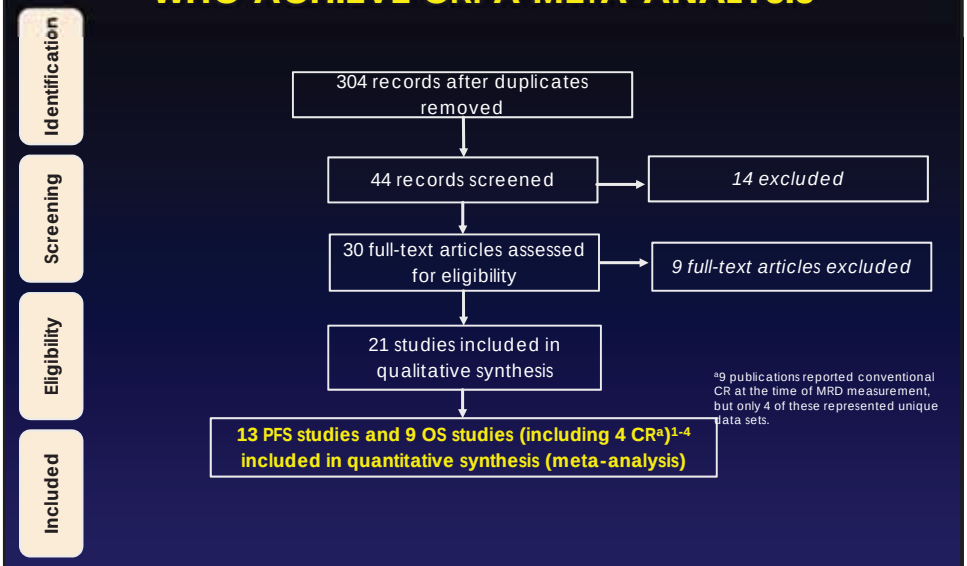
MRD Status is Predictive of Outcome both Pre and Post ASCT



MRD Status 100 days Post-ASCT

Rawstron AC et al. J Clin Oncol. 2013 Jul 10;31(20):2540-7.

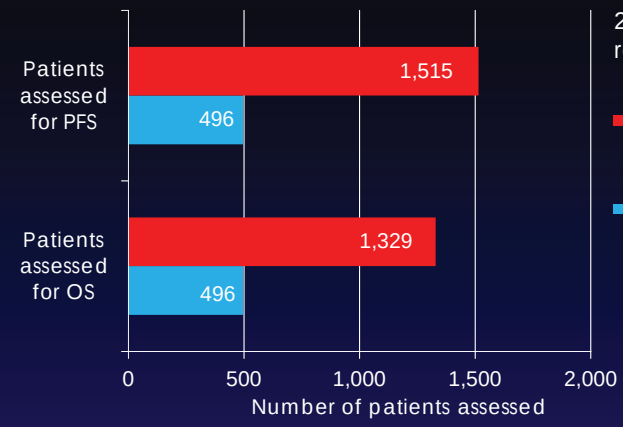
SIGNIFICANT IMPACT OF MRD STATUS ON SURVIVAL OUTCOMES IN PTS WITH MULTIPLE MYELOMA (MM) WHO ACHIEVE CR: A META-ANALYSIS



[a]9 publications reported conventional CR at the time of MRD measurement, but only 4 of these represented unique data sets.

Munshi N et al., JAMA Oncol, 2017

Number of patients with PFS and OS data allowing for analysis

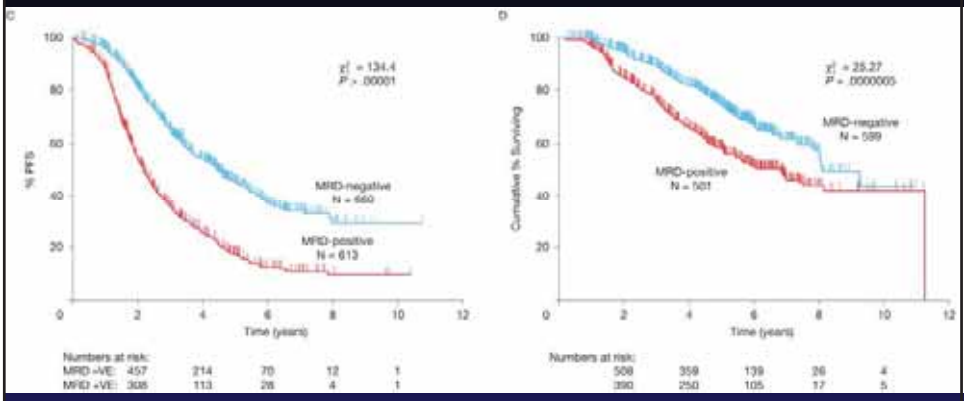


OS, overall survival; PFS, progression-free survival.

1. Paiva B, et al. J Clin Oncol. 2011;29:1627-33.
2. Paiva B, et al. Blood. 2012;119:687-91.
3. Rawstron AC, et al. J Clin Oncol. 2013;31:2540-7.
4. Swedin A, et al. Br J Haematol. 1998;103:1145-51.

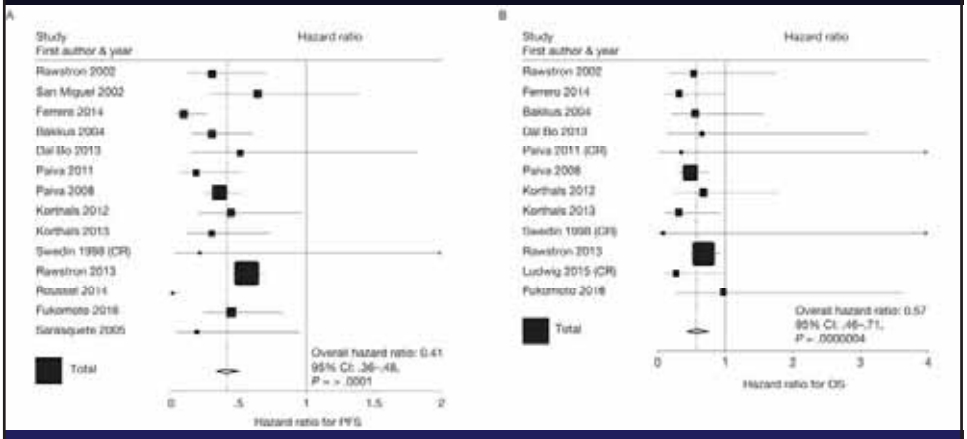
Munshi N et al., JAMA Oncol, 2017

The effect of MRD status on PFS and OS (All patients)



Munshi N et al., JAMA Oncol, 2017

The effect of MRD status on PFS and OS (All patients)



Munshi N, et al. JAMA Oncol 2017

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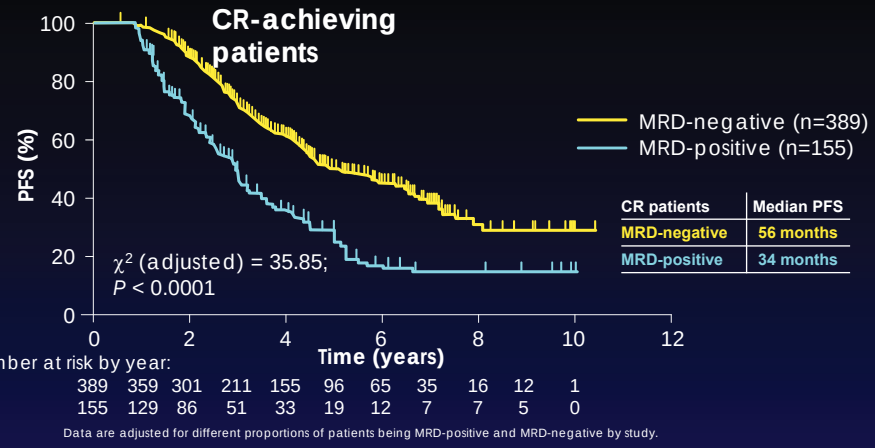
The effect of MRD status on PFS (CR patients)



CR patients	Median PFS
MRD-negative	56 months
MRD-positive	34 months

Number at risk by year:

389	359	301	211	155	96	65	35	16	12	1
155	129	86	51	33	19	12	7	7	5	0

Data are adjusted for different proportions of patients being MRD-positive and MRD-negative by study.

- **3-year PFS: 70% (MRD$^-$) vs. 46% (MRD+)**
- **5-year PFS: 48% (MRD$^-$) vs. 27% (MRD+)**
- **Majority of MRD-positive patients progressed by 6 years; nearly 50% of MRD-negative patients progression free**

Munshi N et al., JAMA Oncol, 2017

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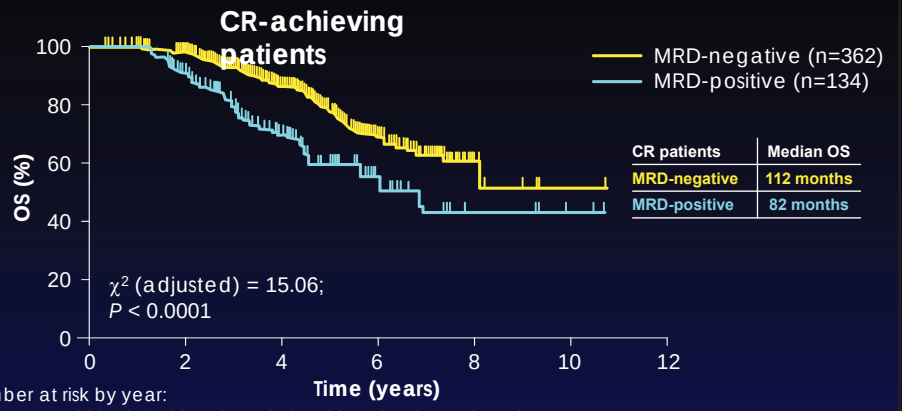
The effect of MRD status on OS (CR patients)



CR patients	Median OS
MRD-negative	112 months
MRD-positive	82 months

Number at risk by year:

362	359	331	274	218	138	76	34	8	3	1
134	131	111	81	55	35	20	10	5	5	2

Data are adjusted for different proportions of patients being MRD-positive and MRD-negative by study.

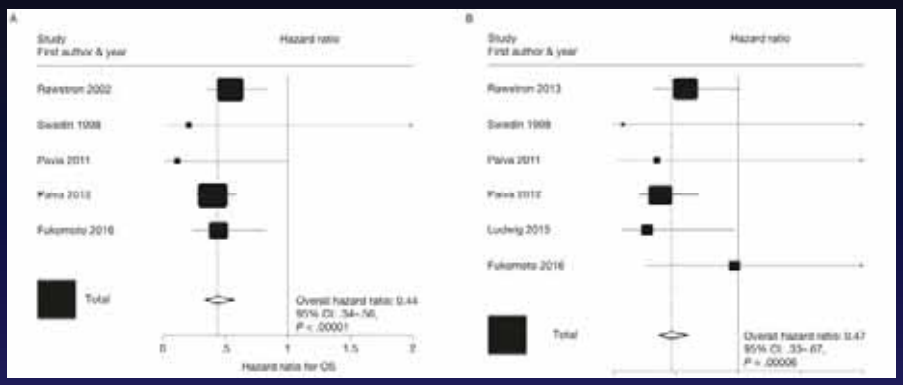
- **OS @ 3-years, 94% versus 80%**
- **OS @ 5-years, 80% versus 61%**
- **OS @ 7-years, 67% versus 47%**

CR, complete response; MRD, minimal residual disease; NR, not reached; OS, overall survival.

Munshi N et al., JAMA Oncol, 2017

The effect of MRD status on PFS and OS (CR patients)

- MRD-negativity reduced the hazard of disease progression by 56%



Munshi N et al., JAMA Oncol, 2017

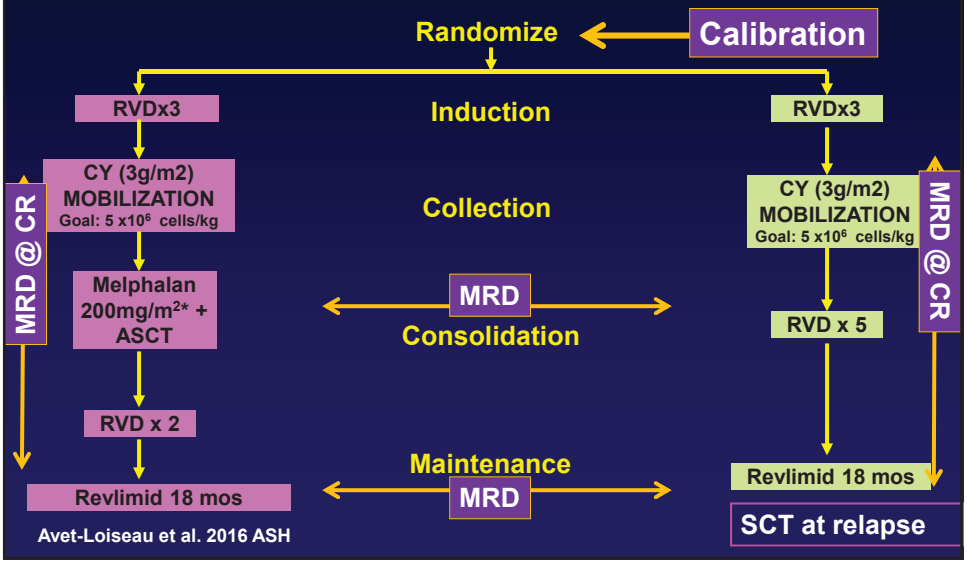
Conclusions of the meta-analysis

MRD is definitely predictive of both longer PFS and OS

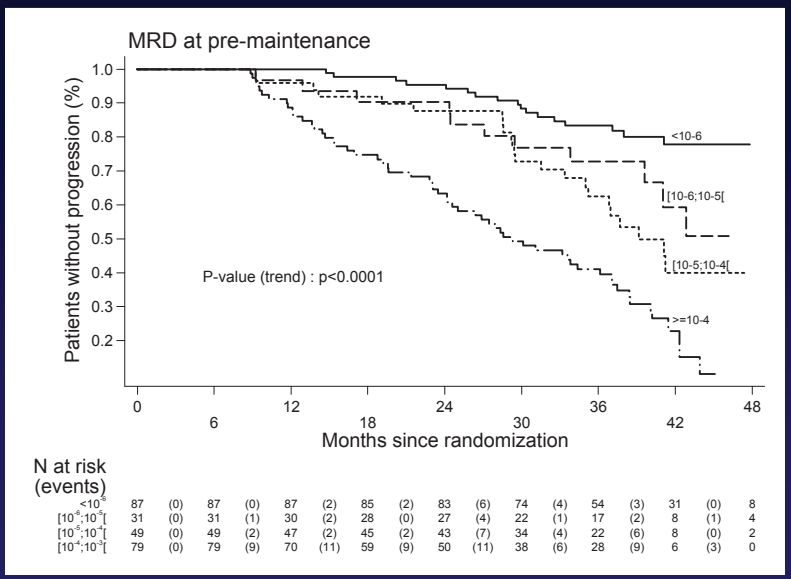
Most of the available results are from MFC

Time to Utilise MRD to direct therapy & MRD should be the surogate for outcome in MM

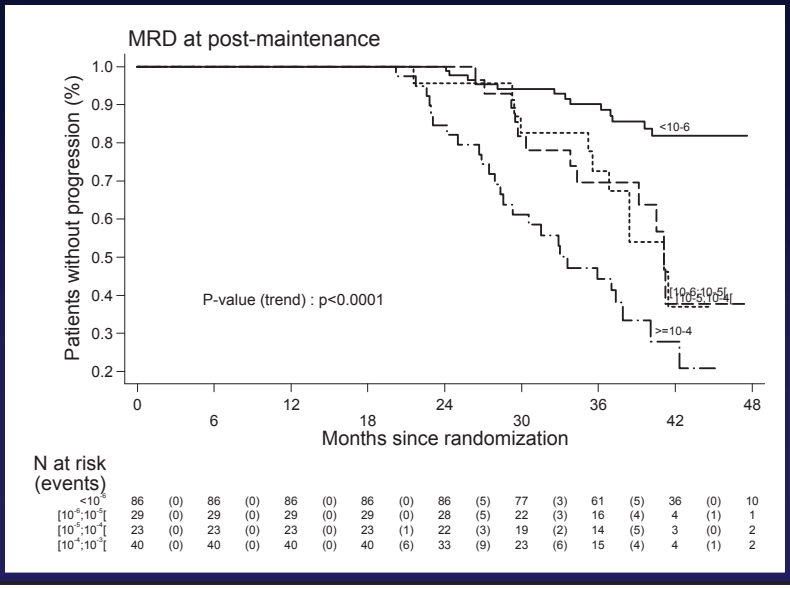
IFM/DFCI 2009 Study
Newly Diagnosed MM (N=700)



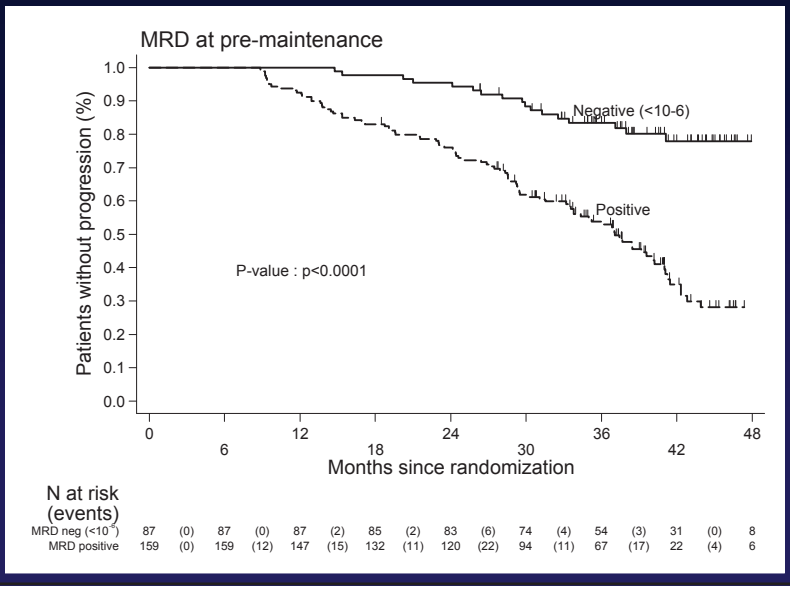
Superior PFS with MRD Negativity



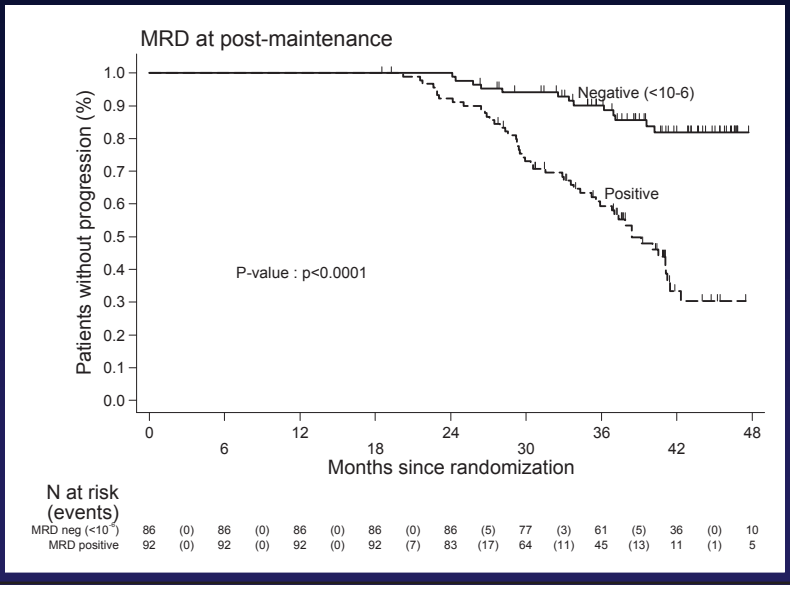
Superior PFS with MRD Negativity Post Maintenance



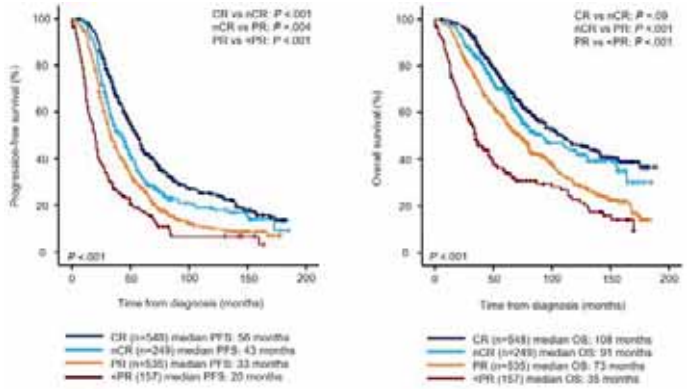
IFM 2009 trial FCM Negative Patients



IFM 2009 trial
FCM Negative Patients



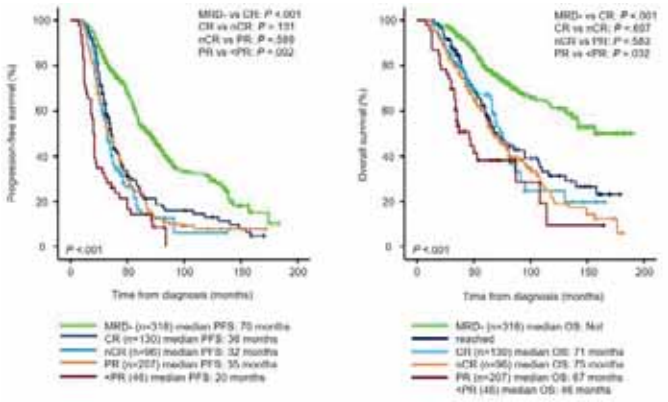
Patients attaining CR experience prolonged PFS and OS…but…



GEM2000, GEM2005MENOS65, GEM2005MAS65, GEM2010MAS65

San Miguel, personal communication.

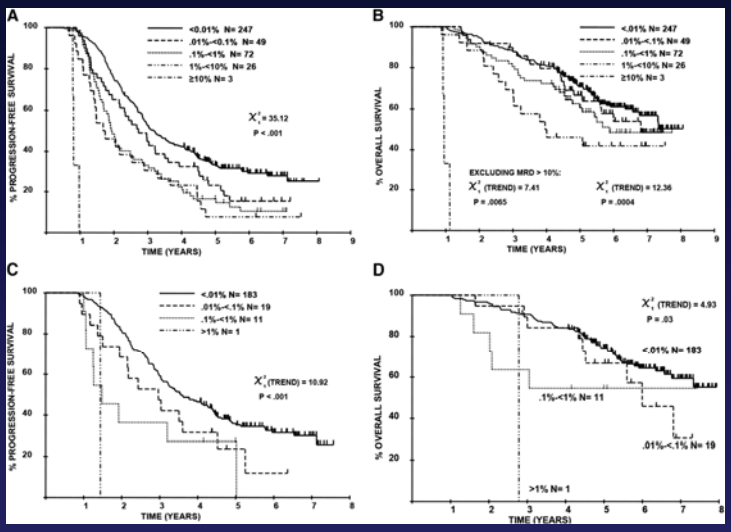
…But the true value of CR relies on the MRD status, and CR w/o MRD is no better than PR



GEM2000, GEM2005MENOS65, GEM2005MAS65, GEM2010MAS65

San Miguel, personal communication.

Higher Levels of Sensitivity Translate into Improved Overall Survival



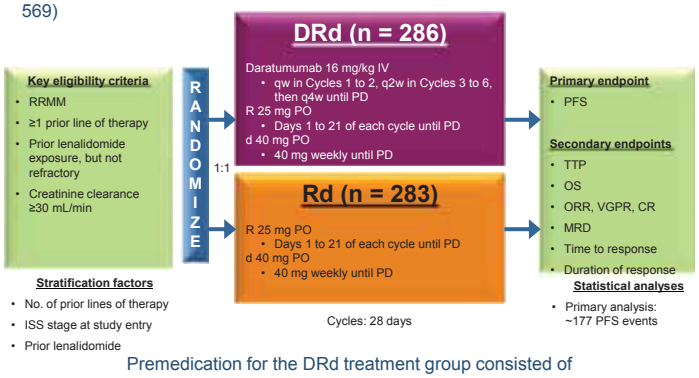
For each log improvement in sensitivity there is 10% improvement in survival

Rawstron et al Blood 2015

Does MRD Predict Outcome in Relapsed Disease

Daratumumab Plus Lenalidomide and Dexamethasone (DRd) Versus Lenalidomide and Dexamethasone (Rd) in Relapsed or Refractory Multiple Myeloma: POLLUX Study Design

Multicenter, randomized (1:1), open-label, active-controlled, phase 3 study (N = 569)



Premedication for the DRd treatment group consisted of dexamethasone 20 mg,[a] acetaminophen, and an antihistamine

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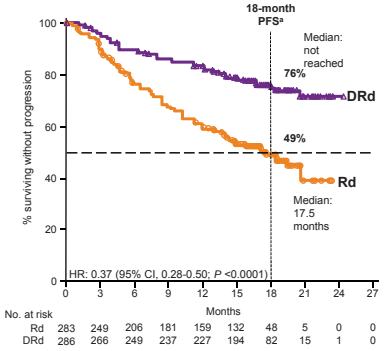
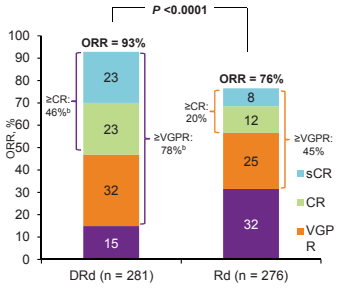
Updated Efficacy





- Median (range) follow-up: 17.3 (0-24.5) months

Responses continue to deepen in the DRd group with longer follow-up

HR, hazard ratio; CI, confidence interval; sCR, stringent complete response; PR, partial response; ITT, intent-to-treat.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate.
[b]P <0.0001 for DRd vs Rd.

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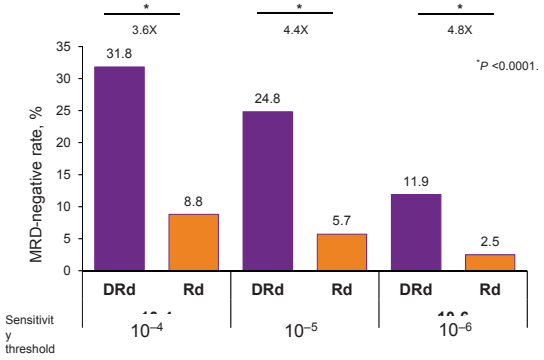
MRD-negative Rates: ITT



MRD-negative rates were >3-fold higher at all thresholds

MRD was assessed with a ClonoSEQ™ next-generation sequencing assay

P values are calculated using a likelihood-ratio chi-square test.

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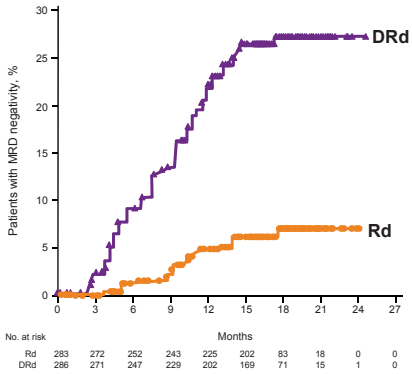
Time to MRD Negativity (10^{-5})[a]



MRD negativity was more rapidly achieved with DRd; the majority of patients maintain MRD negativity

[a]Only 1 MRD-negative sample counted per patient.

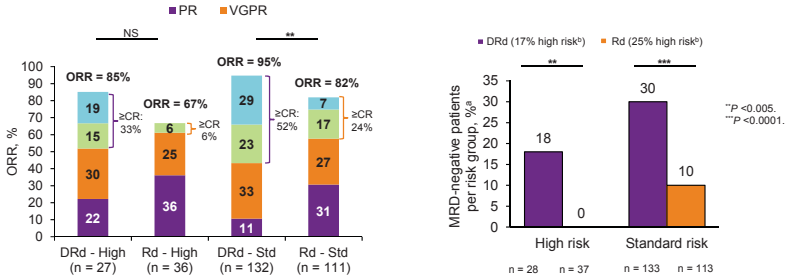
MRD-negative Rates: Subgroups

MRD threshold	Number of prior lines of therapy	DRd	Rd
10^{-4}	1	31%	11%
	≥2	33%	7%
10^{-5}	1	24%	8%
	≥2	26%	4%
10^{-6}	1	9%	4%
	≥2	15%	1%

MRD threshold	ISS stage	DRd	Rd
10^{-4}	I	30%	8%
	II	32%	7%
	III	36%	14%
10^{-5}	I	23%	6%
	II	26%	6%
	III	27%	5%
10^{-6}	I	13%	1%
	II	9%	2%
	III	14%	5%

MRD-negative rates were maintained across subgroups with DRd

ORR and MRD-negative Rates (10^{-5}) by Cytogenetic Risk
(RNA-Seq and WES)

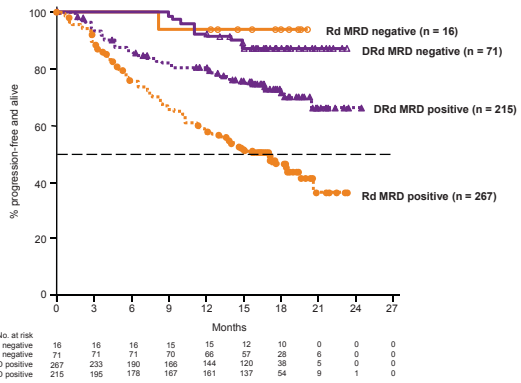


- **No high-risk MRD-negative patients have progressed or converted to MRD positive**
  - High risk = any of t(4;14), t(14;16), del17p abnormalities
  - Standard risk = conclusive absence of all 3 markers

In high-risk patients, MRD-negative status was achieved only in those treated with daratumumab-containing regimens

RNA-Seq, RNA-sequencing; WES, whole exome sequencing; NS, not significant.
[a]Percentage of patients within a given risk group and treatment arm.
[b]Percentage of patients within a given treatment arm within the biomarker-evaluable population.

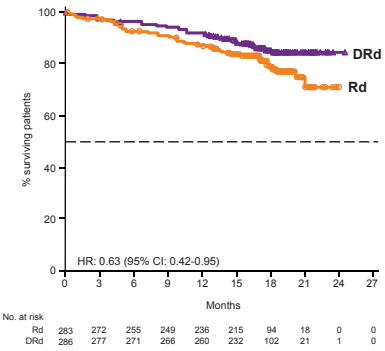
PFS: MRD Status (10^{-5})



MRD negativity is associated with better outcomes

ITT population.

OS

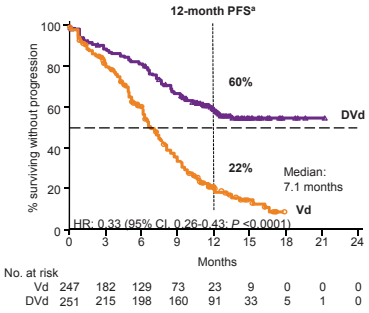


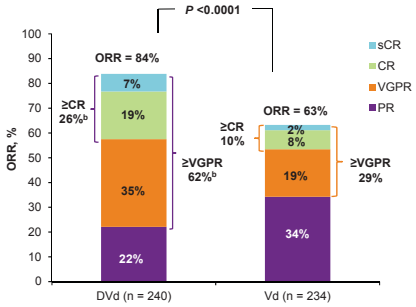
- **OS events**
  - 40 (14%) in DRd
  - 56 (20%) in Rd

Curves are beginning to separate, but OS data are immature

ITT population.
Median OS was not reached; results did not cross the prespecified stopping boundary.

CASTOR Study: Updated efficacy





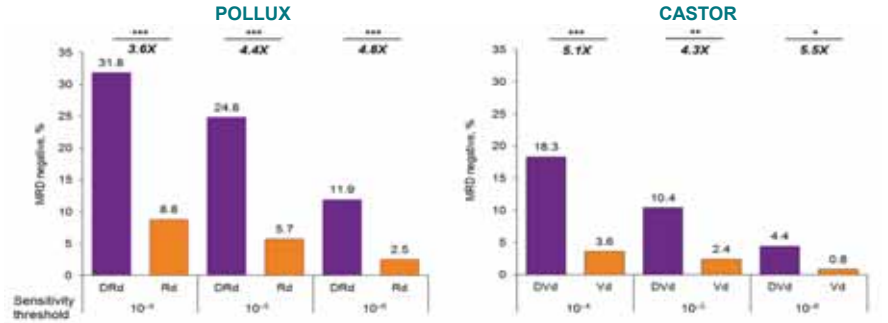
- Median (range) follow-up: 13.0 (0-21.3) months
- An additional 7% of patients receiving DVd achieved ≥CR with longer follow-up

DVd-treated patients had a 67% reduction in the risk of disease progression or death in comparison with Vd Responses continue to deepen in the DVd group with longer follow-up

ITT, intent-to-treat.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate; [b]P <0.0001 for DVd versus Vd.

Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation.

CASTOR & POLLUX:
Proportion of MRD-negative patients at different thresholds

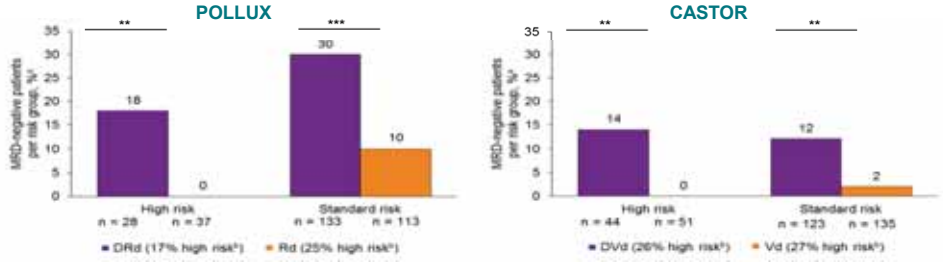


Daratumumab in combination with standard of care significantly improved MRD-negative rates at all thresholds

*** *P* <0.0001.
** *P* <0.005.
* *P* <0.05.
P values calculated using likelihood-ratio chi-square test.

Avet-Loiseau H, et al. Presented at ASH 2016 (Abstract 246), oral presentation.

CASTOR & POLLUX:
MRD at 10^{-5} by Cytogenetic Risk by NGS



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Avet-Loiseau H, et al. Presented at ASH 2016 (Abstract 246), oral presentation.

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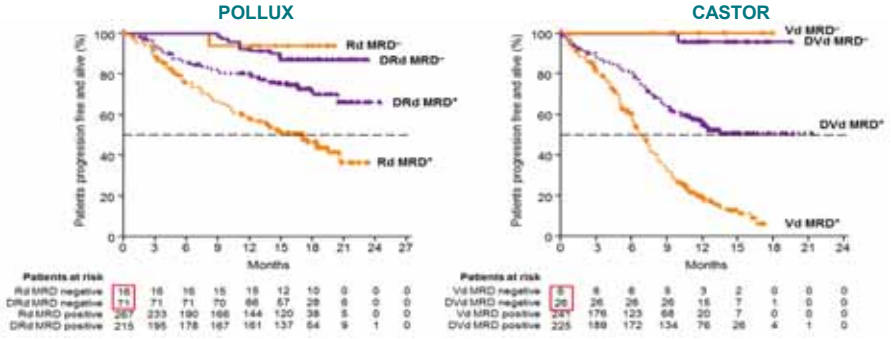
PFS According to MRD Status at 10^{-5}

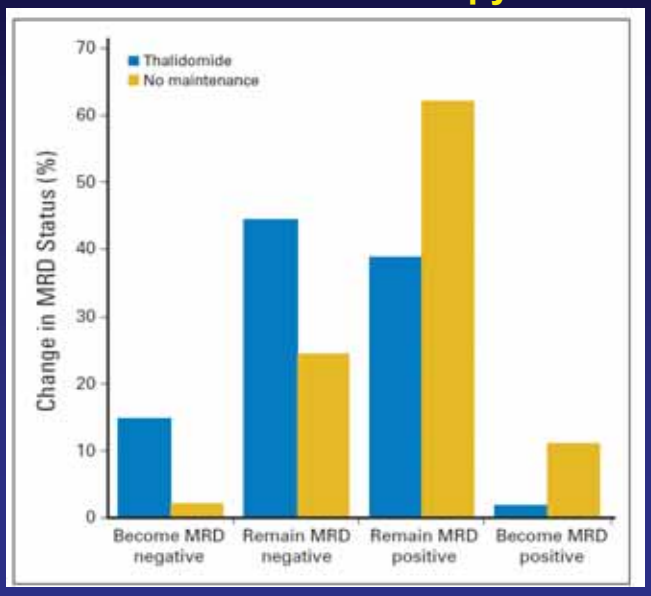


- Lower risk of progression in MRD-negative patients
- More patients achieve MRD negativity when adding daratumumab
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

Avet-Loiseau H, et al. Presented at ASH 2016 (Abstract 246), oral presentation.

Impact of Maintenance on MRD Status And Outcome

MRD Status a Surrogate for Efficacy of Maintenance Therapy



Rawstron AC et al. J Clin Oncol. 2013 Jul 10;31(20):2540-7.

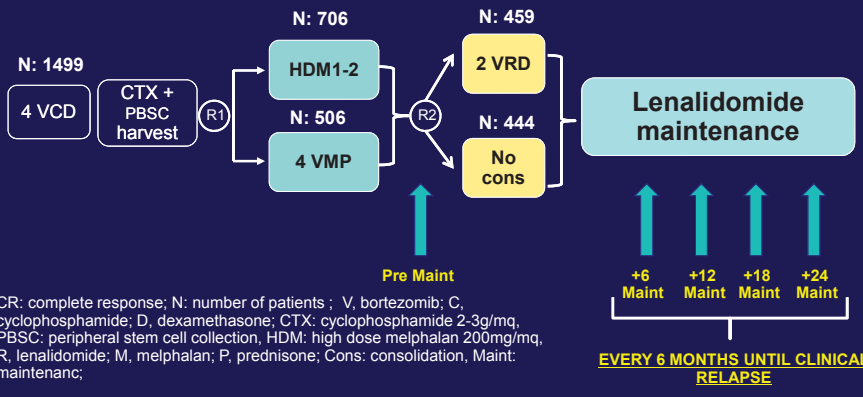
MRD Negativity Increases with Maintenance Therapy

	Minimal Residual Disease Status	
	Negative	Positive
Response at the beginning of maintenance. (%)	24.6%	75.4%
Response after 12 months of maintenance. (%)	38.5%	61.5

Methods

MM patients enrolled in the RV-MM-COOP-0556 (EMN02/HO95 MM; NCT01208766)

- Newly diagnosed ≤ 65 years
- MRD assessement in patients achieving suspected CR before lenalidomide maintenance



CR: complete response; N: number of patients ; V, bortezomib; C, cyclophosphamide; D, dexamethasone; CTX: cyclophosphamide 2-3g/mq, PBSC: peripheral stem cell collection, HDM: high dose melphalan 200mg/mq, R, lenalidomide; M, melphalan; P, prednisone; Cons: consolidation, Maint: maintenanc;

Oliva S et al. EHA 2017; Abstract S102.

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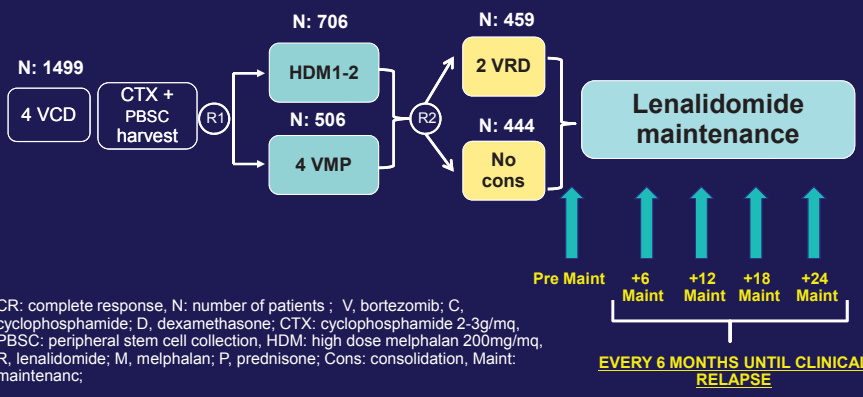

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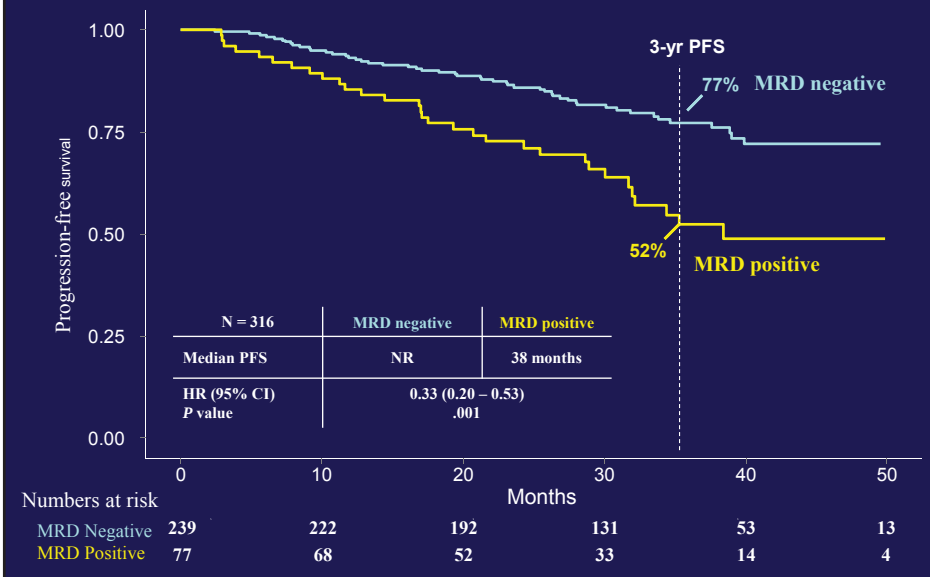
Oliva S et al. EHA 2017; Abstract S102.

Pre-maintenance

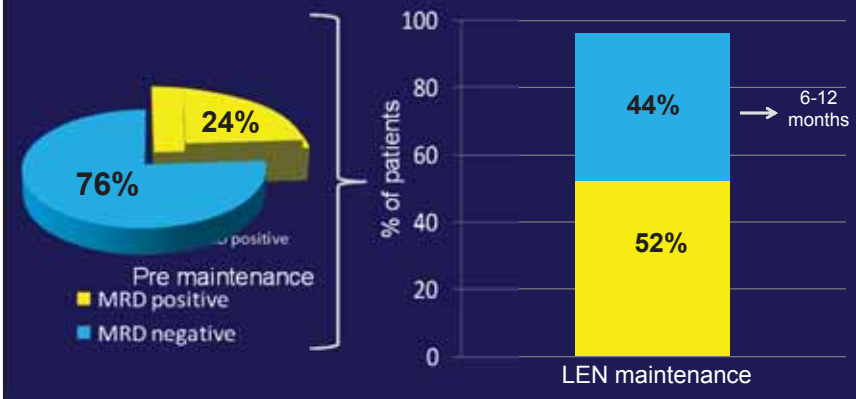
Progression free Survival: Median Follow-Up from MRD enrollement of 33 Months



Oliva S et al. EHA 2017; Abstract S102.

MRD status at pre-maintenance

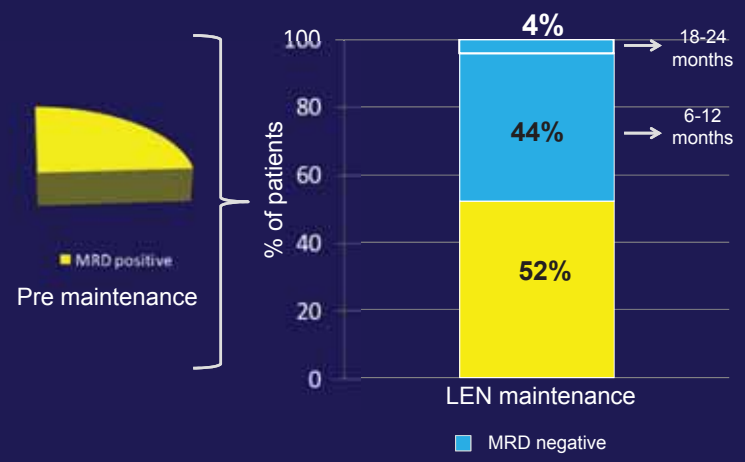
Sub-analysis on MRD positive patients at pre-maintenance who had a second MRD evaluation >1 year of Lenalidomide



Oliva S et al. EHA 2017, Abstract S102.

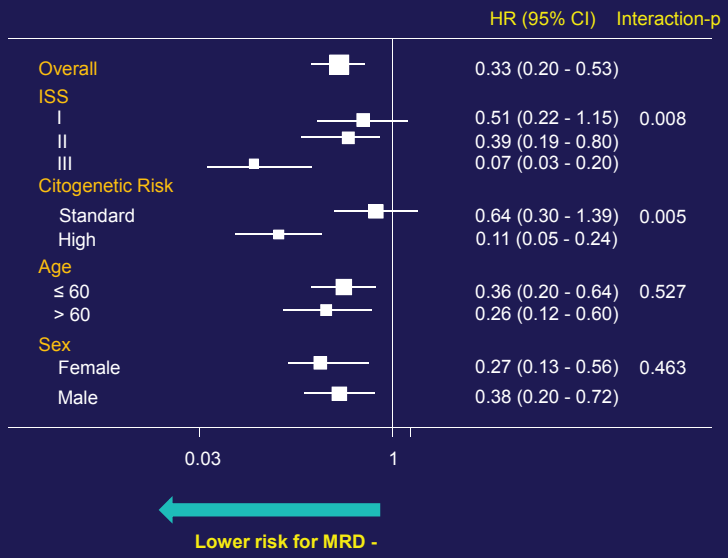
MRD status during maintenance

Sub-analysis on MRD positive patients at pre-maintenance who had a second MRD evaluation >1 year of Lenalidomide



Oliva S et al. EHA 2017; Abstract S102.

Subgroup analyses for PFS



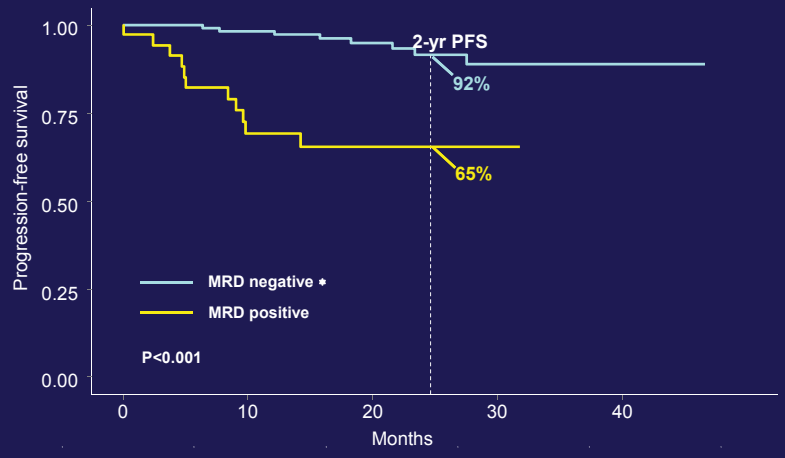
* Adjusted for random therapies

Oliva S et al. EHA 2017; Abstract S102.

Results

Landmark analysis at 1 year of len maintenance

VCD-int-± cons | Lenalidomide Continuous Therapy



Preliminary results: Longer follow-up needed

Int: intensification; Cons: consolidation

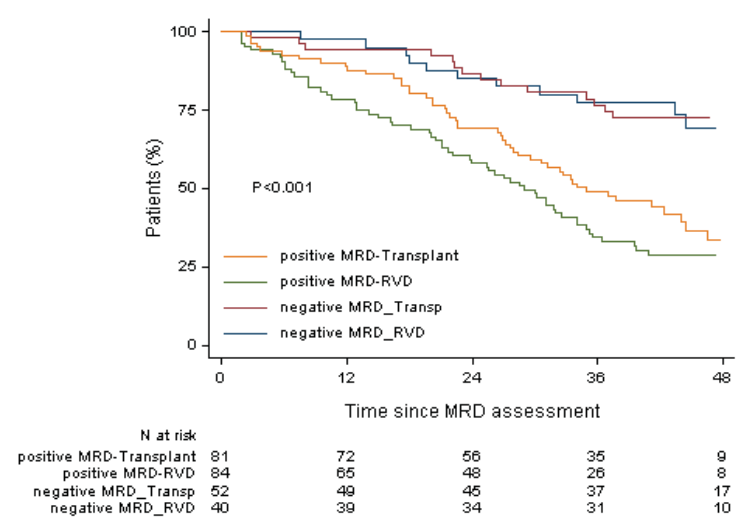
* 85% were persistent MRD negative (first negativity pre-maintenance)

Can MRD Inform Treatment

Higher MRD Negativity With High-dose Therapy

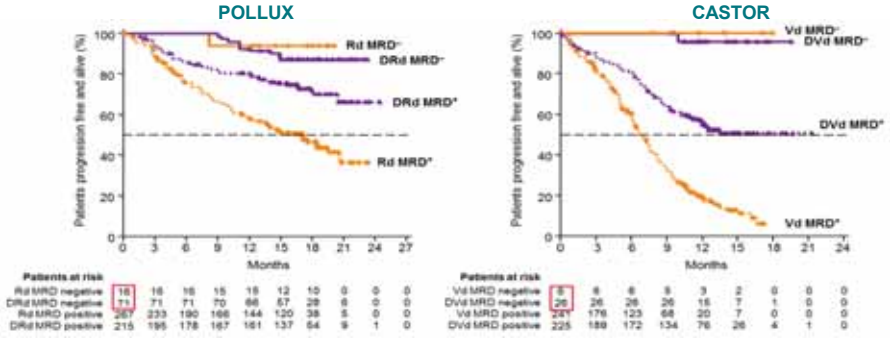
	Minimal Residual Disease Status		
	Negative	Positive	P Value
Treatment arm — no. (%)			0.01
RVD-alone	54 (20.5)	210 (79.5)	
Transplantation	73 (29.8)	172 (70.2)	

MRD Negative Patients Has Improved Outcome Irrespective of Therapy Used



Avet-Loiseau et al., 2017

CASTOR & POLLUX:
PFS According to MRD Status at 10^{-5}

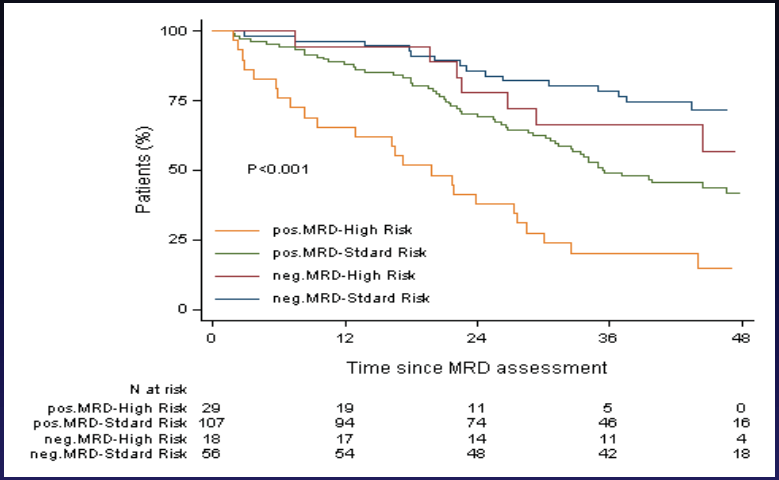


- Lower risk of progression in MRD-negative patients
- More patients achieve MRD negativity when adding daratumumab
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

Avet-Loiseau H, et al. Presented at ASH 2016 (Abstract 246), oral presentation.

Role of MRD in Risk Groups

MRD Negative Patients Has Improved Outcome Irrespective of Risk Category

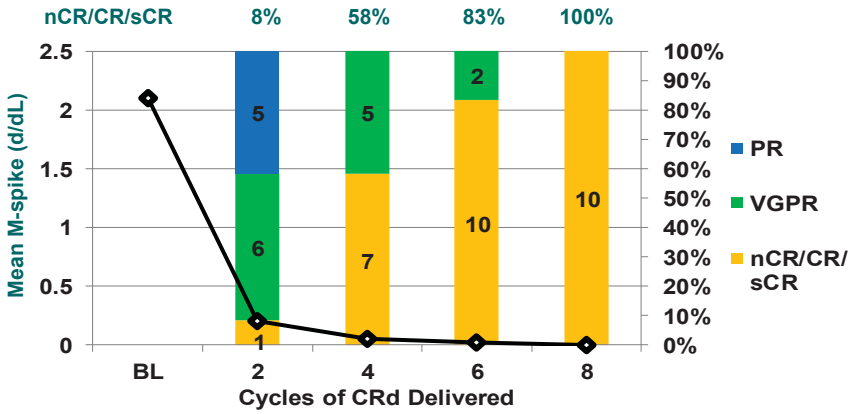


Avet-Loiseau et al., 2017

What other Plasma Cell Disorder Can MRD Measurements be Applied to?

Carfilzomib, Lenalidomide and Dexamethasone for High Risk SMM

- 8 cycles of CRD followed by 24 cycles of lenalidomide maintenance
- Option to harvest stem cells after 4 cycles of induction



11/12 (92%) are MRD negative by 8-color flow cytometry of the bone marrow

16TH INTERNATIONAL Myeloma Workshop

NEW DELHI, INDIA • MARCH 1-4, 2017

Persistence of Minimal Residual Disease by multiparameter flow cytometry can hinder recovery of organ damage in patients with AL amyloidosis

Paolo Milani , Margherita Massa, Marco Basset, Francesca Russo, Andrea Foli, Giovanni Palladini, Giampaolo Merlini

Amyloidosis Research and Treatment Center, Biotechnology Research Laboratories, Fondazione IRCCS Policlinico San Matteo, Department of Molecular Medicine, University of

Results

Variable	MRD+ (N=9) N (%) median (range)	MRD- (N=12) N (%) median (range)	P
Male sex	5 (72)	4 (44)	0.156
Age, years	63 (55-68)	58 (54-76)	0.269
Organ involvement			
heart / kidney	**3 (33) / 9 (100)**	**7 (58) / 10 (83)**	**0.301/0.337**
Liver / >2 organs	**0 (0) / 4 (44)**	**1 (8) / 6 (50)**	**0.543 / 0.820**
Cardiac response at CR (8 patients evaluable)	**1/2 (50)**	**4/6 (66)**	**0.750**
Renal response at CR (18 evaluable)	**3/9 (33)**	**6/9 (66)**	**0.201**
BMPC (%) (diagnosis)	9 (4-30)	7 (3-20)	0.306

Results

- A further improvement of **cardiac function** compared to the time of CR attainment
  - All 5 evaluable patients with MRD-; while Zero of 2 MRD + (P=0.047).
- **Renal response**
  - 7 of 8 (87%) subjects with MRD-; while 4 of 8 (50%) with MRD+ (P=0.153).
- Overall, further improvement of cardiac or renal function after CR was significantly associated with absence of MRD (P=0.012).

Methodological Limitations

- BM-based MRD evaluation limited to one site
  - Plasmacytoma?

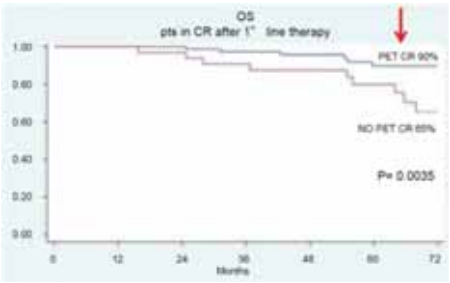
Solutions

- Imaging techniques: PET-CT
- cfDNA sequencing analyses? → ongoing
- Circulating tumor cell Analysis

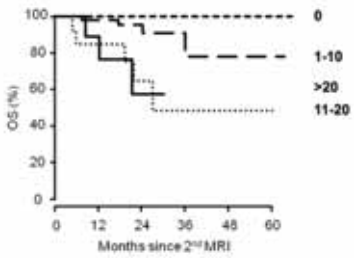
dkfz.

Prognostic Significance of Imaging CR

PET-CT



MRI



Jens Hillengass University of Heidelberg S.D.G.

Zamagni 2013 ASH, Hillengass 2012 Haematologica

Prognostic significance of residual lesions in PET-CT

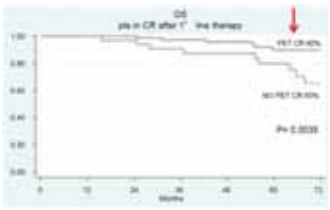
N = 189 PET-CT after therapy - 55% CR

29% CR pts had residual lesions in PET-CT

Median PFS

PET+ -- 44 months

PET- -- 84 months



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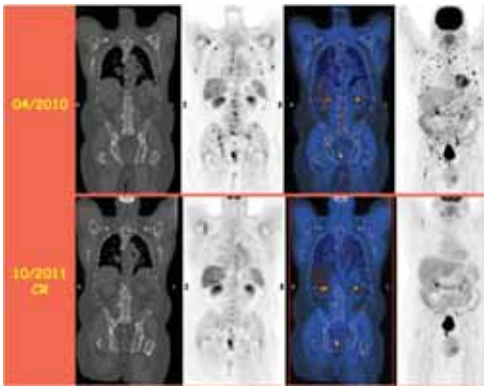


Zamagni 2015 Clin Cancer Res

Prognostic significance of residual lesions in PET-CT – IFM-DFCI 2009 study

<u>At diagnosis</u>:

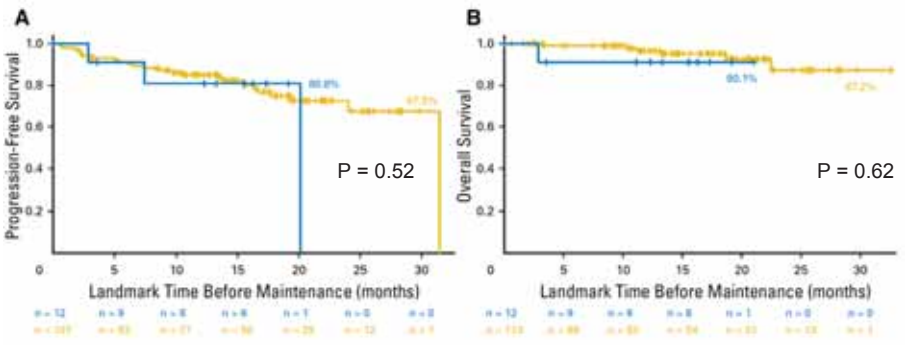
MRI positive in 127/134 (95%),

PET-CT positive in 122/134 (91%)

(McNemar test = 0.94, p-value = 0.33).

Moreau 2017 JCO

Prognostic Significance of Residual Lesions in MRI before Maintenance



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Moreau 2017 JCO

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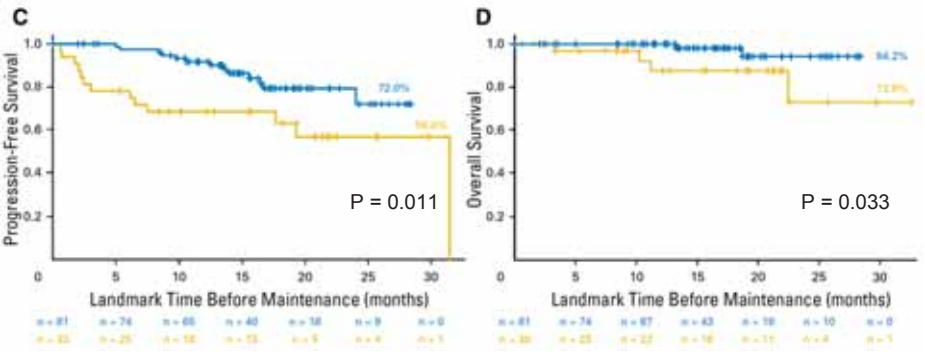


Jens Hillengass University of Heidelberg S.D.G.

Moreau 2017 JCO

We Need To Move On….

- Do we treat patients with MRD- vs MRD+ status differently?

- Develop MRD-based studies to decide
  - Whether MRD
    - needs consolidation and/or maintenance
    - Type and length of maintenance?
  - Should all patient achieve MRD- status
  - Whether MRD+ should get more treatment, do we treat them as resistant patients?
  - Does early detection of appearance of clonal cells indicative of clinically meaningful relapse?
    - Does it suggest need for intervention?

MRD Assessment Is a Tool to Measure Response in Patients With MM

MRD negativity is correlated with longer PFS[1-3]

Establish standard definition for MRD negativity and timing of MRD assessment

- 2016 IMWG criteria definition of 10^{-5} sensitivity[4]* But may need revision
- Optimal timing of MRD assessment at CR. VGPR?

Optimize MRD assessment techniques[4]

- Sensitivity
- Accessibility
- Feasibility
- Cost

- **The highest sensitivity is the most discriminant → 10^{-6} is required**
- **MRD should be the objective of future trials**
- **MRD could identify cured patients**

Management of Renal Disease in monoclonal gammopathies

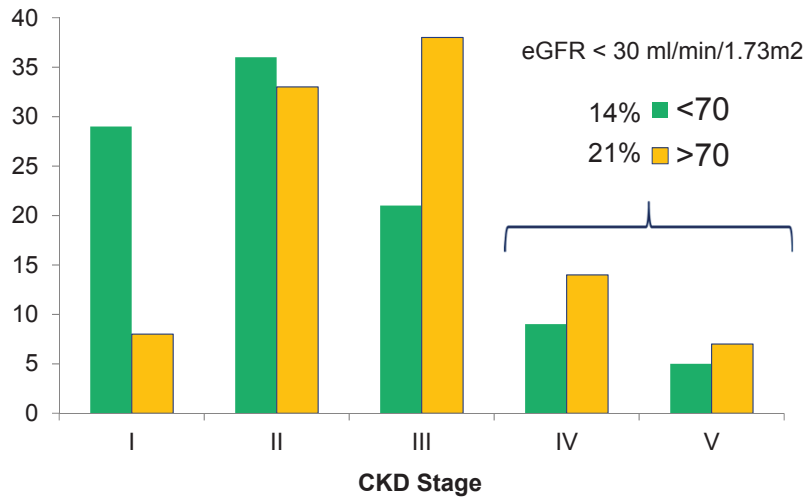
Nelson Leung
Division of Nephrology and Hypertension/ Division of Hematology
Mayo Clinic Rochester

Conflict of interest

Grant from Omeros Corporation

Advisor for Thrasos Therapeutics and Prothena.

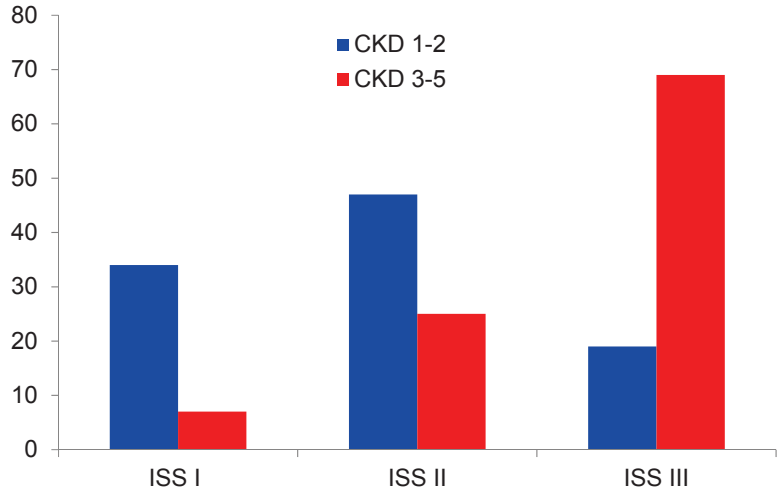
Renal Function in Newly Diagnosed MM Patients



MAYO CLINIC

Terpos et al. European J Haematol 2013

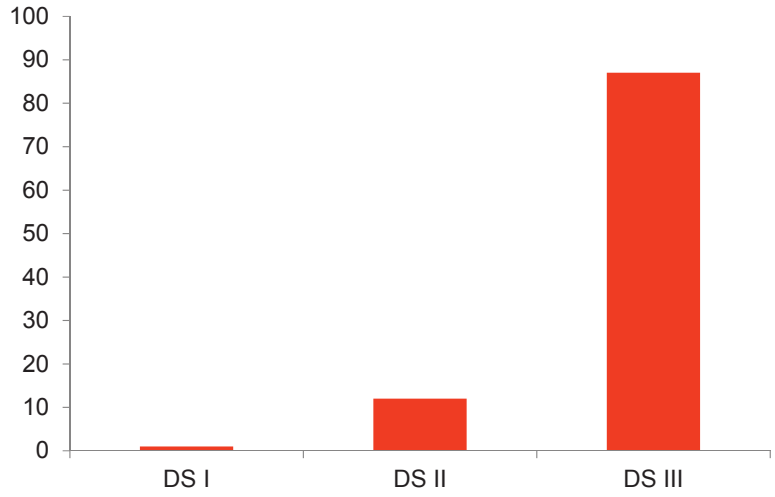
Chronic Kidney Disease by ISS Staging



MAYO CLINIC

Eleftherakis-Papapiakovou et al. Leukemia Lymphoma 2011

Renal impairment (Scr > 177 µmol/L) increases with more advanced disease (Durie Salmon)

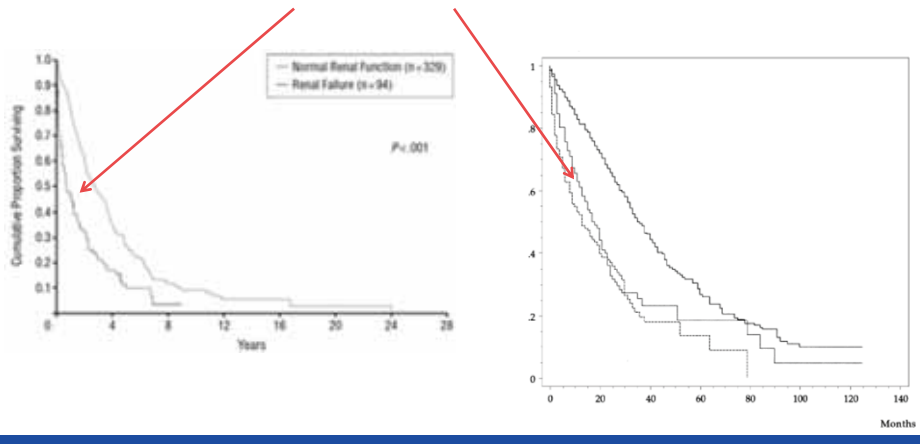


MAYO CLINIC

Blade et al. Arch Int Med 1998

Renal impairment is a high risk myeloma defining events

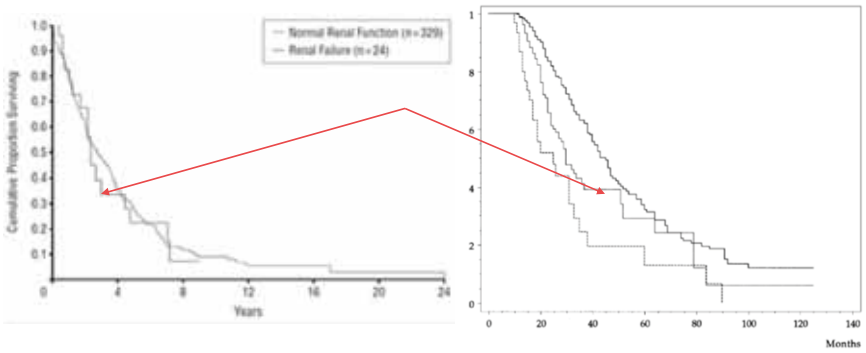
Scr >177 umol/L (2.0 mg/dl)
Scr > 200 umol/L (2.3 mg/dl)



MAYO CLINIC

Blade et al. Arch Int Med 1998
Knudsen et al. Eur J Haematol 2000

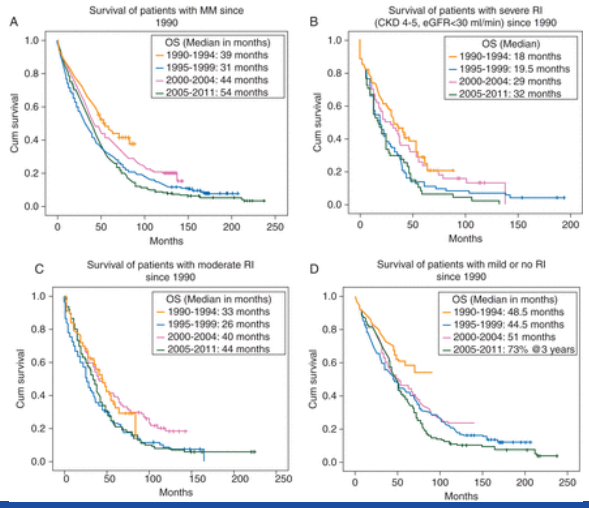
Reversing Renal Impairment Improves Overall Survival



MAYO CLINIC

Blade et al. Arch Int Med 1998
Knudsen et al. Eur J Haematol. 2000

Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents

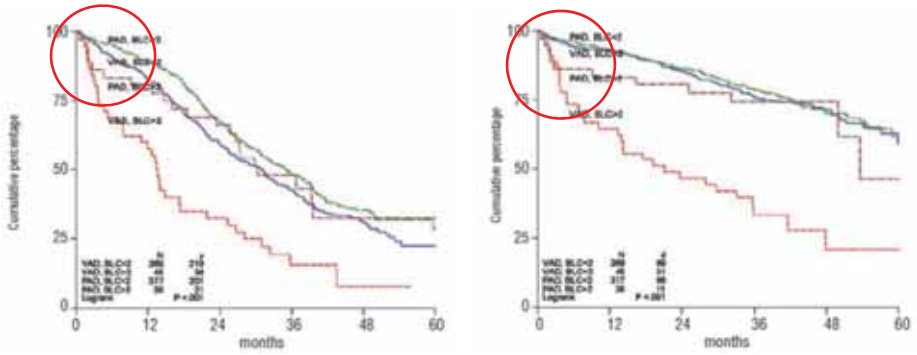


MAYO CLINIC

Dimopoulos et al. Ann Oncol. 2014

Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial

Christof Scheid,[1] Pieter Sonneveld,[2] Ingo G.H. Schmidt-Wolf,[3] Bronno van der Holt,[2] Laila el Jarari,[2] Uta Bertsch,[4] Hans Salwender,[5] Sonja Zweegman,[2] Igor Wolfgang Blau,[3] Edo Vellenga,[2] Katja Weisel,[6] Michael Pfreundschuh[7], Kon-Siong Jie,[2] Kai Neben,[4] Helgi van de Velde,[8] Ulrich Duehrsen,[9] M. Ron Schaafsma,[2] Walter Lindemann,[2] Marie José Kersten,[2] Norma Peter,[3] Mathias Hänel,[5] Sandra Croockewit,[2] Hans Martin,[3] Shulamiet Wittebol,[2] Gerard MJ Bos,[2] Marinus van Marwijk-Kooy,[2] Pierre Wijermans,[2] Hartmut Goldschmidt,[4] and Henk M. Lokhorst[1]



MAYO CLINIC

Scheid et al. Haematologica 2014

Diagnostic criteria of plasma cell dyscrasias

	MGUS	SMM	MM
M-spike	< 3 g/dL	≥ 3 g/dL	≥ 3 g/dL
Bone Marrow PC	< 10%	≥ 10%	≥ 10%
Hypercalcemia (C)	absent	absent	+/-
Renal impairment (R)*	absent	absent	+/-
Anemia (A)	absent	absent	+/-
Lytic lesions (B)	absent	absent	+/-
Free light chain ratio	<100	<100	>100
Bone marrow plasma cells	< 60%	< 60%	> 60%
Bone lesion on MRI	≤ 1	≤ 1	> 1
	Observe	**Observe/Clin trial**	**Treat**

*Cast nephropathy

MAYO CLINIC

Rajkumar et al. Lancet Oncol 2014

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, Maria-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

Myeloma defining events:

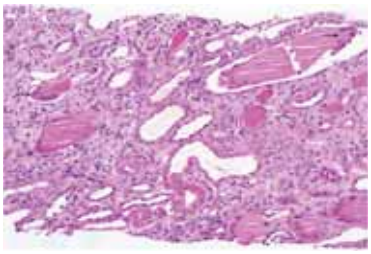
- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
  - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
  - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage§ ≥60%
  - Involved:uninvolved serum free light chain ratio‖ ≥100
  - >1 focal lesions on MRI studies¶

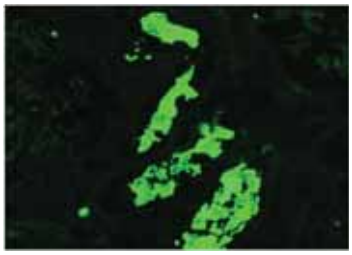
The criteria have also been updated to clarify that only renal failure caused by light-chain cast nephropathy (based on typical histological changes or presumptive diagnosis based on the presence of high involved FLC levels, typically >1500 mg/L) is regarded as a myeloma-defining events.

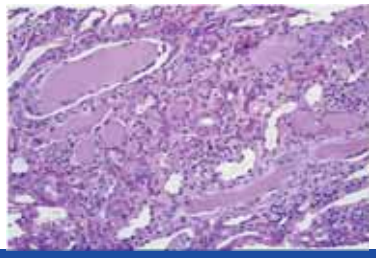
Lancet Oncol 2014; 15: e538–48

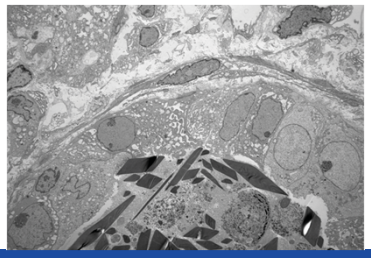
MAYO CLINIC

Light Chain Cast Nephropathy





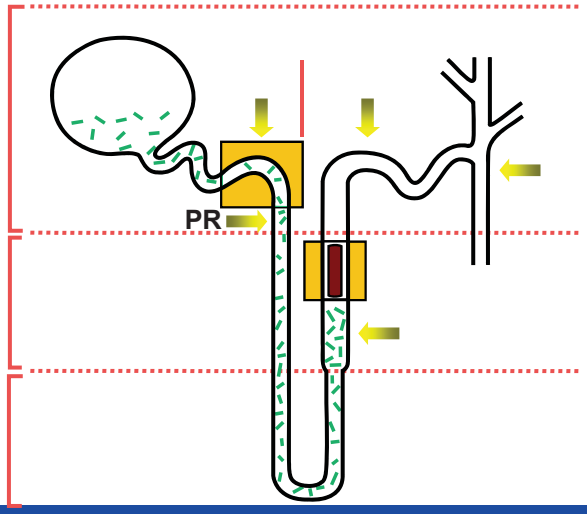




MAYO CLINIC

Courtesy of Dr. Samih Nasr

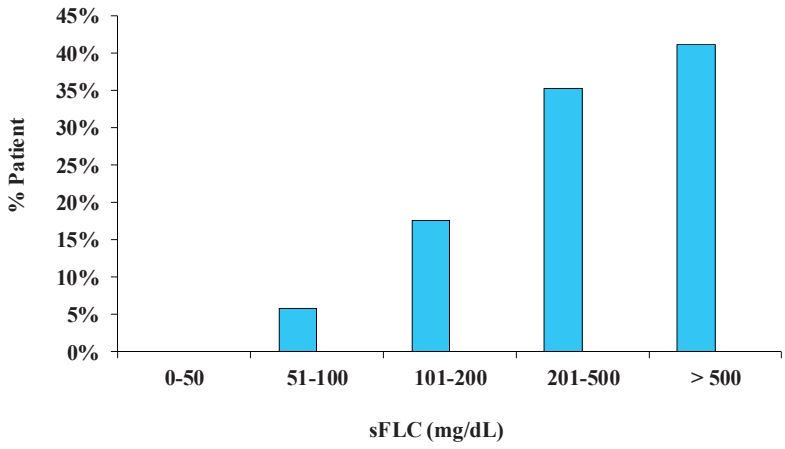
High levels of monoclonal FLC are required to form light chain cast nephropathy



MAYO CLINIC

Winearls. Kidney Int, 1995

Risk of Cast Nephrology by sFLC level



MAYO CLINIC

Leung et al. Kidney Int 2005
Hutchison et al. Clin JASN 2009

Effects of paraprotein heavy and light chain types and free light chain load on survival in myeloma: an analysis of patients receiving conventional-dose chemotherapy in Medical Research Council UK multiple myeloma trials

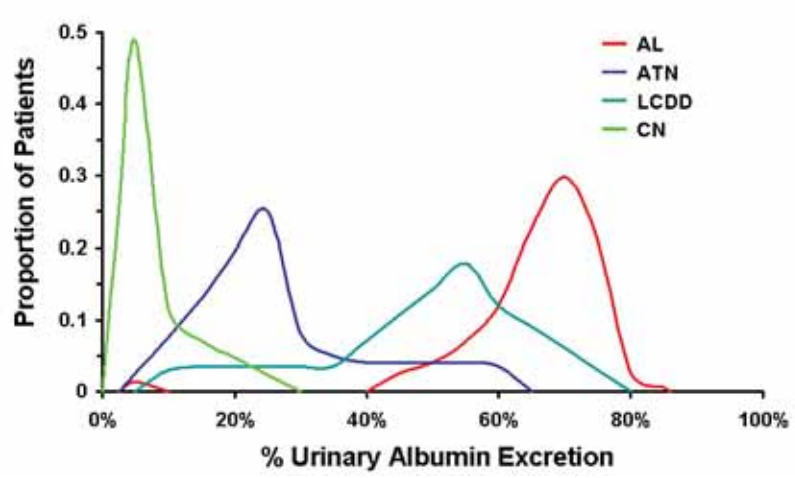
Mark Drayson, Gulnaz Begum, Supratik Basu, Sudhaker Makkuni, Janet Dunn, Nicola Barth, and J. Anthony Child

Urinary flc excretion, g/g creatinine	Patients with renal failure, no. (%)		
	IgG	IgA	LCO
0 g/g	28 (2)	29 (3)	0 (0)
Less than 4 g/g	48 (8)	46 (11)	22 (18)
4-12 g/g	13 (29)	12 (28)	18 (38)
More than 12 g/g	11 (48)	13 (48)	60 (54)

MAYO CLINIC

Drayson et al. Blood 2012

Urinary Albumin Excretion



MAYO CLINIC

Leung et al. CJASN 2012

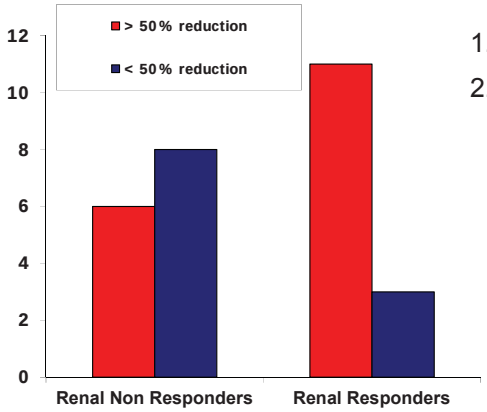
Precipitants of cast nephropathy

Series	Number of patients	Dehydration	Infection	Hypercalcemia	Contrast medium	NSAIDs	None	Renal recovery
Pozzi et al [13]	50	24	8	34	4	0	44	50
Rota et al [14]	34	65	44	44	0	26	–	47
Geneval et al [28]	80	10	9	30	11	–	35	55
Oxford	42	–	–	19	–	10	71	17

MAYO CLINIC

Winearls. Kidney Int. 1995

Improvement of acute renal function in patients with MM

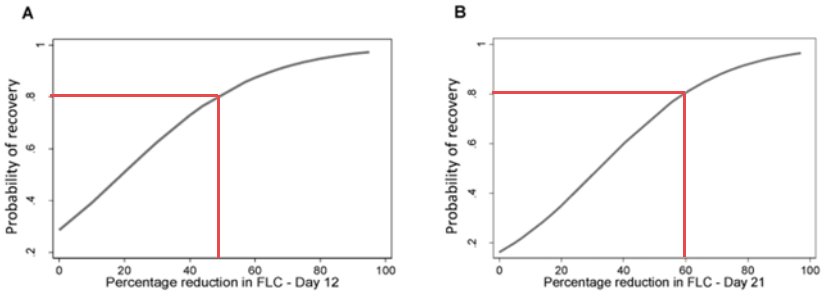


1. Cast nephropathy
2. > 50% reduction in the involved sFLC

MAYO CLINIC

Leung et al. Kidney Int 2008

Probability of Renal Response by Depth and Speed of sFLC Reduction

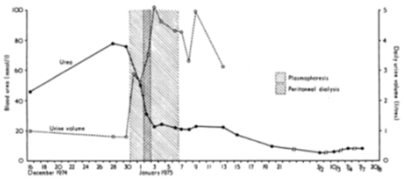


MAYO CLINIC

Hutchison et al. J Am Soc Nephrol 2011

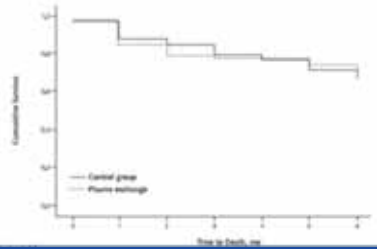
Plasmapheresis and cast nephropathy

Successful treatment of myeloma kidney by diuresis and plasmaphoresis



Plasma Exchange When Myeloma Presents as Acute Renal Failure

A Randomized, Controlled Trial



MAYO CLINIC

Feest et al, BMJ; 1976
Clark et al. Ann Int Med 2005

HCO dialyzer trials

Positive

Negative

MAYO CLINIC

Management of cast nephropathy

1. Hydration
   a) Half normal saline
2. Eliminate and avoid nephrotoxins
   a. NSAIDs
   b. ACE inhibitor/ARB
   c. antibiotics/antifungal
   d. Contrast agents
3. Correct hypercalcemia
   1. Pamidronate
4. Start chemotherapy
   1. Bortezomib
   2. High dose dexamethasone

MAYO CLINIC

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, Maria-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

Although other forms of renal damage (eg, AL amyloidosis, monoclonal immunoglobulin deposition disease, light-chain Fanconi syndrome, monoclonal gammopathy-associated membranoproliferative glomerulonephritis) can occur in multiple myeloma, this association is not characteristic of multiple myeloma and can be seen with other types of plasma cell dyscrasias (eg, MGUS) or lymphoproliferative disorders. Although they can occur in conjunction with multiple myeloma, in most patients they occur independently without evidence of other myeloma-defining events. For this reason, these renal disorders are not regarded as myeloma-defining events, and should not lead to multiple myeloma diagnosis, unless they meet criteria for multiple myeloma as listed in the panel. These entities represent unique disease states with clearly defined pathological features, diagnostic criteria, prognosis, and therapy. Some investigators have collectively referred to these disorders under the term monoclonal gammopathy of renal significance.[82] Other causes of acute and chronic

Lancet Oncol 2014; 15: e538–48

MAYO CLINIC

International Kidney and Monoclonal Gammopathy Research Group

blood

2012 120: 4292-4295
Prepublished online October 9, 2012;
doi:10.1182/blood-2012-07-445304

Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant

Nelson Leung, Frank Bridoux, Colin A. Hutchison, Samih H. Nasr, Paul Cockwell, Jean-Paul Fermand, Angela Dispenzieri, Kevin W. Song and Robert A. Kyle

MAYO CLINIC

Monoclonal Gammopathy of Renal Significance (MGRS)

	MGUS		SMM		MM
M-spike	< 3 g/dL		≥ 3 g/dL		≥ 3 g/dL
Bone Marrow PC	< 10%		≥ 10%		≥ 10%
Hypercalcemia (C)	absent		absent		+/-
Renal impairment (R)*	absent	✓	absent	✓	+/-
Anemia (A)	absent		absent		+/-
Lytic lesions (B)	absent		absent		+/-
Free light chain ratio	<100		<100		>100
Bone marrow plasma cells	< 60%		< 60%		> 60%
Bone lesion on MRI	≤ 1		≤ 1		> 1
	Observe		**Observe/Clin trial**		**Treat**

*Cast nephropathy

MAYO CLINIC

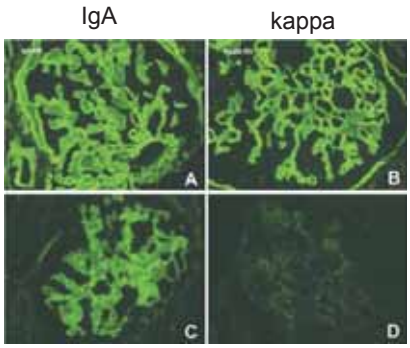
Rajkumar et al. Lancet Oncol 2014

MGRS

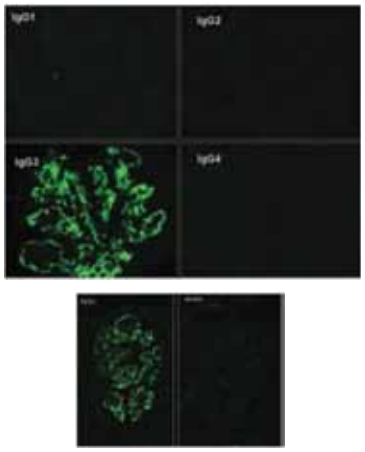
- A hematologic condition that produces nephrotoxic monoclonal immunoglobulin or fragment which do not meet criteria for multiple myeloma, malignant lymphoma, chronic lymphocytic leukemia

MAYO CLINIC

Light chain restriction with or without heavy chain restriction



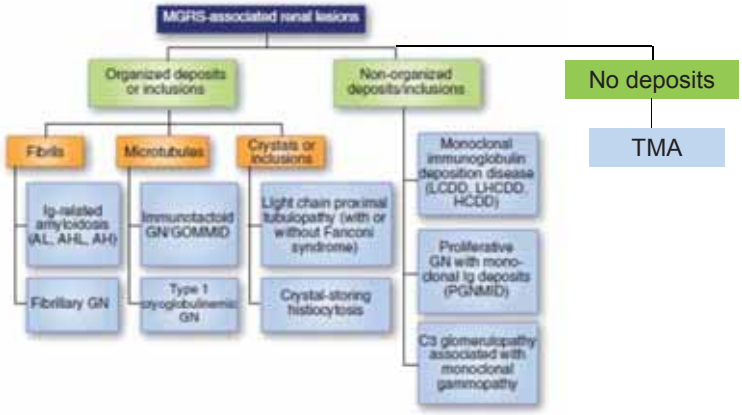
IgA_1 IgA_2



MAYO CLINIC

Diagnosis of monoclonal gammopathy of renal significance

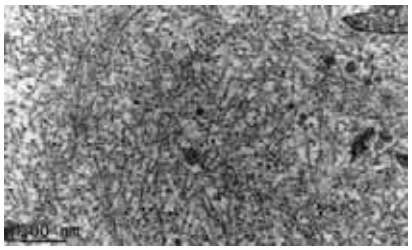
Frank Bridoux[1], Nelson Leung[2,3], Colin A. Hutchison[4], Guy Touchard[5], Sanjeev Sethi[6], Jean-Paul Fermand[8], Maria M. Picken[7], Guillermo A. Herrera[9], Efstathios Kastritis[10], Giampaolo Merlini[11], Murielle Roussel[11], Fernando C. Fervenza[2], Angela Dispenzieri[3], Robert A. Kyle[3], Samih H. Nasr[3]
on behalf of the International Kidney and Monoclonal Gammopathy Research Group



MAYO CLINIC

Bridoux et al. Kidney Int 2015

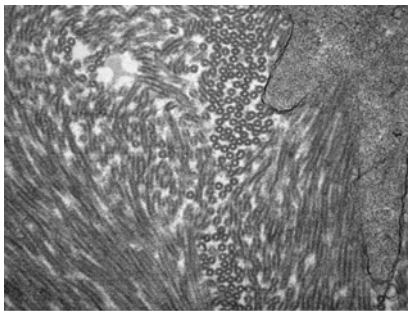
Fibrils



- Solid
- Randomly arranged
- 7 – 12 nm
- Diseases
  - Alg amyloidosis
    - AL
    - AHL
    - AH
  - Fibrillary glomerulonephritis with monoclonal deposits

MAYO CLINIC

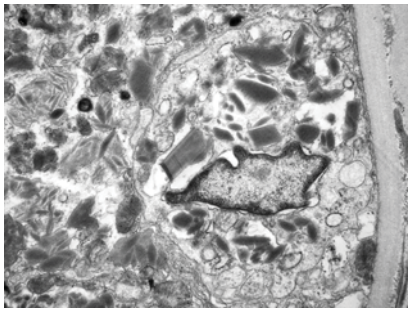
Microtubules



- 19 – 52 nm
- Hollow center
- Parallel arrays
- Diseases
  - Immunotactoid glomerulopathy
  - Cryoglobulinemic glomerulonephritis

MAYO CLINIC

Crystals/ Inclusions



- Light chain proximal tubulopathy (acquired Fanconi syndrome)
- Crystal storage histiocytosis
- (Cryo)crystalglobulinemic glomerulonephritis

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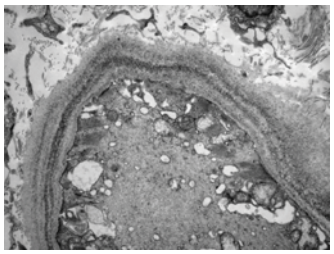
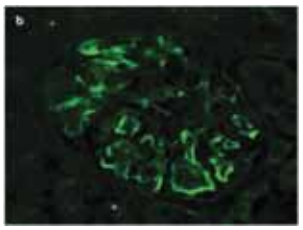
Unorganized Deposits





C3

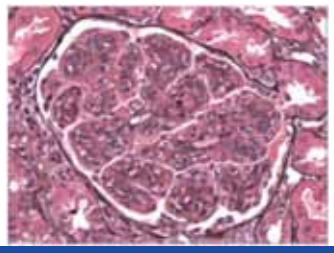
- MIDD
  - LCDD
  - LHCDD
  - HCDD
- PGNMID/ MPGN
- C3 glomerulopathy with monoclonal gammopathy

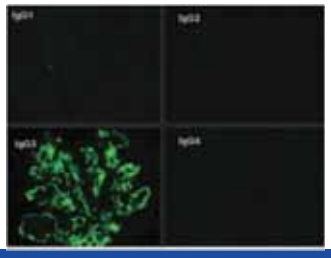
MAYO CLINIC

Lloyd et al. CKJ 2016
Zand et al. AJKD 2013
Sethi et al. AJKD 2010

Case 1

- A 17-year-old female patient presented to the ED in December, 2015 complaining of nausea, lower abdominal pain and lower extremity swelling that developed gradually during the previous month.
  - proteinuria of 9 g/day.
  - a serum creatinine of 0.8 mg/dl (88 mmol/L).





IgGλ

MAYO CLINIC

Case continue

- Prednisone 60 mg/d plus mycophenolate mofetil – no response
- High dose methylprednisolone and rituximab – response
  - Proteinuria 0.6 g/d
- Relapsed 3 months later with proteinuria and hematuria
  - high dose methylprednisolone
- Relapsed 2 moths later again with proteinuria
  - high dose methylprednisolone

MAYO CLINIC

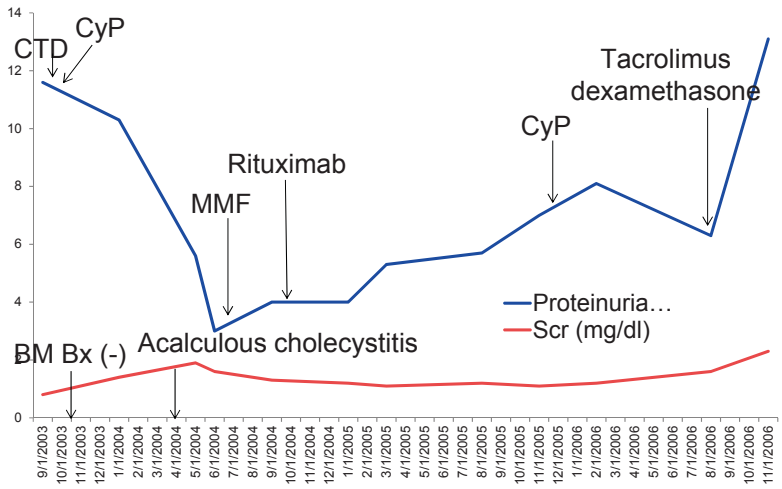
Case #2

- 08/2003
  - 35 yo female presents with edema and hypertension
    - Scr was 0.8 mg/dl (70 µmol/L)
    - Proteinuria 10 g/d
- 09/2003
    - Renal biopsy was performed
    - Proliferative glomerulonephritis with monoclonal immunoglobulin deposits

MAYO CLINIC

A Proliferative Glomerulonephritis Secondary to a Monoclonal IgA

Sandra M. Soares, MD, Donna J. Lager, MD, Nelson Leung, MD, Eric N. Haugen, MD, and Fernando C. Fervenza, MD, PhD



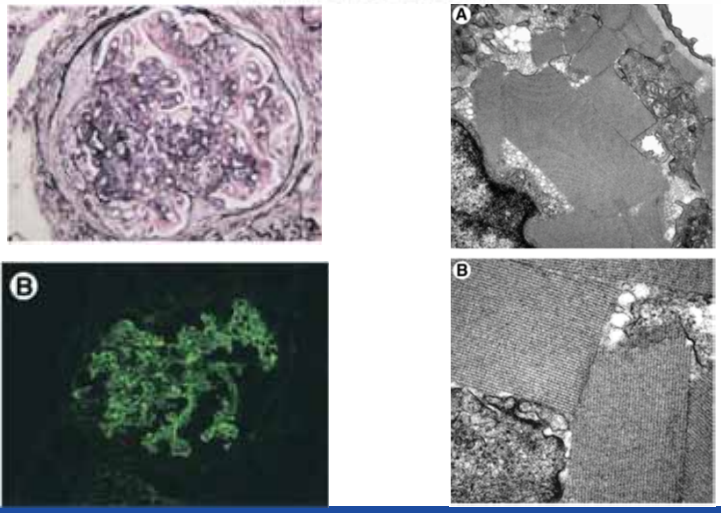
MAYO CLINIC

Soares et al. Am J Kidney Dis 2006

CASE REPORTS

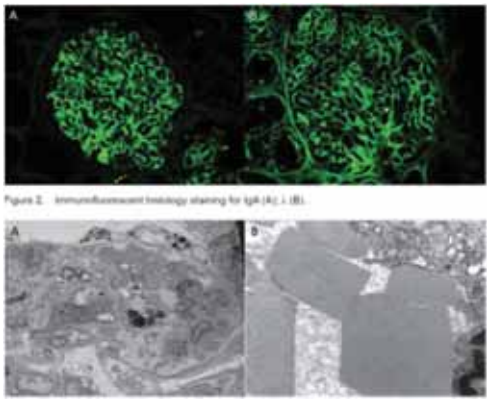
A Proliferative Glomerulonephritis Secondary to a Monoclonal IgA

Sandra M. Soares, MD, Donna J. Lager, MD, Nelson Leung, MD, Eric N. Haugen, MD, and Fernando C. Fervenza, MD, PhD



MAYO CLINIC

Recurrence of monoclonal IgA lambda glomerulonephritis in kidney allograft associated with multiple myeloma

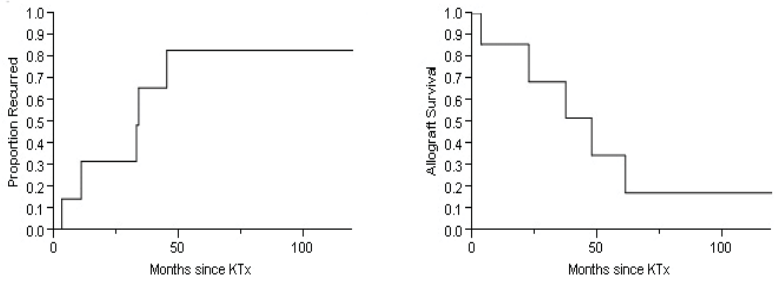


MAYO CLINIC

Herrmann et al. Clin Nephrol 2014

Long-Term Outcome of Renal Transplantation in Light-Chain Deposition Disease

Nelson Leung, MD, Donna J. Lager, MD, Morie A. Gertz, MD, Kirk Wilson, Sharan Kanakiriya, MD, and Fernando C. Fervenza, MD



MAYO CLINIC

Am J Kidney Dis 2004; 43:147-153

Proliferative Glomerulonephritis with Monoclonal IgG Deposits Recurs in the Allograft

Samih H. Nasr, Sanjeev Sethi,* Lynn D. Cornell,* Mary E. Fidler,* Mark Boelkins,† Fernando C. Fervenza,* Fernando G. Cosio,* and Vivette D. D'Agati‡*

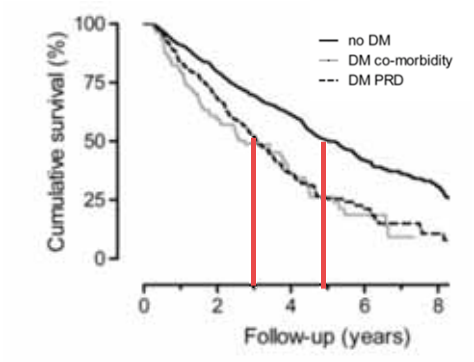
	Patient 1	Patient 2	Patient 3	Patient 4
Age at transplant	57	62	75	40
Kidney source	Living-unrelated donor	Deceased donor	Living-related donor	Living-unrelated donor
HLA mismatch	4 of 6 HLA antigens	0 of 6 HLA antigens	2 of 6 HLA antigens	4 of 6 HLA antigens
Percent PRA*	1% for class I 13% for class II	0% for class I 0% for class II	0% for class I 0% for class II	0% for class I 0% for class II
Maintenance immunosuppressive regimen	FK506/PRED/MMF	FK506/PRED/Mytonic acid	FK506/PRED/MMF	FK506/PRED/MMF
Time from transplant to diagnosis of recurrent disease	3	4	5	3
Baseline serum creatinine (mg/dl)	1.0	1.2	1.4	0.9
Parameters at the time of first biopsy showing recurrence				
serum creatinine (mg/dl)	2.8	3.7	4.8	1.2
24-hour urine protein	0.790	7.4	5.8	0.061
serum albumin	3.5	2.0	3	4.4

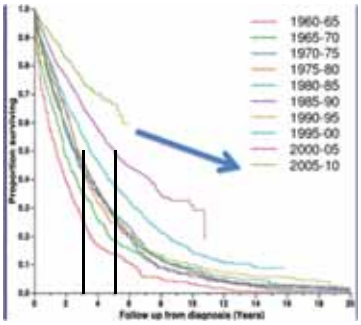
Early recurrence is a major obstacle for kidney transplantation

MAYO CLINIC

Nasr et al. Clin J Am Soc Nephrol 2011

Overall Survival of ESRD Patients vs Multiple Myeloma Patients





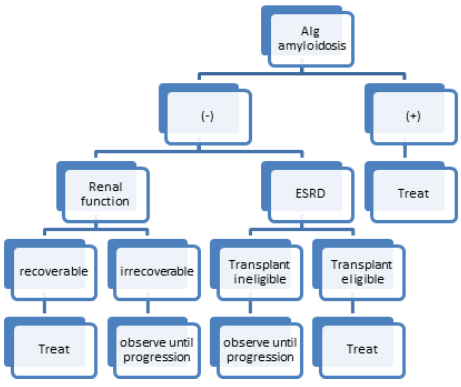
Schroijen et al. BMC Nephrol 2011

blood
2013 122: 3583-3590
Prepublished online October 9, 2013;
doi:10.1182/blood-2013-05-495929

How I treat monoclonal gammopathy of renal significance (MGRS)

Jean-Paul Fermand, Frank Bridoux, Robert A. Kyle, Efstathios Kastritis, Brendan M. Weiss, Mark A. Cook, Mark T. Drayson, Angela Dispenzieri and Nelson Leung

- Goals of therapy
  - Preservation of life (Amyloidosis)
  - Preservation of kidney function
  - Restore the eligibility for kidney transplantation



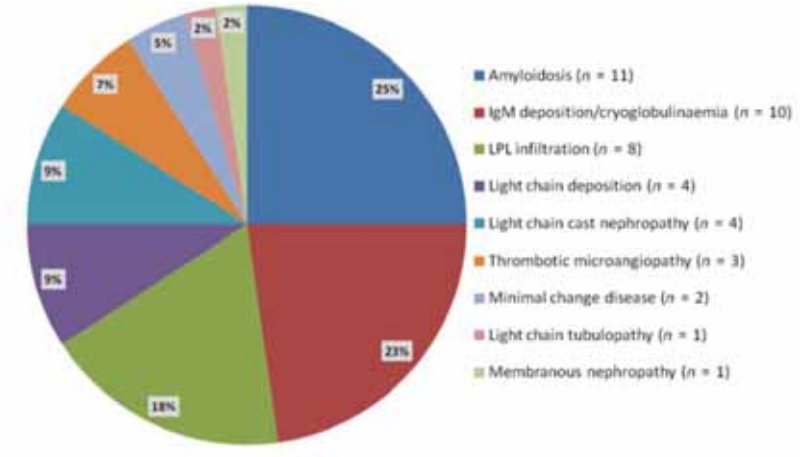
Clinicopathologic Correlations in Multiple Myeloma: A Case Series of 190 Patients With Kidney Biopsies

Paraprotein-associated renal lesions	
Myeloma cast nephropathy	62 (33)
Monoclonal immunoglobulin deposition disease	41 (22)
Amyloidosis	40 (21)
Fibrillary glomerulonephritis	2 (1)
Immunotactoid glomerulopathy	1 (0.5)
Light chain proximal tubulopathy	1 (0.5)
Interstitial infiltration by malignant plasma cells	2 (1)

MAYO CLINIC

Nasr et al. AJKD 2012

Renal disease related to Waldenström macroglobulinaemia: incidence, pathology and clinical outcomes



MAYO CLINIC

Vos et al. Br J Haematol 2016

Renal complications in chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis: the Mayo Clinic experience

Paolo Strati, Samih H. Nasr, Nelson Leung, Curtis A. Hanson, Kari G. Chaffee, Susan M. Schwager, Sara J. Achenbach, Timothy G. Call, Sameer A. Parikh, Wei Ding, Neil E. Kay, and Tait D. Shanafelt

	Number (%)	Co-existent CLL infiltration n (%)	Therapy prior to biopsy n (%)
Related to chronic lymphocytic leukemia			
Membranoproliferative glomerulonephritis	10 (20)	6/10 (60)	0/10 (0)
CLL infiltrate as primary etiology	8 (12)	NA	4/8 (47)
Minimal change disease	5 (10)	0/5 (0)	1/5 (20)
Acute interstitial nephritis	4 (8)	3/4 (75)	1/4 (25)
Amyloidosis	3 (7)	1/3 (33)	0/3 (0)
Light chain cast nephropathy	3 (7)	0/3 (0)	0/3 (0)
Membranous glomerulonephritis	2 (4)	2/2 (100)	0/2 (0)
Mesangial proliferative glomerulonephritis (unclassified)	2 (4)	1/2 (50)	0/2 (0)
Indirectly related to chronic lymphocytic leukemia			
Thrombotic microangiopathy	6 (12)	2/6 (33)	5/6 (83)
Adenovirus acute interstitial nephritis	1 (2)	0/1 (0)	1/1 (100)
Infection-related CGN	1 (2)	0/1 (0)	1/1 (100)
p-ANCA-associated pauci-immune CGN	1 (2)	0/1 (0)	1/1 (100)
Unrelated to chronic lymphocytic leukemia			
Diabetic glomerulosclerosis	2 (4)	1/2 (50)	0/2 (0)
Obesity-related focal segmental glomerulosclerosis	2 (4)	0/2 (0)	0/2 (0)
Hypertension-related nephrosclerosis	1 (2)	0/2 (0)	0/2 (0)

MAYO CLINIC

Strati et al. Haematologica 2015

Treatment of MGRS

1. Make the diagnosis of MGRS related disease
2. Identify the clone

MAYO CLINIC

Sensitivity of monoclonal protein tests in monoclonal gammopathies

	n	All 5 tests	Serum PEL and IFE; urine IFE	Serum PEL, IFE, and FLC	Serum PEL and FLC	Serum IFE	Serum PEL	Serum FLC
Diagnosis, n								
All	1877	1851	1821	1828	1770	1632	1482	1395
MM	467	467	461	467	467	441	409	452
Macroglobulinemia	26	26	26	26	26	26	26	19
SMM	191	191	191	191	190	188	180	155
MGUS	524	524	524	509	465	486	429	222
Plasmacytoma	29	26	26	26	25	21	21	16
POEMS	31	30	30	30	23	30	23	3
Extramedullary plasmacytoma	10	2	2	1	1	1	1	1
Primary AL	581	570	547	564	559	429	383	513
LCDD	18	15	14	14	14	10	10	14
Diagnosis, %								
All		98.6	97.0	97.4	94.3	87.0	79.0	74.3
MM		100.0	98.7	100.0	100.0	94.4	87.6	96.8
Macroglobulinemia		100.0	100.0	100.0	100.0	100.0	100.0	73.1
SMM		100.0	100.0	100.0	99.5	98.4	94.2	81.2
MGUS		100.0	100.0	97.1	88.7	92.8	81.9	42.4
Plasmacytoma		89.7	89.7	89.7	86.2	72.4	72.4	55.2
POEMS		96.8	96.8	96.8	74.2	96.8	74.2	9.7
Extramedullary plasmacytoma		20.0	20.0	10.0	10.0	10.0	10.0	10.0
Primary AL		98.1	94.2	97.1	96.2	73.8	65.9	88.3
LCDD		83.3	77.8	77.8	77.8	55.6	55.6	77.8

MAYO CLINIC

Katzman et al. Clin Chem 2009

Monoclonal protein is detected in only 30% of cases involving PGNMID

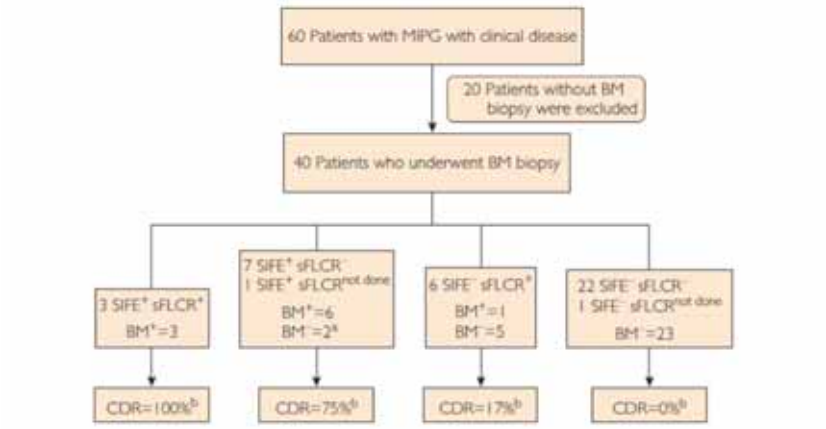
Cohort	SPEP	SIFE	UPEP	UIFE	sFLCR	SIFE and/or sFLCR
PGNMID						
No. tested	54	53	46	44	50	53
+Mg (No.)	7	10	1	4	11	16
Detection rate (%)	13	19[a]	2	9	22[a]	30
Non-IgG PGN						
No. tested	6	6	6	6	6	6
+Mg (No.)	2	2	0	1	1	3
Detection rate (%)	33	33[b]	0	17	17[b]	50
AI (N=60)						
+Mg (No.)	9	12	1	5	12	19
Detection rate (%)	15	20	2	10	21	32

Characteristic	Value
Peripheral edema (n [%])	23 (42.2)
24-h urine protein (g/d; mean [range])	3.70 (0.36 to 17.00)
Proteinuria <1 g/24 h (n [%])	1/35 (2.9)
Proteinuria 1–3g/24 h (n [%])	10/35 (28.6)
Proteinuria >3g/24 h (n [%])	24/35 (68.6)
Full nephrotic syndrome (n [%])	17/35 (48.6)
Serum albumin (g/dl; mean [range])	3.1 (1.1 to 4.9)
Hematuria (n [%])	27/35 (77.1)
Serum creatinine at biopsy (mg/dl; mean [range])	2.77 (0.70 to 17.00)
Renal insufficiency at presentation (n [%])	28 (87.5)
Evidence of dysproteinemia (n [%])*	9/37 (29.7)
Serum paraprotein only	2
Serum and urine paraprotein	7
Multiple myeloma	1
AL-amyloid	1

MAYO CLINIC

Bhutani et al. Mayo Clinic Proc 2015
Nasr et al. JASN 2009

Detection of the monoclonal protein correlates with clonal detection rate



MAYO CLINIC

Bhutani et al. Mayo Clin Proc 2015

Clones identified in PGNMID

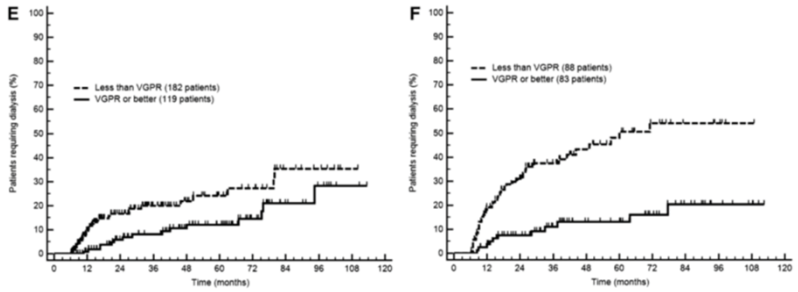
BM+ patient No.	BM microscopy (aspirate/biopsy)	Flow cytometry	Immunohistochemistry
1	Two small- to medium-sized suspicious nodular lymphocyte aggregates (10% BM)	λ-restricted CD20+ B cells	Nodular collections of lymphocytes, predominantly CD20+ B cells with only a few intermixed CD3+ T cells
2	An atypical lymphoid infiltrate composed of small lymphocytes involving ~30% of the BM cellularity	A monotypic κ B-cell population expressing CD20	Not performed
3	Per outside BM report, 8.3% κ-restricted plasma cells that were	CD138+, CD20+, and CD19+	
4	Per outside BM report, <5% clonal and atypical plasma cells		
5	Per outside BM report, 5% κ-restricted plasma cells in 50% cellular BM		
6	Slight increased plasma cells in quantity (5%), single interstitial cells and tiny aggregates	Monotypic λ (bright) CD20+ B-cell population forming 0.8% of cells in the sample; rare polytypic plasma cells	Slight increase in CD20+ B cells and CD138+ plasma cells; light chain restriction could not be assessed owing to technical artifact
7	Touch imprint; BM differential within reference limits	Not performed	5%-10% CD138-staining plasma cells showing λ light chain restriction
8	No substantial abnormality	κ light chain–restricted plasma cells identified	Plasma cells number 5%, interstitial distribution (CD138+)
9	Touch imprint; BM differential within reference limits	Small, abnormal plasma cell population (0.2%) with κ light chain restriction noted in a background of polyclonal plasma cells	CD138+ plasma cells (5%); lack definitive light chain restriction
10	Abnormal lymphocytic infiltrates present (30% of cellularity)	λ restricted, CD20+ B cells (82% of total events)	Not performed

+CD antigen testing = positive results; −CD antigen testing = negative results; BM = bone marrow; BM+ = detectable bone marrow clone.

MAYO CLINIC

Bhutani et al. Mayo Clin Proc 2015

Achievement of VGPR helps preserve renal function in AL amyloidosis



MAYO CLINIC

Palladini et al. Blood 2014

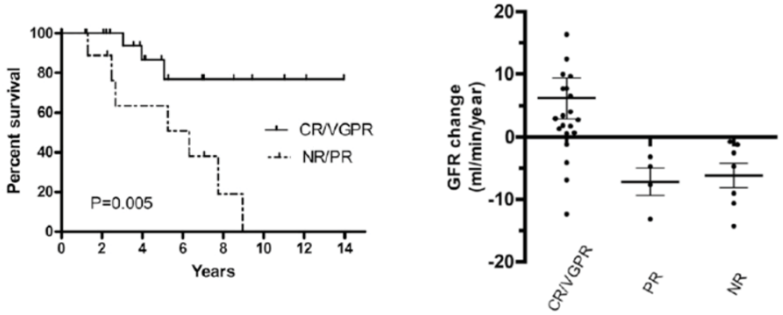
CLINICAL TRIALS AND OBSERVATIONS

CME Article

Natural history and outcome of light chain deposition disease

Rabya H. Sayed,[1,2] Ashutosh D. Wechalekar,[1] Janet A. Gilbertson,[1] Paul Bass,[2] Shameem Mahmood,[1] Sajitha Sachchithanantham,[1] Marianna Fontana,[1] Ketna Patel,[1] Carol J. Whelan,[1] Helen J. Lachmann,[1] Philip N. Hawkins,[1] and Julian D. Gillmore[1]

[1]National Amyloidosis Centre and [2]Centre for Nephrology, Division of Medicine, University College London, London, United Kingdom



MAYO CLINIC

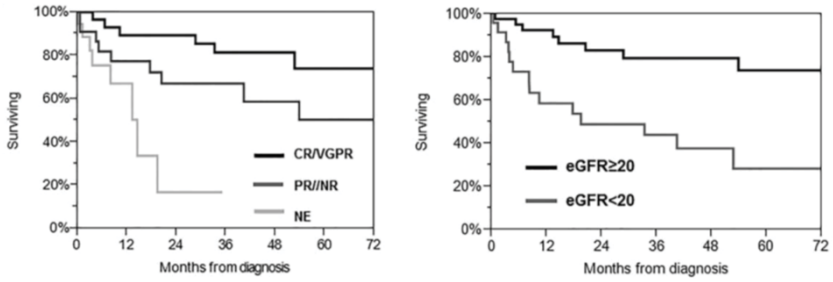
Sayed et al. Blood 2015

RESEARCH ARTICLE

AJH

Outcomes of patients with renal monoclonal immunoglobulin deposition disease

Taxiarchis V. Kourelis,[1] Samih H. Nasr,[2] Angela Dispenzieri,[1] Shaji K. Kumar,[1] Morie A. Gertz,[1] Fernando C. Fervenza,[3] Francis K. Buadi,[1] Martha Q. Lacy,[1] Stephen B. Erickson,[3] Fernando G. Cosio,[3] Prashant Kapoor,[1] John A. Lust,[1] Suzanne R. Hayman,[3] Vincent Rajkumar,[1] Steven R. Zeldenrust,[1] Stephen J. Russell,[1] David Dingli,[1] Yi Lin,[1] Wilson Gonsalves,[1] Elizabeth C. Lorenz,[3] Ladan Zand,[3] Robert A. Kyle,[1] and Nelson Leung[1,3]*



MAYO CLINIC

Kourelis et al. Am J Hematol 2016

Treatment and Outcomes for MIDD


CLINICAL TRIALS AND OBSERVATIONS

CME Article

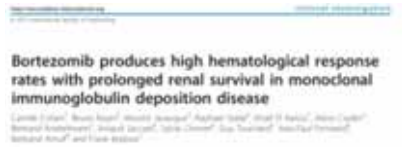
Natural history and outcome of light chain deposition disease


RESEARCH ARTICLE

Outcomes of patients with renal monoclonal immunoglobulin deposition disease

AJH

VGPR or better is required for improvement in renal outcomes


Bortezomib produces high hematological response rates with prolonged renal survival in monoclonal immunoglobulin deposition disease


Haematologica

Treatment of light chain deposition disease with bortezomib and dexamethasone

MAYO CLINIC

Hematologic response based on front line treatment in MIDD

	n	CR	VGPR	PR	NR
Thalidomide based	11	3	2	1	5
Bortezomib based	9	8	0	1	0
Alkylator based	6	3	1	1	1
Melphalan autologous stem cell transplant	4	4	0	0	0
Lenalidomide based	1	0	0	1	0
Steroids alone	1	0	0	0	1
ASCT (any time)	16	13	0	2	0

MAYO CLINIC

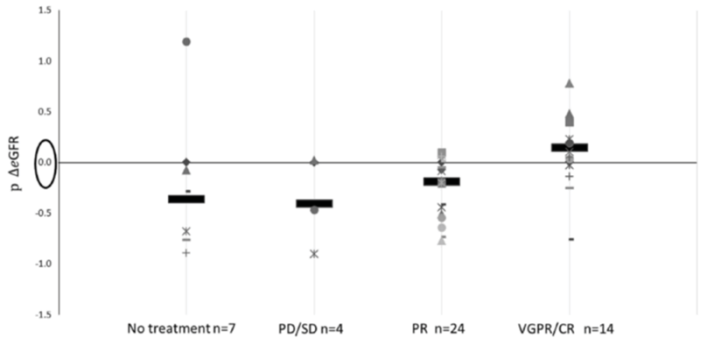
Sayed et al. Blood 2015

LCPT	SCT + Chemo (N = 10)	Chemo Alone (N = 12)	None (N = 8)	P - value
Scr (mg/dl)	1.43 (1.45)	2.27 (2.07)	3.11 (1.75)	0.05
Proteinuria	0.85 (0.80)	1.56 (1.59)	1.96 (1.92)	0.05
Hem Response				0.12
CR	20%	25%	0%	0.39
VGPR	10%	0%	0%	0.62
PR	20%	0%	12.5%	0.35
SD	50%	75%	87.5%	0.24
Renal Response				0.07
Improved	40%	25%	14.3%	
Stable	60%	41.7%	57.1%	
Progression	0%	33.3%	0%	
ESRD	0%	0%	28.6%	
Death	0%	33%	37.5%	0.12

MAYO CLINIC

Stokes et al. JASN 2015

Renal response by Hematologic response

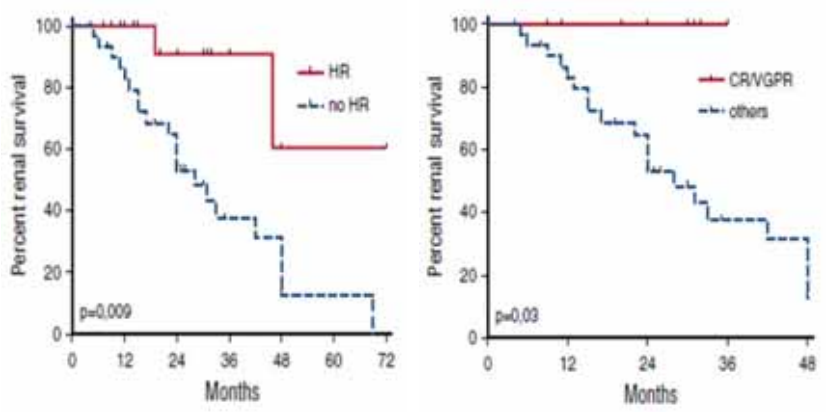


MAYO CLINIC

Vignon et al. Leukemia 2016

Treatment of B-cell disorder improves renal outcome of patients with monoclonal gammopathy–associated C3 glomerulopathy

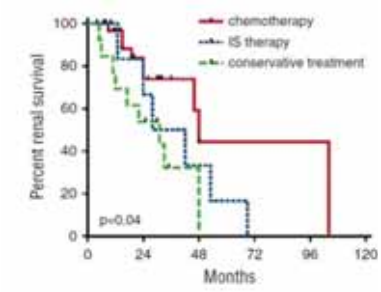
Sophie Chauvet,[1-3] Véronique Frémeaux-Bacchi,[2,4] Florent Petitprez,[5] Alexandre Karras,[1] Laurent Daniel,[6] Stéphane Burtey,[7] Gabriel Choukroun,[8] Yahsou Delmas,[9] Dominique Guerrot,[10] Arnaud François,[11] Moglie Le Quintrec,[12] Vincent Javaugue,[13,14] David Ribes,[15] Laurence Vrigneaud,[16] Bertrand Arnulf,[17] Jean Michel Goujon,[14,18] Pierre Ronco,[19] Guy Touchard,[13,14] and Frank Bridoux[13,14]



MAYO CLINIC

Chauvet et al. Blood 2017

Treatment modality of outcomes

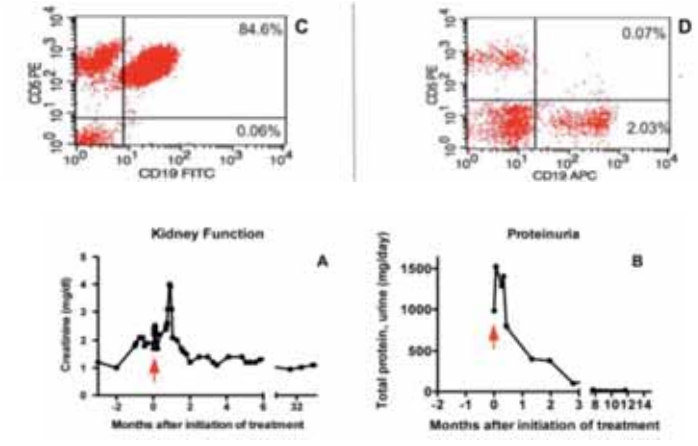


	Treated patients (N = 37)
Chemotherapy adapted to the clone, n (%)	29 (78%)
Median time to treatment, mo	3 (1-20)
Alkylating agent-dexamethasone*	5 (17%)
Bortezomib based regimen-dexamethasone†	22 (76%)
Prednisone-rituximab‡	2 (7%)
Immunosuppressive therapy, n	8 (22%)
Median time to treatment, mo	4 (1-54)
Prednisone-dexamethasone	4 (50%)
Prednisone-cyclophosphamide	1 (12.5%)
Prednisone-rituximab	1 (12.5%)
Prednisone-mycophenolate mofetil	1 (12.5%)
Prednisone-azathioprine	1 (12.5%)

MAYO CLINIC

Chauvet et al. Blood 2017

Chronic lymphocytic leukemia associated with immunotactoid glomerulopathy: a case report of successful treatment with high-dose methylprednisolone in combination with rituximab followed by alemtuzumab



MAYO CLINIC

Castro et al. Leukemia & Lymphoma 2012

Thank you for your attention

Questions

Towards Risk Adapted Induction Therapy for Transplant-eligible Myeloma Patients

Robert Z. Orlowski, Ph.D., M.D.

Florence Maude Thomas Cancer Research Professor

Chair, *ad interim*, Department of Lymphoma/Myeloma

Principal Investigator, MD Anderson SPORE in Multiple Myeloma and SCOR in High-risk Plasma Cell Dyacrasias

Chair, SWOG Myeloma Committee

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

NCCN Guidelines

Preferred Regimens

- Bortezomib/lenalidomide[5]/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone[6]

Other Recommended Regimens

- Bortezomib/doxorubicin/dexamethasone (category 1)
- Carfilzomib[7,8]/lenalidomide[5]/dexamethasone
- Ixazomib/lenalidomide[5]/dexamethasone (category 2B)

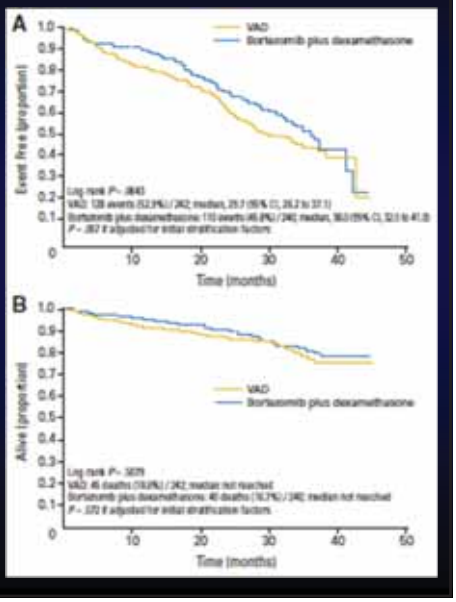
Useful In Certain Circumstances

- Bortezomib/dexamethasone (category 1)[9]
- Bortezomib/thalidomide/dexamethasone (category 1)
- Lenalidomide[5]/dexamethasone (category 1)[9]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)

https://www.nccn.org; Version 2.2018

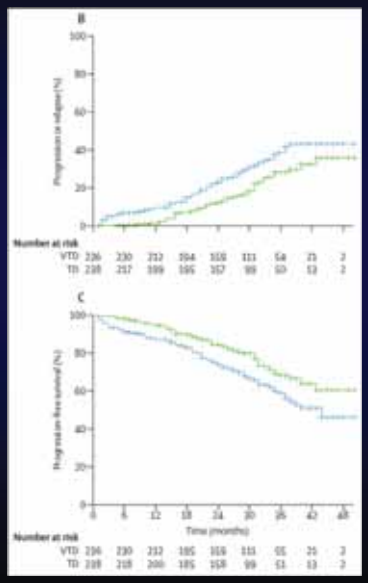
IFM 2005/01 : VAD vs. VD

- Bortezomib/Dex (VD) superior to VAD in response rate
  - ≥VGPR 37.7 vs 15.1%
- Trend towards better EFS & OS with lesser duration of therapy, fewer 2nd transplants



Harousseau, J-L et al. J Clin Oncol. 28:4621, 2010.

GIMEMA Study : VTD vs. TD



- Induction with bortezomib/thalidomide/dex (VTD) gave superior response rate an quality (CR/nCR 31% vs. 11%)
- Superior EFS and PFS maintained after transplant

Cavo, M et al. Lancet 376:2075, 2010.

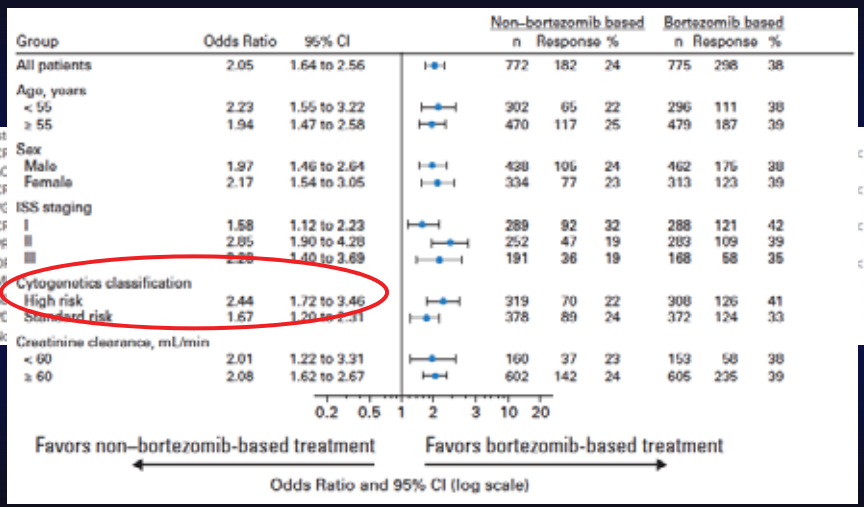
Value of Bortezomib in Induction

- Meta-analysis of IFM 2005-01 (Vd vs. VAD), HOVON-65/GMMG-HD4 (PAD vs. VAD), PETHEMA GEM05MENOS65 (VTd vs. TD)

	Bortezomib-Based Induction (n = 775)			Nonbortezomib-Based Induction (n = 772)					
Response	No.	%	95% CI	No.	%	95% CI	OR	95% CI*	P†
Postinduction									
CR	105	14	11 to 16	32	4	3 to 6	3.92	2.57 to 6.00	< .001
nCR	70	9	7 to 11	31	4	3 to 6	—		—
CR plus nCR	175	23	20 to 26	63	8	6 to 10	3.45	2.52 to 4.72	< .001
VGPR	187	24	21 to 27	76	10	8 to 12	—		
CR plus nCR plus VGPR‡	362	47	43 to 50	139	18	15 to 21	4.03	3.19 to 5.08	< .001
PR	284	37	33 to 40	341	44	41 to 48	—		—
ORR (≥ PR)	646	83	81 to 86	480	62	59 to 66	3.05	2.40 to 3.87	< .001
MR	35	5	3 to 6	109	14	12 to 17	—		—
SD	29	4	3 to 5	76	10	8 to 12	—		—
PD	24	3	2 to 5	55	7	5 to 9	—		—
Not evaluable	38	5	3 to 7	50	6	5 to 8	—		—

Sonneveld, P et al. J Clin Oncol. 31:3279, 2013.

Sustained Post-ASCT



Sonneveld, P et al. J Clin Oncol. 31:3279, 2013.

Lenalidomide/Bortezomib/Dex

- Excellent overall response rate and quality
- Does not compromise stem cell collection

Table 4. Best response to treatment for the treated population and the phase 2 population

	All patients (N = 66)			Phase 2 population (n = 35)		
Response*	n	%	90% CI	n	%	90% CI
CR	19	29	20-39	13	37	24-52
nCR	7	11	5-19	7	20	10-34
VGPR	18	27	18-38	6	17	8-31
PR	22	33	24-44	9	26	14-41
CR + nCR	26	39	29-50	20	57	42-71
CR + nCR + VGPR	44	67	56-76	26	74	59-86
At least PR	66	100	96-100	35	100	92-100

CI indicates confidence interval; CR, complete response; nCR, near-complete response; PR, partial response; VGPR, very good partial response.
*Per EBMT criteria,[23] all response categories, including VGPR, required a confirmatory assessment at 6 weeks.

Richardson, PG et al. Blood 116:679, 2010.

IMF RVD Study

- RVD induction, ASCT, RVD consolidation, and then R maintenance

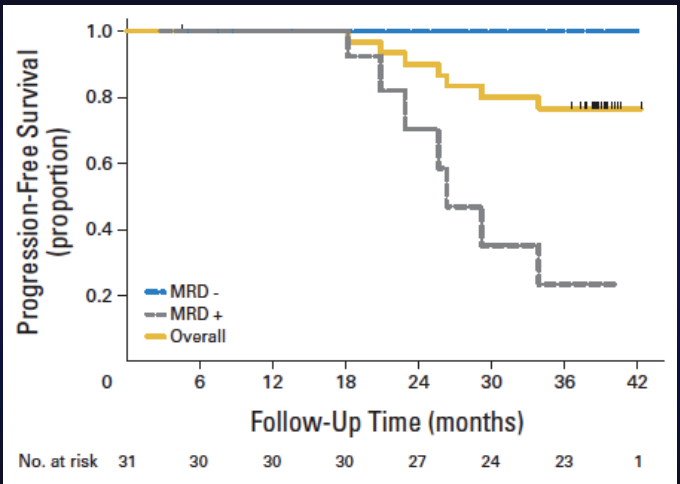
Table 2. Summary of Responses

	After Induction Therapy (N = 31)		After ASCT (n = 30)*		After Consolidation Therapy (n = 30)*		Best Response at Any Time (N = 31)	
Response	No.	%	No.	%	No.	%	No.	%
sCR	3	10	8	27	12	40	15	48
CR	4	13	6	20	3	10	3	10
VGPR	11†	35	7	23	11†	37	8	26
PR	11	35	7	23	3	10	5	16
SD	2	6	2	7	1	3	0	0
PD	0	0	0	0	0	0		
MRD negative by flow cytometry‡	4 of 25	16	14 of 26	54	15 of 26	58	21 of 31	68
sCR plus CR	7	23	14	47	15	50	18	58
sCR plus CR plus VGPR	18	58	21	70	26	87	26	84
At least PR	29	94	28	93	29	97	31	100

Abbreviations: ASCT, autologous stem-cell transplantation; CR, complete response; MRD, minimal residual disease; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.
*One patient, who had achieved PR after induction therapy, did not receive planned ASCT because of mobilization failure.
†One patient with negative serum and urine immunofixation but without bone marrow evaluation was assessed as having achieved VGPR.
‡Irrespective of other response criteria.

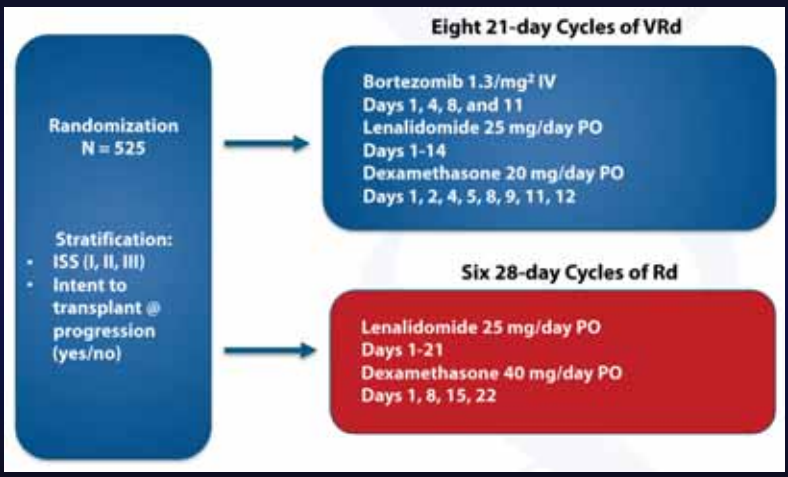
Roussel, M et al. J Clin Oncol. 32:2712, 2014.

PFS Data



Roussel, M et al. J Clin Oncol. 32:2712, 2014.

RVD From SWOG S0777



Durie, BGM et al. Lancet 389:519, 2017.

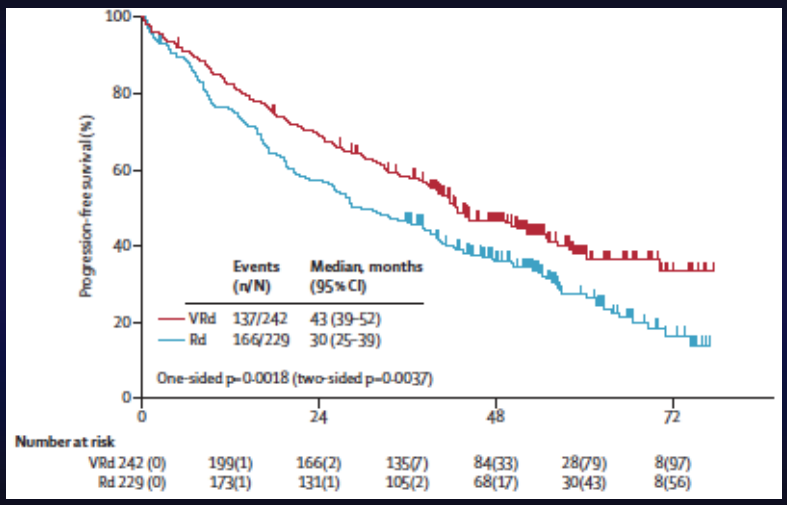
Response Data

	Patients given bortezomib with lenalidomide and dexamethasone (VRd group; n=216)*	Patients given lenalidomide and dexamethasone (Rd group; n=214)*
Confirmed response	34 (15·7%)	18 (8·4%)
Very good partial response	60 (27·8%)	50 (23·4%)
Partial response	82 (38%)	85 (39·7%)
Overall response rate (partial response or better)	176 (81·5%)	153 (71·5%)
Stable disease	34 (15·7%)	52 (24·3%)
Stable disease or better	210 (97·2%)	205 (95·8%)
Progressive disease or death	6 (2·8%)	9 (4·2%)

* The p value for differences in those with confirmed response was 0·02. The results section provides more details (unconfirmed responses are collapsed into the response category one level below).

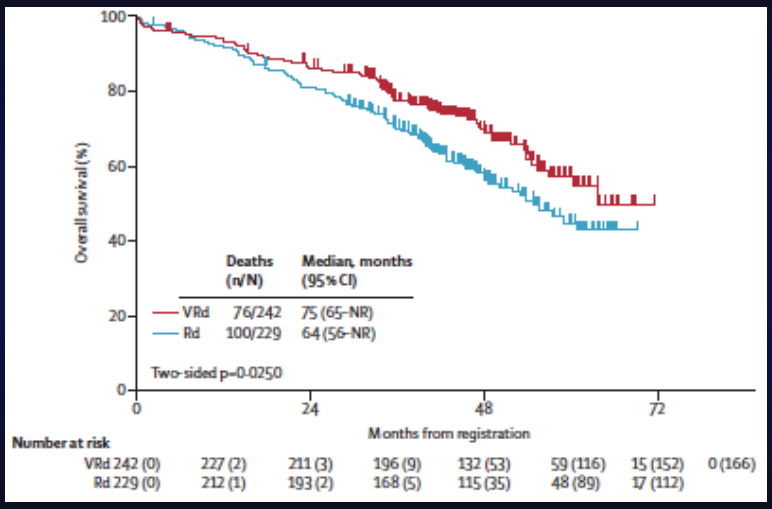
Durie, BGM et al. Lancet 389:519, 2017.

S0777 : PFS



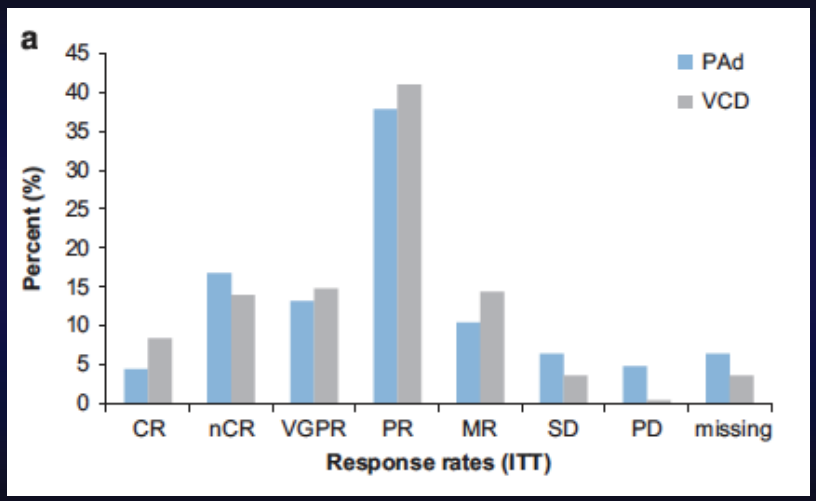
Durie, BGM et al. Lancet 389:519, 2017.

S0777 : OS



Durie, BGM et al. Lancet 389:519, 2017.

PAD vs. VCd



Mai, EK et al. Leukemia 29:1721, 2015.

VTD vs. VCD

Table 2. Response to induction

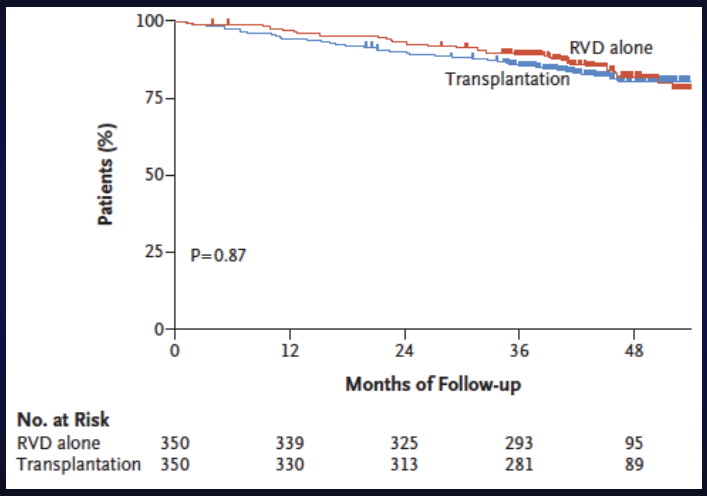
	VTD (n = 169)	VCD (n = 169)	*P* value
Intent to treat			
≥CR	13.0%	8.9%	.22
≥VGPR	66.3%	56.2%	.05
≥PR	92.3%	83.4%	.01
Per protocol	n = 157	n = 154	
≥CR	14.0%	9.1%	.17
≥VGPR	70.7%	60.4%	.05
≥PR	98.7%	90.3%	.001

Moreau, P et al. Blood 127:2569, 2016.

Overview

- Two or three drugs (with one being a novel agent) are better than three conventional drugs
- Vd and PAD are better than VAD
- VCd is better than PAD
- VTd is better than VCd
- RVd is better than Rd
- RVd is better than VTd

IFM/DFCI 2009 Study



Attal, M et al. N Engl J Med. 376:1311, 2017.

KRd as an Alternative

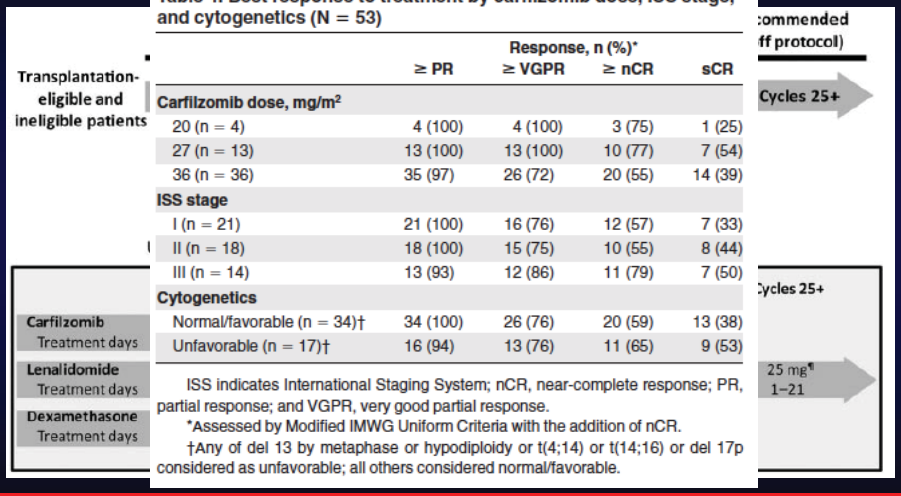


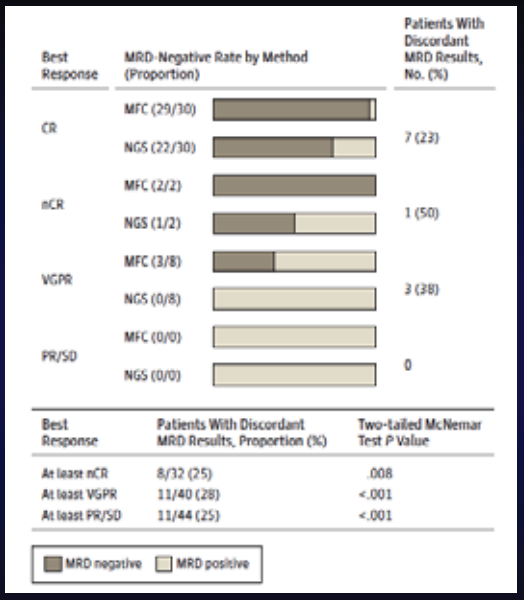
Table 4. Best response to treatment by carfilzomib dose, ISS stage, and cytogenetics (N = 53)

	Response, n (%)*			
	≥ PR	≥ VGPR	≥ nCR	sCR
Carfilzomib dose, mg/m²				
20 (n = 4)	4 (100)	4 (100)	3 (75)	1 (25)
27 (n = 13)	13 (100)	13 (100)	10 (77)	7 (54)
36 (n = 36)	35 (97)	26 (72)	20 (55)	14 (39)
ISS stage				
I (n = 21)	21 (100)	16 (76)	12 (57)	7 (33)
II (n = 18)	18 (100)	15 (75)	10 (55)	8 (44)
III (n = 14)	13 (93)	12 (86)	11 (79)	7 (50)
Cytogenetics				
Normal/favorable (n = 34)†	34 (100)	26 (76)	20 (59)	13 (38)
Unfavorable (n = 17)†	16 (94)	13 (76)	11 (65)	9 (53)

ISS indicates International Staging System; nCR, near-complete response; PR, partial response; and VGPR, very good partial response.
*Assessed by Modified IMWG Uniform Criteria with the addition of nCR.
†Any of del 13 by metaphase or hypodiploidy or t(4;14) or t(14;16) or del 17p considered as unfavorable; all others considered normal/favorable.

Jakubowiak, AJ et al. Blood 120:1801, 2012.

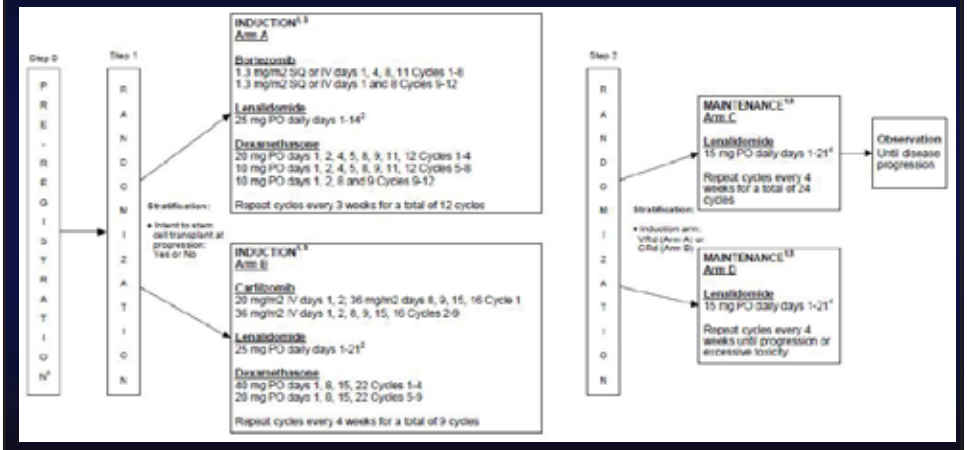
High MRD Negative Rates



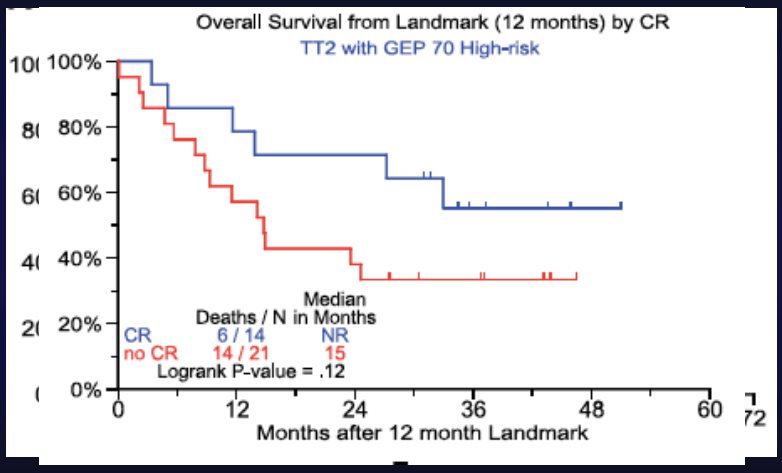
- Possibly higher than with RVD

Korde, N et al. JAMA Oncol. 1:746, 2015.

ECOG/ACRIN ENDURANCE Study

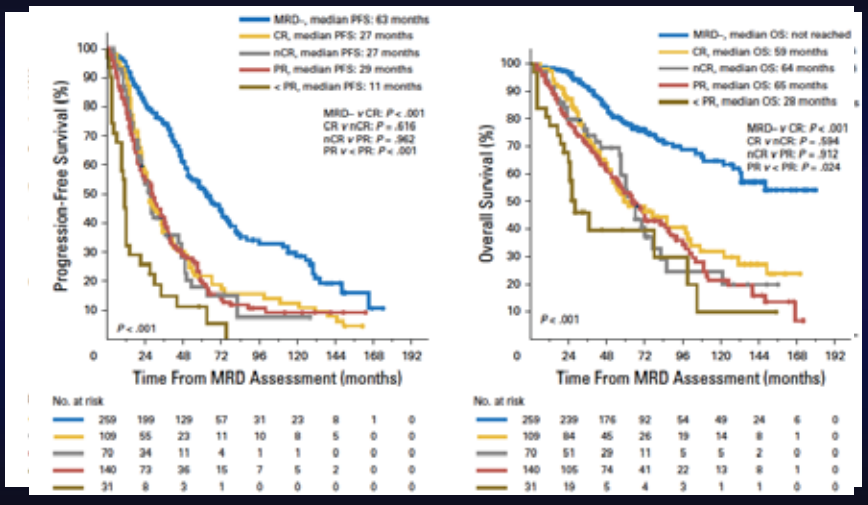


CR is Important in High Risk



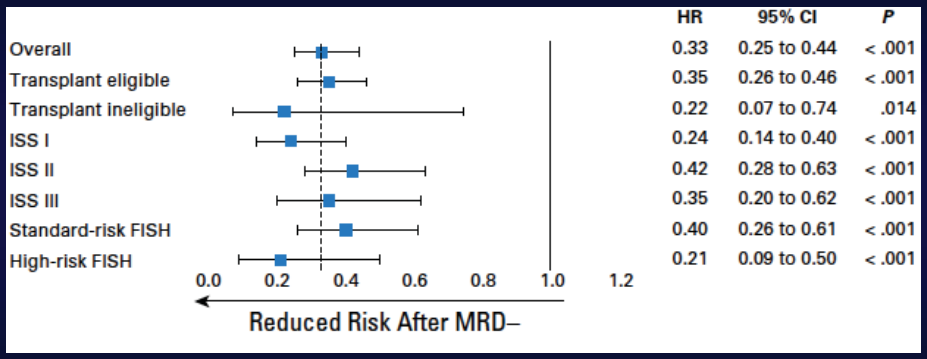
Haessler, J et al. Clin Cancer Res. 13:7073, 2007.

Is MRD a Better Endpoint?



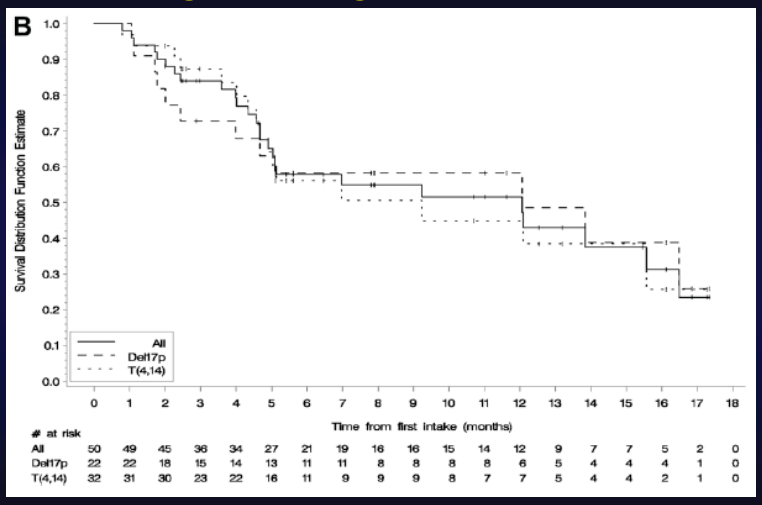
Lahuerta, J-J et al. J Clin Oncol. 35:2900, 2017.

Overall Survival & MRD



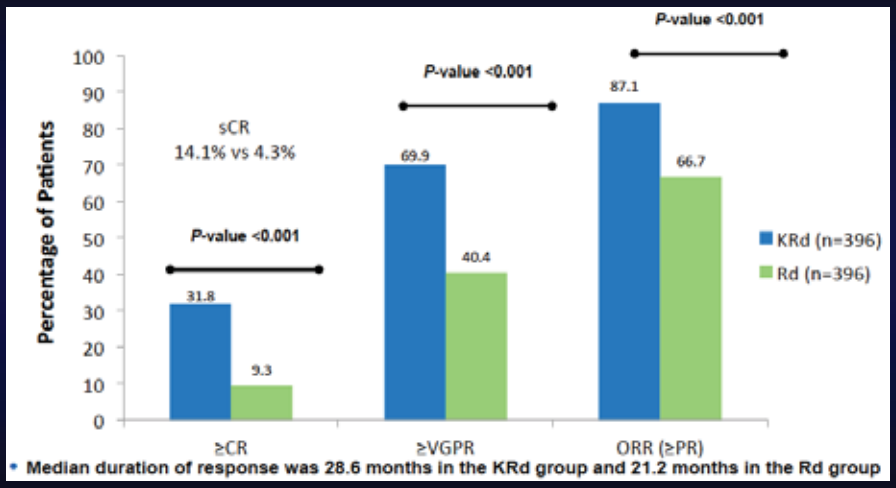
Lahuerta, J-J et al. J Clin Oncol. 35:2900, 2017.

Drugs for High Risk : Pom?



Leleu, X et al. Blood 125:1411, 2015.

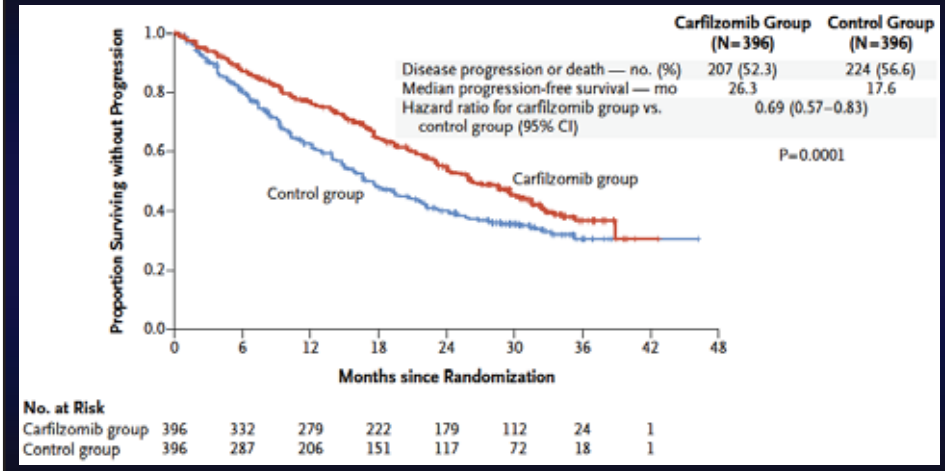
ASPIRE Study : Response Rates



• Median duration of response was 28.6 months in the KRd group and 21.2 months in the Rd group

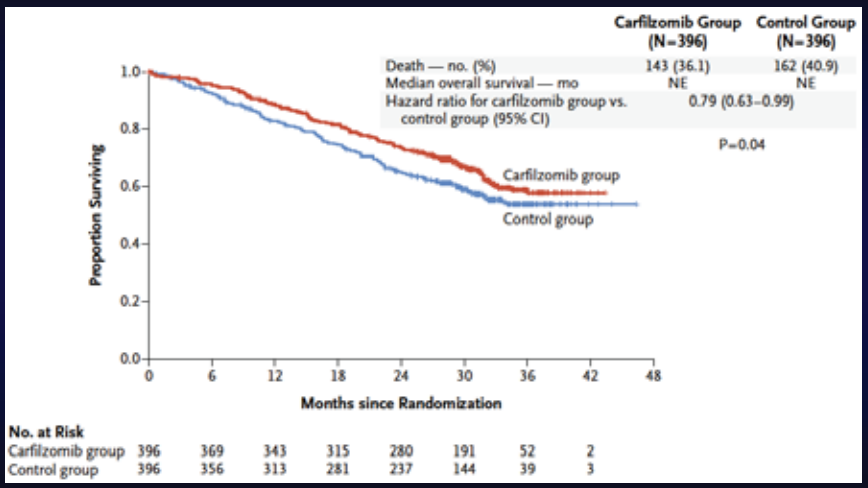
Stewart, AK et al. N Engl J Med. 372:142, 2015.

PFS Data



Stewart, AK et al. N Engl J Med. 372:142, 2015.

OS Data



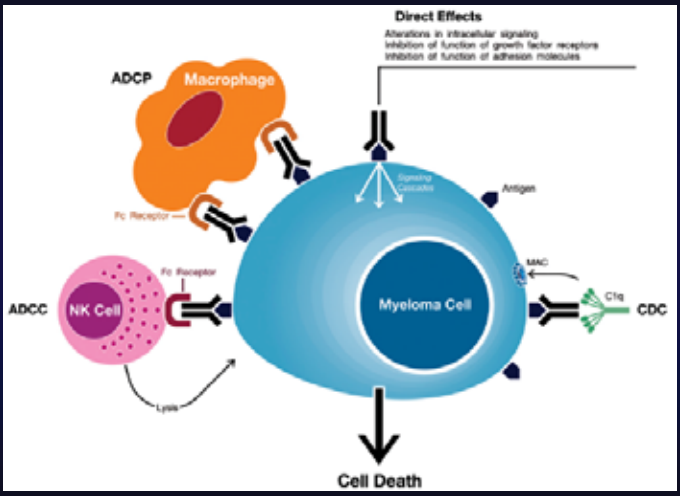
Stewart, AK et al. N Engl J Med. 372:142, 2015.

High Risk : Carfilzomib?

Subgroup	Carfilzomib (no.)	Control (no.)	Hazard Ratio (95% CI)
All patients	396	396	0.69 (0.57–0.83)
Sex			
Female	181	164	0.68 (0.51–0.92)
Male	215	232	0.74 (0.58–0.95)
Age			
18–64 yr	211	188	0.60 (0.46–0.79)
≥65 yr	185	208	0.85 (0.65–1.11)
Cytogenetic risk at study entry			
High risk	48	52	0.70 (0.43–1.16)
Standard risk	147	170	0.66 (0.48–0.90)
β_2-microglobulin			
<2.5 mg/liter	68	71	0.60 (0.36–1.02)
≥2.5 mg/liter	324	319	0.71 (0.58–0.87)

Stewart, AK et al. N Engl J Med. 372:142, 2015.

Antibodies : Mechanisms of Action



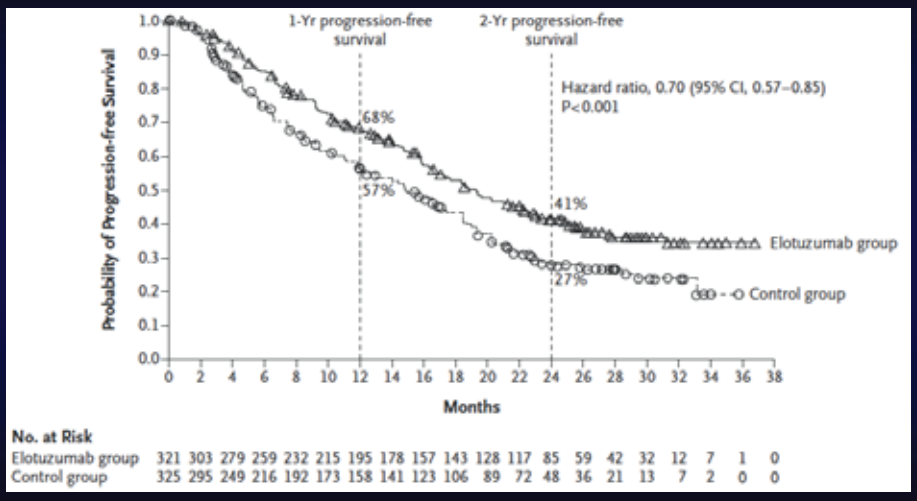
Van de Donk, NWCJ et al. Blood 127:681, 2016.

ELOQUENT2 : Treatment Response

Response	Elotuzumab Group (N = 321)	Control Group (N = 325)
Overall response rate		
Patients with response — no. (%)†	252 (79)	213 (66)
95% CI — %	74–83	60–71
Best overall response — no. (%)		
Complete response (sCR + CR)	14 (4)‡	24 (7)
Very good partial response	91 (28)	67 (21)
Combined response (sCR + CR + VGPR)	105 (33)	91 (28)
Partial response	147 (46)	122 (38)
Minimal response	22 (7)	33 (10)
Stable disease	30 (9)	54 (17)
Progressive disease	8 (2)	8 (2)
Could not be evaluated	9 (3)	17 (5)

Lonial, S et al. N Engl J Med. 373:621, 2015.

PFS Curves

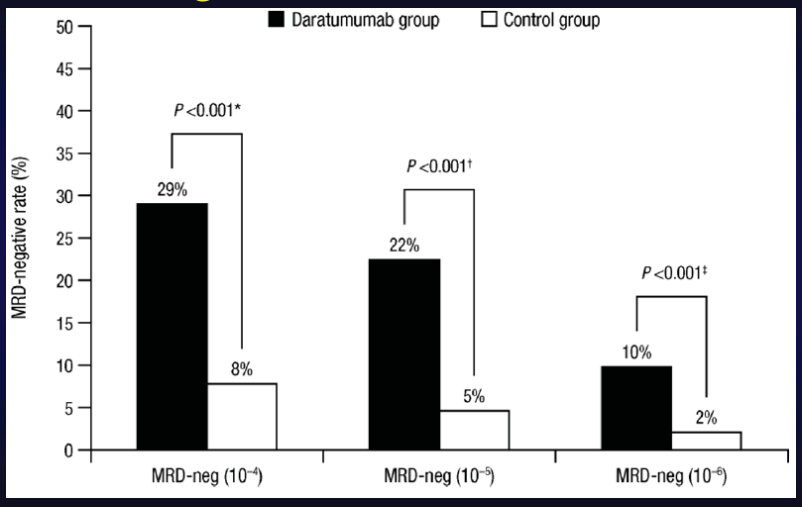


Lonial, S et al. N Engl J Med. 373:621, 2015.

High Risk : Elotuzumab

Lonial, S et al. N Engl J Med. 373:621, 2015.

High Risk : Daratumumab

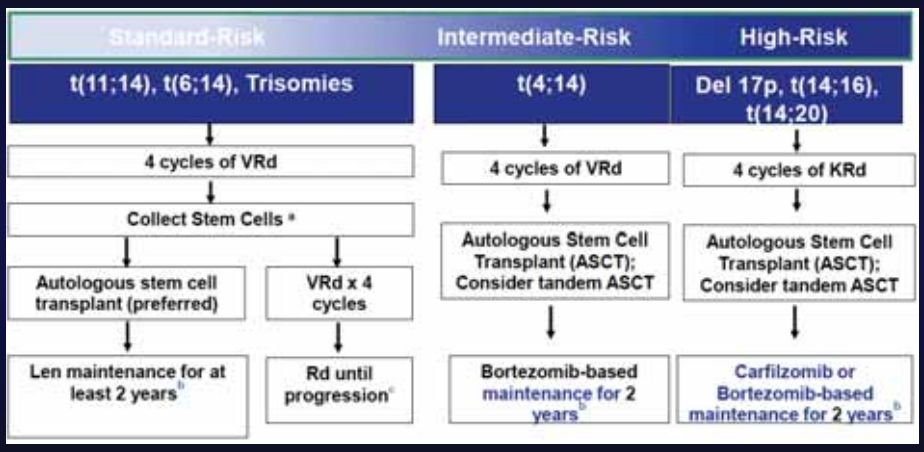


Dimopoulos, MA et al. N Engl J Med. 375:1319, 2016.

Conclusions

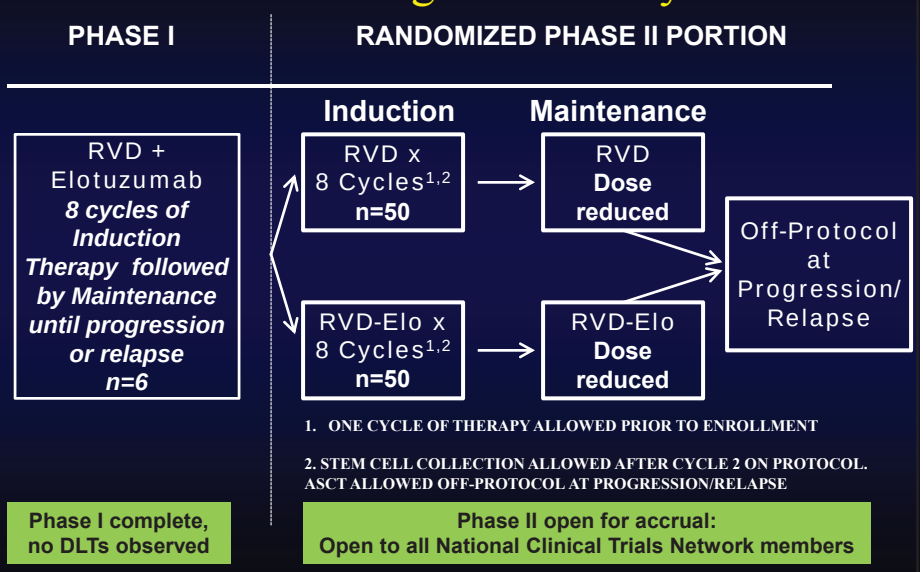
- The current standard of care for induction therapy pre-transplant is RVD
- KRD is a reasonable alternative given the possibly higher CR rate and overall better tolerability
- High risk patients should probably be treated more aggressively to achieve not just CR but MRD-negativity

Mayo Suggestions

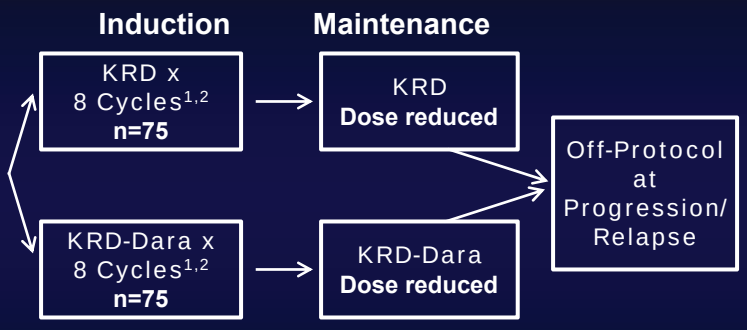


https://msmart.org

S1211A High Risk Study



S1211B High Risk Study



1. ONE CYCLE OF THERAPY ALLOWED PRIOR TO ENROLLMENT

2. STEM CELL COLLECTION ALLOWED AFTER CYCLE 2 ON PROTOCOL. ASCT ALLOWED OFF-PROTOCOL AT PROGRESSION/RELAPSE

Phase II open soon for accrual:
Open to all National Clinical Trials Network members

Possible Future Approaches

- RVD or KRD for standard risk patients
- RVD or KRD + elotuzumab or daratumumab for high risk patients
- RVD or KRD + later addition of elo or dara if response is less than ideally robust
- CR and MRD-negativity may be the preferred endpoint, especially for patients with high-risk disease

Illustrative Case

- 69 yo female with a history from 5 years ago of an elevated total protein
- 09/2014 p/w back pain; radiographs negative
  - Work-up showed Hgb 8.5, WBC 11.3 (20% plasma cells), BUN 37, Cr 3.3, Ca 11.2
- BM : 90% plasma cells, t(11;14) by FISH
- Serum : 4.0 g/dL IgG kappa paraprotein
- PET scan : Multiple small lytic lesions

Induction Therapy

- You would recommend induction therapy with
  - A. VD
  - B. RD
  - C. RVD
  - D. KRD
  - E. CyBorD

Further Course

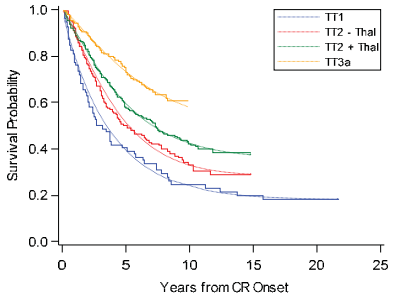
- Induction is given with modified CVD which normalizes her renal function and resolves her circulating plasma cells
- She enrolls on S1211A and is randomized to the RVD-Elo arm, which she starts in 01/2015
- Achieves a VGPR with nadir M-protein of 0.4 in 08/2016
- M-protein slowly rises from there, and increases to 1.0 in 07/2017

Autotransplant 2020
IMS 2017
Washington, DC

Sundar Jagannath, MD
Professor of Medicine
Icahn School of Medicine at Mount Sinai
Tisch Cancer Institute
New York, NY

Introduction: Historical perspective

- **Tim McElwain – dose response to intravenous melphalan**
  - Lancet 2:822, 1983
- **Randomized trial**
  - Attal: IFM 90 Std chemo vs Mel140 + TBI
  - Child: MRC7 trial Std chemo vs Mel
- **Bart Barlogie – Total Therapy with tandem transplants**
  - Tantamount to cure
- **<u>Goal of high-dose therapy with ASCT</u>**
  - Increase the depth of response
  - Prolong duration of response
  - Improve PFS and OS

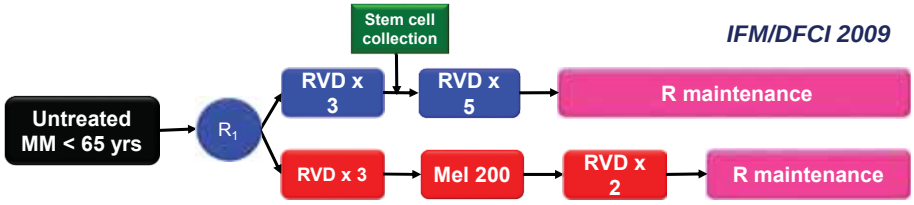


Barlogie, et al. Blood. 2014 Nov 13; 124(20): 3043–3051.

Evolving role of high-dose Melphalan and ASCT in the era of novel agents and antibodies

- **Goal of high-dose therapy with ASCT**
  - Increase the depth of response
  - Prolong duration of response
  - Improve PFS and OS
- With improved induction, consolidation and maintenance is there a role for Tx
- Early vs. late transplantation
- Single vs. tandem transplantation
- Role of transplants in high-risk disease
- Future:
  - Immuno-oncology with cellular therapy
  - Immuno-oncology with check point inhibitors
  - Immuno-oncology with post-transplant vaccine therapy

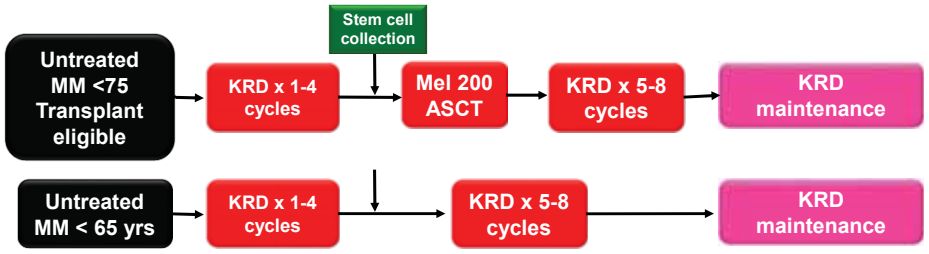
With improved induction, consolidation, and maintenance, transplant is required



	RVD arm N=350	Transplant arm N=350	p-value
CR	48%	59%	
VGPR	29%	29%	0.02
PR	20%	11%	
At least VGPR	78%	88%	0.001
Neg MRD by FCM, n (%)	171 (65%)	220 (79%)	<0.001
Median PFS	32	50	HR: 0.65 (*P* < .001)
4-yr OS	95	89	HR: 1.2 (*P* = NS)

Attal, N Engl J Med 2017; 317:1311

With more effective induction, consolidation, and maintenance, transplant is still required

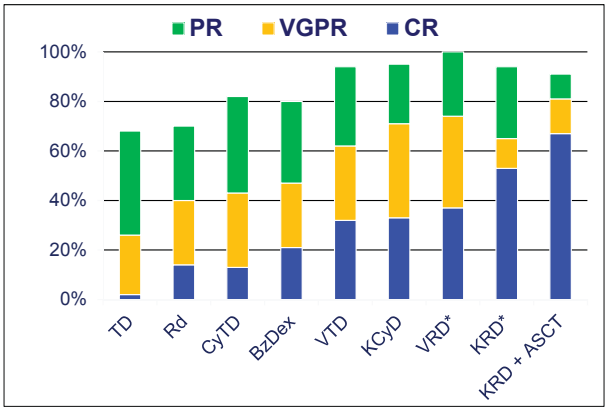


Treatment Arm	Induction		ASCT	Consolidation		Post maintenance	
	≥VGPR	≥CR	≥CR	≥VGPR	≥CR	≥VGPR	≥CR
ASCT	73%	16%	27%	91%	67%	94%	86%
No ASCT	69%	18%		89%	34%	90%	59%

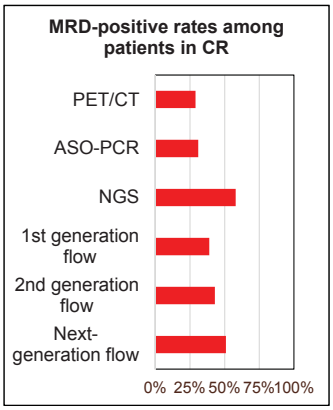
Zimmerman T, et al. ASH 2016. Abs#675

Transplant increases MRD-neg CR

NOVEL AGENT BACKBONE



Quadruplets – add antibodies



NGS – next generation sequencing
ASO – allele-specific oligonucleotide

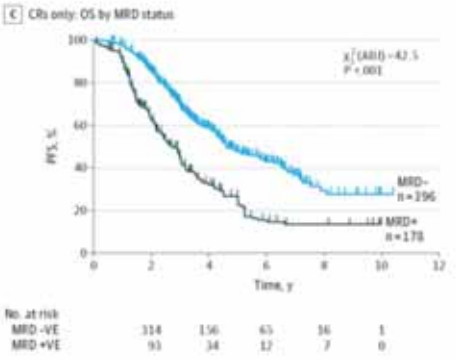
Rajkumar et al., Lancet Oncol. 11: 29, 2010
Morgan et al. Haematologica 2012.
Harousseau J-L et al. *J Clin Oncol*. 2010;28:4621
Cavo et al., . *Lancet* 2010; 376:2075

Richardson et al., Blood 2010; 116:679
Jakubowiak et al. Blood. 2012 Aug 30;120(9):1801-9
Zimmerman T, et al. ASH 2016. Abs#675

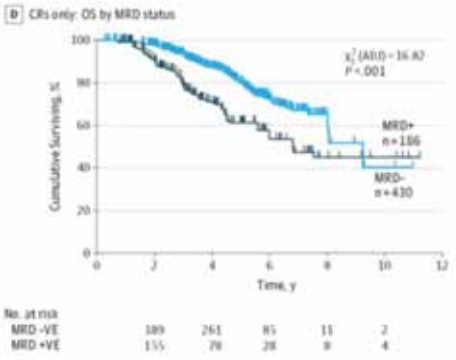
1. Zamagni et al. Blood 2011;118(23):5989-95
2. Rawstron AC, et al. Blood 2002; 100(9):3095-3100
3. Paiva B et al; Blood. 2008; 15;112(10):4017-23
4. Paiva B et al; J Clin Oncol. 2011;29(12):1627-33
5. Paiva B, et al. Blood. 2012;119:687-91.
6. Rawstron A, et al. J Clin Oncol. 2013;31(20):2540-7
7. Paiva B et al. ASH 2014; abstract 3390

MRD-neg improves outcomes for patients in "CR"

PFS by MRD status



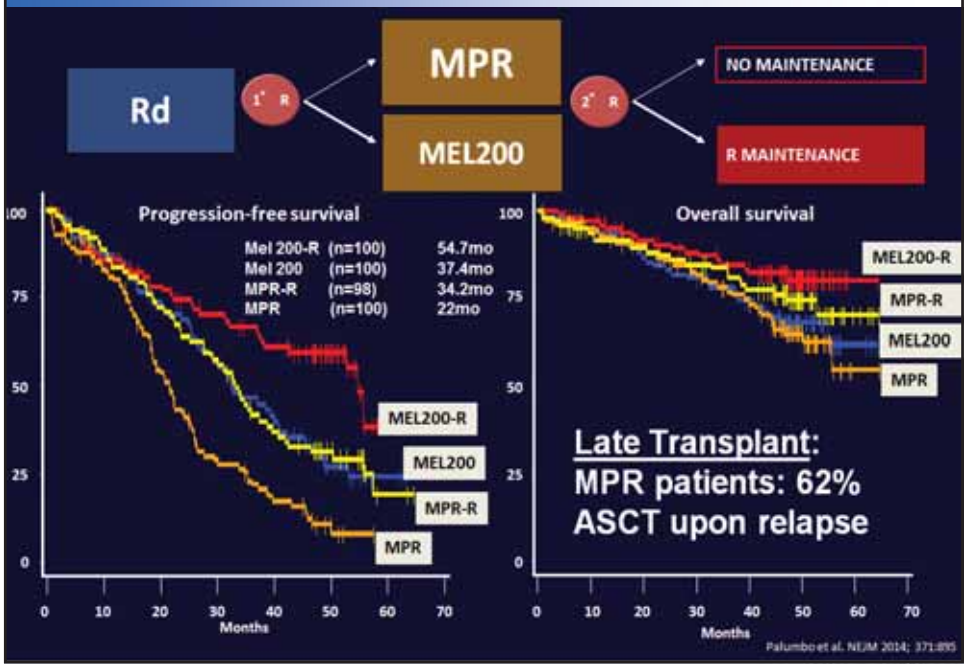
OS by MRD status



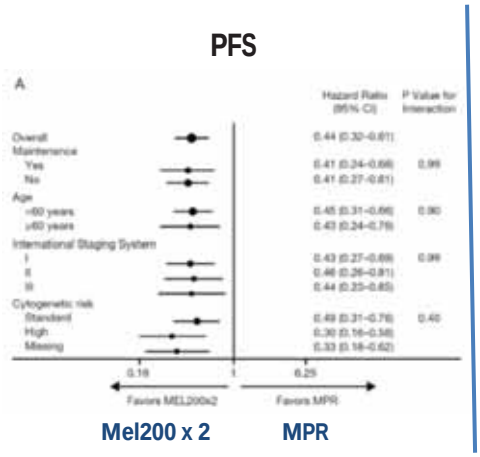
One time MRD negativity does not preclude relapse

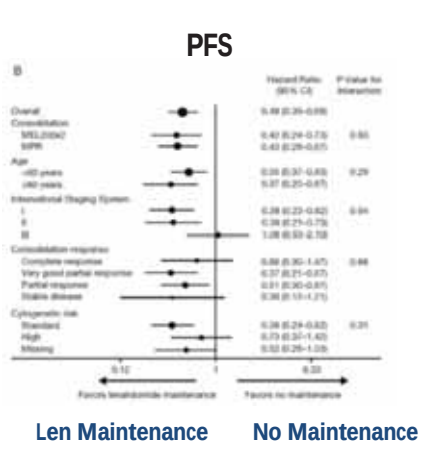
Munshi et al. JAMA Oncol. 3:28, 2016

Early vs. late transplant: Early is better!



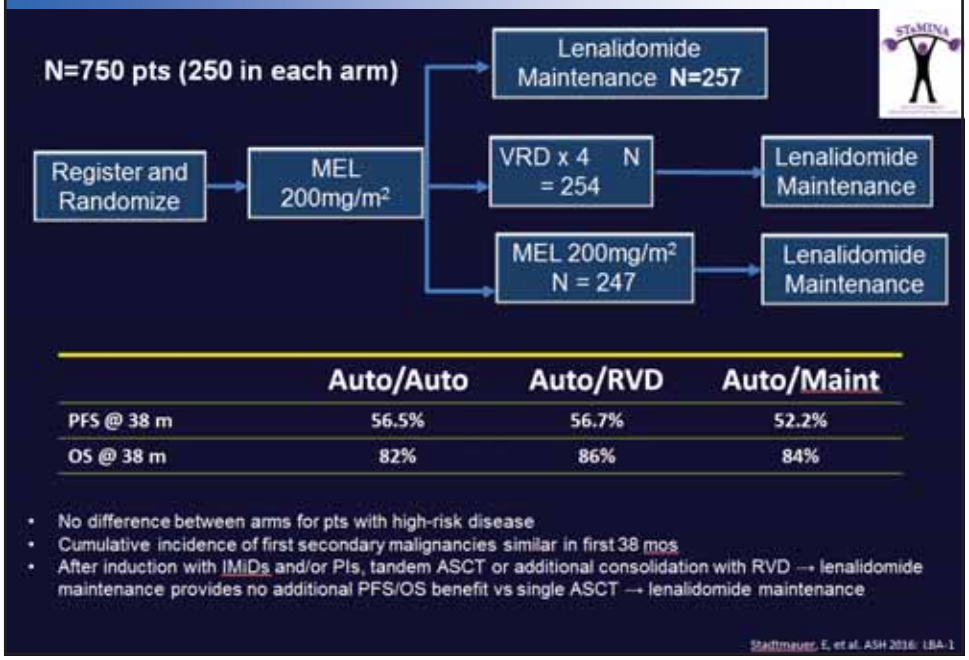
Transplant Improves Outcomes for ALL (maintenance does not)





Palumbo et al. NEJM 2014; 371:895

One transplant + maintenance may suffice

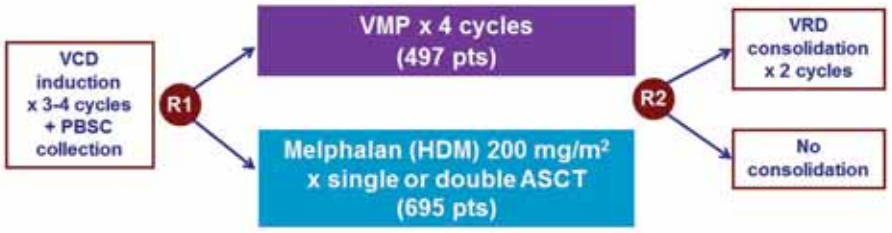


	Auto/Auto	Auto/RVD	Auto/Maint
PFS @ 38 m	56.5%	56.7%	52.2%
OS @ 38 m	82%	86%	84%

- No difference between arms for pts with high-risk disease
- Cumulative incidence of first secondary malignancies similar in first 38 mos
- After induction with IMiDs and/or PIs, tandem ASCT or additional consolidation with RVD → lenalidomide maintenance provides no additional PFS/OS benefit vs single ASCT → lenalidomide maintenance

Stadtmauer, E, et al. ASH 2016: LBA-1

EMN02/HO95 MM trial: Study design



All pts received lenalidomide maintenance until PD

Stratification: ISS I vs. II vs. III

Randomization to VMP or HDM was 1:1 in centers with a fixed single ASCT policy

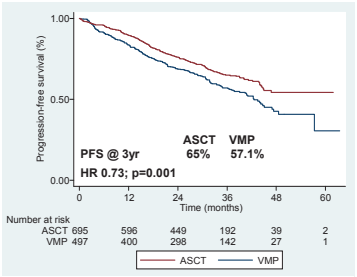
Randomization to VMP or HDM-1 or HDM-2 was 1:1:1 in centers with a double ASCT policy

VMP
Bortezomib 1.3 mg/m²d
1,4,8,11,22,25,29,32/42
Melphalan 9 mg/m² d 1-4/42
Prednisone 60 mg/m² d 1-4/42

Cavo M et al, ASH 2016: Abs#673

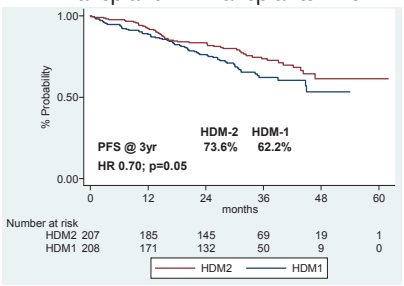
1 Transplant is essential
2 Transplants improves outcomes and benefits high risk

1 Transplant:
VMP vs ASCT: PFS

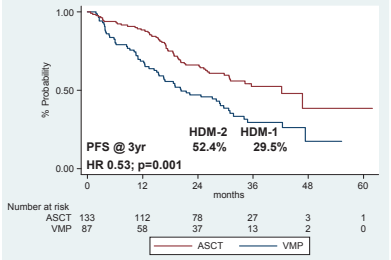


Median follow-up: 32 months

1 Transplant v. 2 Transplants: PFS



1 Transplant v. 2 Transplants, high risk: PFS



Cavo M et al, ASH 2016: Abs#673

Sonneveld P et al, Abs 242, ASH 2016

Future: Immuno-oncology

- Monoclonal antibodies:
  - Elotuzumab: NK-cell activation
  - Daratumumab: direct cytotoxicity and indirect immune mediated
- Immune checkpoint inhibitors: mAbs directed against inhibitory receptors on immune or tumor cells
- Ab-Drug conjugates (ADC): mAbs directed against tumor-associated surface targets conjugated to cytotoxic agents:
  - Anti-CS1 immunoconjugate (ABBV)
  - Anti-BCMA immunoconjugate (GSK2857916)
- Bispecific T-cell engager (BiTE) antibodies against BCMA
- CAR-T cells: autologous T cells transduced to express chimeric antigen receptor (CAR) for tumor-associated surface targets. Myeloma → BCMA, CS1

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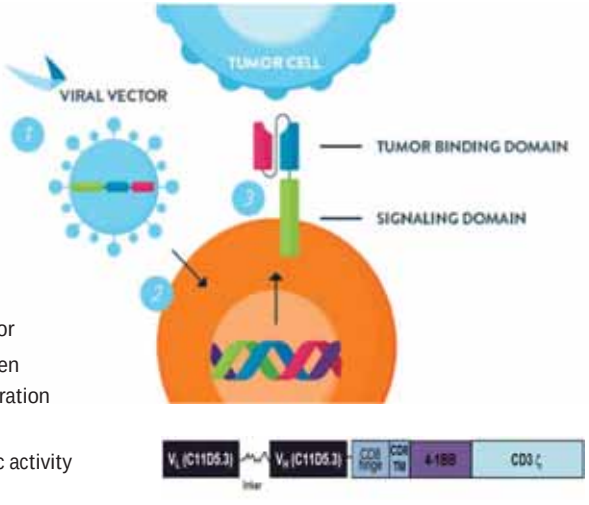
Future: Immuno-oncology

- Autologous T-cells engineered to express a T-cell receptor that specifically targets an antigen (BCMA) on the myeloma cells



- C11D5.3 scFv
- Transduced using a lenti-viral vector
- 4-1BB Co-signaling domain has been selected to promote CAR-T proliferation and survival
- Limited antigen-independent tonic activity

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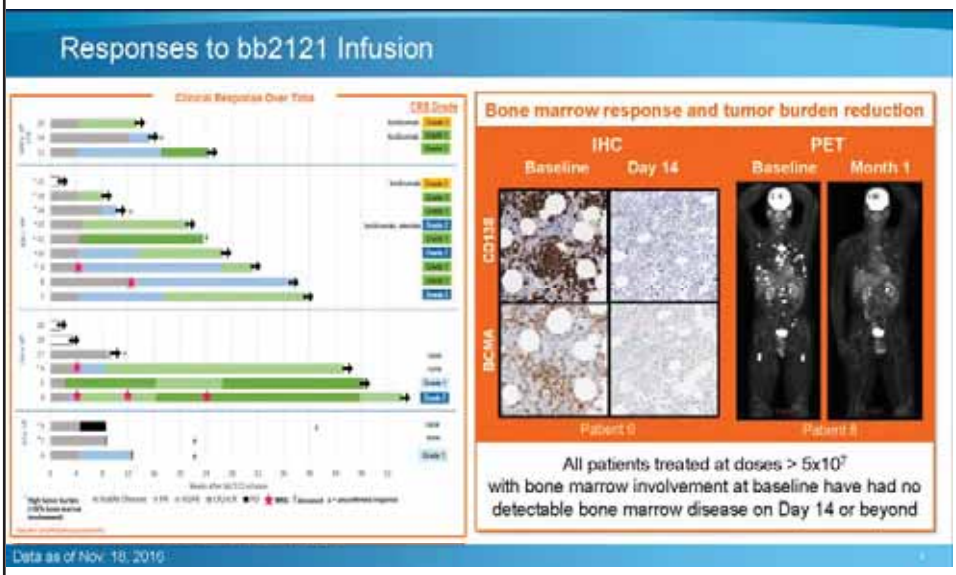
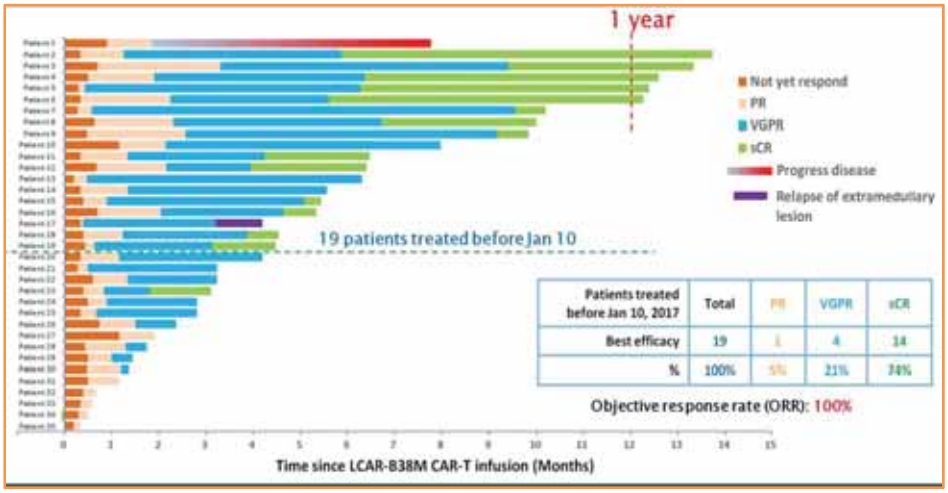
Future: Immuno-oncology: CAR-T Cell for Refractory MM



Berdeja et al. JCO 2017;35:15(suppl), 3010-3010

15

LCAR-B38M CAR-T Cell



Fan et al. ASCO 2017

16

Future: Immuno-oncology: CTLA-4 and PD1 antibodies

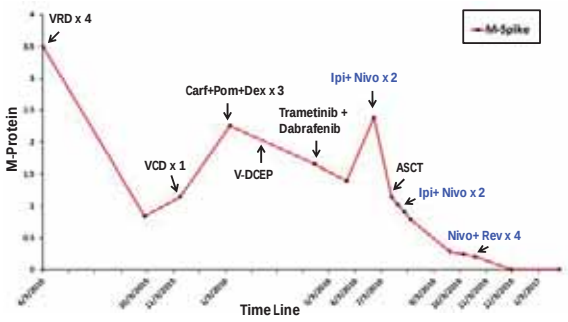


Figure 4. Clinical response of a MM patient showing complete response M-spike after double checkpoint inhibitor (anti-CTLA4 +anti-PD-1) therapy.

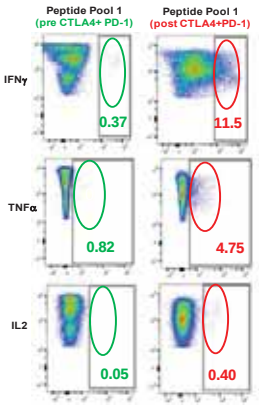


Figure 5. CD8+ T cell activation measured by IFN-γ, TNF-α and IL2 before and after double checkpoint inhibitor therapy

High Risk: complex karyotype (>5 abnormalities) with t(4;14) and del TP53
High recurrence score by gene expression profiling (MyPRS Score >67)

Parekh S, Cho HJ et al. IMW 2017

Evolving Role of High-Dose Melphalan and ASCT In the era of novel agents and antibodies

- High dose melphalan and ASCT is required in the era of
  - Improved induction
  - Improved consolidation
  - Improved maintenance
- Early vs Late transplantation:
  - Early is always better
- Single vs. Tandem transplantation:
  - Some additional gain from tandem
- Role of transplants in high-risk disease
  - Added benefit
- Future:
  - cellular therapy: CAR-T cells, NK cells
  - Immuno-oncology with check point inhibitors
  - Immuno-oncology with post-transplant vaccine therapy

When should we use consolidation and maintenance?

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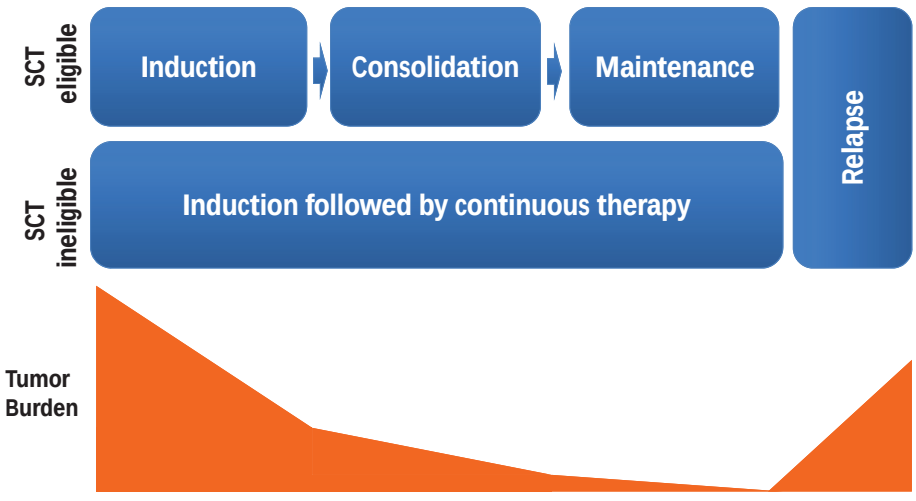
Professor of Medicine
Washington University School of Medicine
Section of Stem Cell Transplant and Leukemia
St. Louis, Missouri

Myeloma treatment paradigm



Conclusion From Meta-Analysis

N = 1,218

	Continuous Therapy	Fixed Duration of Therapy	*P* value
1-year landmark analysis			
Median PFS1	32 months	16 months	<0.001
Median PFS2	55 months	40 months	<0.001
4-year OS	69%	60%	0.003

N = 687

	Continuous Therapy	Fixed Duration of Therapy	*P* value
Median second PFS	15 months	15 months	0.313

Palumbo A et al. *J Clin Oncol*. 2014;32. Abstract

Post-ASCT Consolidation

Rationale

- Consolidation therapy following autologous stem cell transplant (ASCT) implies a short period of intensive treatment with single-agent or combination therapy.
- Since depth of response is widely accepted as prognostic for overall outcome in MM, this strategy aims to further reduce disease burden following high-dose chemotherapy and stem-cell rescue.

Historical perspective

- Initial efforts at post-transplant consolidation consisted of aggressive attempts to eradicate disease with tandem autologous transplantation, often combined with consolidation cytotoxic chemotherapy.

Tandem Transplants

Trial	N	ASCT	CR+VGPR (%)	Median PFS (months)	Median OS (months)
Attal et al, 2003	399	Single	42	25	48
		Tandem	50	30*	58*
Fermand et al, 2003	227	Single	39	31	49
		Tandem	37	33	73†
Cavo et al, 2007	321	Single	33	23	65
		Tandem	47*	35*	71
Goldschmidt et al, 2005	268	Single	NR	23	NYR
		Tandem	NR	29*	NYR
Sonneveld et al, 2007	303	Single	13 (CR only)	27*	50

< .05.;†OS significant for non-CD34 selected tandem transplants in subset analysis.;NR = not reported; NYR:not yet reached

Engl J Med. 2003;349:2495-502. Fermand JP, et al. Hematol J. 2003;4(Suppl 1):S59. Lazarus, Harry M. and Laughlin, Mary J. Allogeneic Stem Cell Transplantation. Second Edition. Cleveland, OH; umana Press, 2010. Cavo M, et al. J Clin Oncol. 2007;25:2434–2441. http://myeloma.org/pdfs/Sydney2005_Goldschmidt_P8.pdf. Accessed July 18, 2012. Sonneveld P, et al. Haematologica. 007;92(7):928–935.

Tandem transplant and cytotoxic chemotherapy

Trial	Consolidation	Maintenance	5-yr PFS	5-yr OS
TT1 (N=231)	Mel200 x 2	IFN	28%	58%
TT2 (N=668)	Mel200 x 2 DPACE x 4	IFN vs IFN + Thal*	42% vs 56%	65% vs 68%
TT3a (N=303)	Mel200 x 2 V-DTPACE x 2	VDT$→ Thal*+Dex	65%	74%

*: Thalidomide; $: Velcade, Dexamethasone and Thalidomide

Barlogie B et al, Blood 93:55-65, 1999

Modern perspective

- With an expanding number of well-tolerated therapies, evaluation of post-transplant short course consolidation therapy is now a more attractive option to study.

Immunomodulatory agent based consolidation therapy

Consolidation Regimen	Induction Regimen	Comparator Arm	Duration	Before Consolidation	After Consolidation	4-yr PFS	4-yr OS
Lenalidomide Attal et al N=614	VAD* (46%) VD$ (46%)	None (All treated)	2 cycles	≥VGPR&: 58%	≥VGPR&: 69% P<0.001	43%& vs 22%	73%& vs 75%

Vincristine, Adriamycin and Dexamethasone;$:Velcade and Dexamethasone;&: Very good partial response (VGPR)

Attal M et al New England Journal of Medicine 366:1782-1791, 2012

Bortezomib based consolidation therapy

Consolidation Regimen	Induction Regimen	Comparator Arm	Duration	Before Consolidation	After Consolidation	PFS	3-yr OS
Bortezomib Uy et al N=40	Bortezomib naieve	None	6 cycles	CR+VGPR:43%	CR+VGPR: 43%	NR	63.1%
Bortezomib Mellqvist et al N=187	Bortezomib naieve	Placebo	6 cycles	≥nCR: 20.1% ≥VGPR:39.7%	≥nCR:45.1% ≥VGPR:70.9%	27 m vs 20 m	80% vs 80%

Uy GL et al. Bone Marrow Transplant 43:793-800, 2009; Mellqvist UH et al Blood 121:4647-54, 2013

Bortezomib and Thalidomide based consolidation therapy

Consolidation Regimen	Induction Regimen	Comparator Arm	Duration	Before Consolidation	After Consolidation	3yr-PFS	3yr-OS
VTD Cavo et al N=160	VTD X 3	TD N=161	2 cycles	CR: 48.7% ≥VGPR: 86.2%	CR: 60.6% ≥VGPR: 91.9% P=NS	60%	90%
TD Cavo et al N=161	TD X 3	VTD N=160	2 cycles	CR: 40.4% ≥VGPR: 81.4%	CR: 46.6% ≥VGPR: 88.2% P=NS	48%	88%
VTD Leleu et al N=121	VTD	No Consolidation N=96	2 cycles	CR:33% ≥VGPR: 43%	CR:52% ≥VGPR: 31% P<0.001	NR	NR vs 22m

Cavo M et al Blood 120:9-19, 2012; Leleu X et al Leukemia 27:2242-2244, 2013

Bortezomib and Lenalidomide based consolidation therapy

Consolidation Regimen	Induction Regimen	Comparator Arm	Duration	Before Consolidation	After Consolidation	PFS	OS
RVD Roussel et al N=31	RVD	None	2 cycles	CR: 47% ≥VGPR: 70%	CR: 50% ≥VGPR: 87%	77% 3-yr	100% 3-yr
RVD Nooka	RVD	None	3 years	sCR ≈20% ≥VGPR≈85%	sCR: 51% ≥VGPR: 96%	32m	93% 3-yr
RVD Moreau et al	RVD	No transplant	2 cycles	≥VGPR:73%	≥VGPR: 81%	34m vs 43m	81% vs 83% 4-yr

Roussel M et al Journal of Clinical Oncology 32:2712-2717, 2014; Nooka AK et al Leukemia 28:690-3, 2014 Attal M et al Blood 126:391-391, 2015

Carfilzomib and Immunomodulatory agent based consolidation therapy

Consolidation Regimen	Induction Regimen	Comparator Arm	Duration	Before Consolidation	After Consolidation	PFS	OS
KTd Sonneveld et al N=91	KTd	None	4 cycles	CR: 33% ≥VGPR: 76%	CR: 63% ≥VGPR: 89%	60% 3-yr	90% 3-yr
KRd Jakubowiak et al N=71	KRd	None	4 cycles	≥CR:27% ≥sCR:22%	≥CR:77% ≥sCR:70%	99% 11m	100% 11m

Sonneveld P et al Blood 125:449-456, 2015; Jakubowiak A et al *Haematologica*. 2015;100(Suppl 1):1-800., 2015

Consolidation and MRD

Consolidation Regimen	Induction Regimen	Comparator Arm	Duration	Before Consolidation	After Consolidation
VTD Ladetto et al N=39	VAD	None	4 cycles	CR: 15% MRD-: 3% MRD: 4.15 log reduction	CR: 49% MRD-:18% MRD: 10.09 log reduction (PCR)
VRD Roussel et al	VRD	None	2 cycles	MRD: 54% negative	MRD: 58% negative (7 color Flowcytometry)
KRd Jakubowiak et al N=71	KRd	None	4 cycles	MRD: 79% negative	MRD: 90% negative (10 color Flow)

Ferrero S et al Leukemia 29:689-695, 2015 Jakubowiak Aet al *Haematologica*. 2015;100(Suppl 1):2015 Roussel M et al Journal of Clinical Oncology 32:2712-2717, 2014;

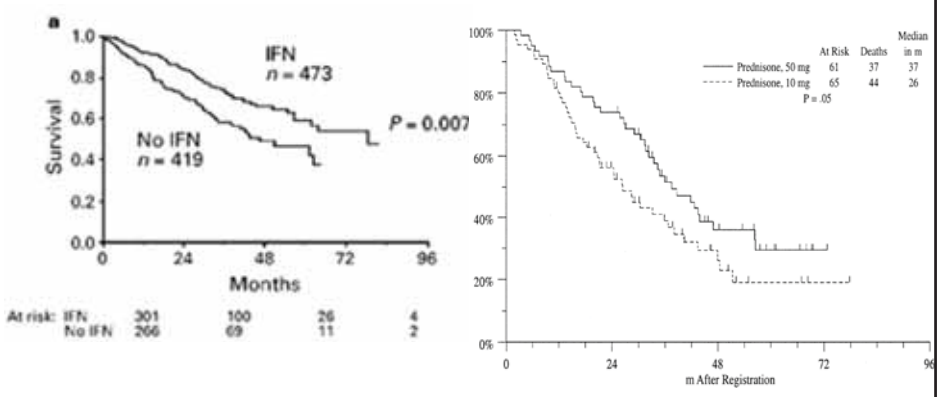
Post-ASCT Maintenance

Rationale

- Multiple phase 3 trials indicate that maintenance or continuous therapy prolongs PFS[1-6]
- Several trials also show OS advantage[1,4,5]
- Meta-analyses suggest continuous therapy produces better PFS1, PFS2, second PFS, and OS[7,8]

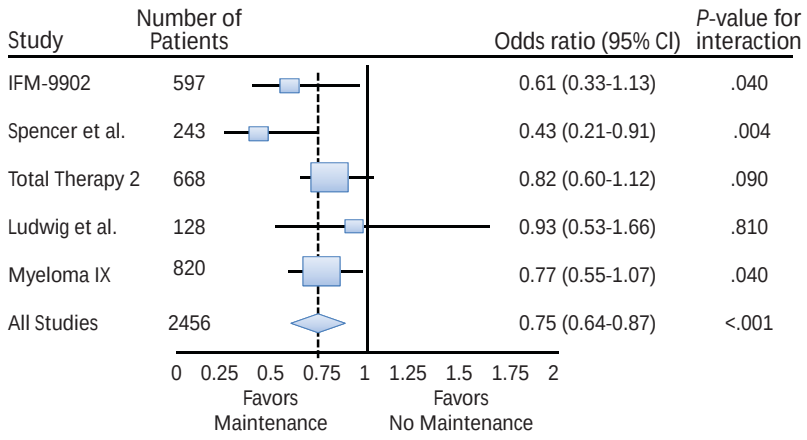
1. McCarthy PL et al. *N Engl J Med*. 2012;366:1770. 2. Attal M et al. *N Engl J Med*. 2012;366:1782.
3. Palumbo A et al. *N Engl J Med*. 2012;366:1759. 4. Attal M et al. *Blood*. 2006;108:3289.
5. Spencer A et al. *J Clin Oncol*. 2009;27:1788. 6. Sonneveld P et al. *J Clin Oncol*. 2012;30:2946.
7. Ludwig H et al. *Blood*. 2012;119:3003. 8. Palumbo A et al. *J Clin Oncol*. 2014;32. Abstract

Historical perspective



Bjorkstrand, B., et al BMT 27(5): 511-515; Berenson J R et al. Blood 2002;99:3163-3168

Meta-analysis of Thalidomide Maintenance



Morgan GJ, et al. *Blood*. 2012 ;119:7-15.

Lenalidomide Maintenance after ASCT

Trial	Pre-ASCT Regimen	N	# ASCT	Median PFS/TTP (months) L	Median PFS/TTP (months) PBO	*P* Value	OS (%) L	OS (%) PBO	*P* Value
Attal et al, 2012 IFM 2005-02	VAD or VD	614	1 or 2	43	22	<0.001	73 at 4-year survival	75 at 4-year survival	NS
McCarthy et al, 2012 CALBG 100104	L 32% V 42% T 16%	460	1	46	27	<0.001	88 at 3-year survival	80 at 3-year survival	<0.05

ASCT = autologous stem cell transplant; TTP = time to progression; PBO = placebo; VAD = vincristine, doxorubicin (A), dexamethasone; VD = bortezomib (V), dexamethasone; L = lenalidomide; T = Thalidomide.

Attal M, et al. *N Engl J Med*. 2012;366(19):1782-1791. McCarthy PL, et al. *N Engl J Med*. 2012;366(19):1770-81.

Toxicity with Lenalidomide Maintenance

Adverse Event (Grade 3 or 4)	IFM 2005-02		CALGB	
	L	PBO	L	PBO
Neutropenia	51%	18%	45%	15%
Thrombocytopenia	14%	7%	14%	4%
Anemia	3%	2%	5%	<1%
Discontinuation due to AE	27%	15%	10%	1%
Secondary malignancy	N=26 (8%)	N=11 (4%)	N=22 (9.5%)	N=4 (4%)

IFM = Intergroupe Francophone du Myelome CALGB = The ***Cancer and Leukemia Group B***

Attal M, et al. *N Engl J Med*. 2012;366(19):1782-91. McCarthy PL, et al. *N Engl J Med*. 2012;366(19):1770-1781.

Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD)

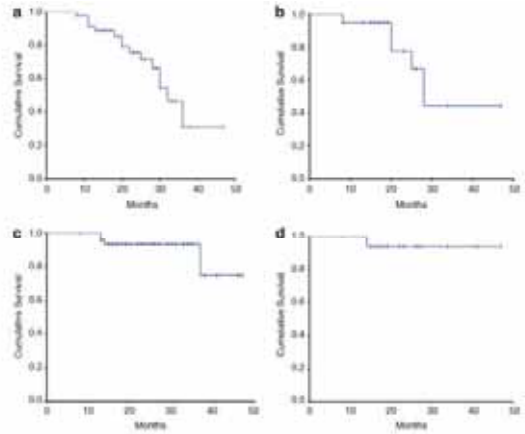
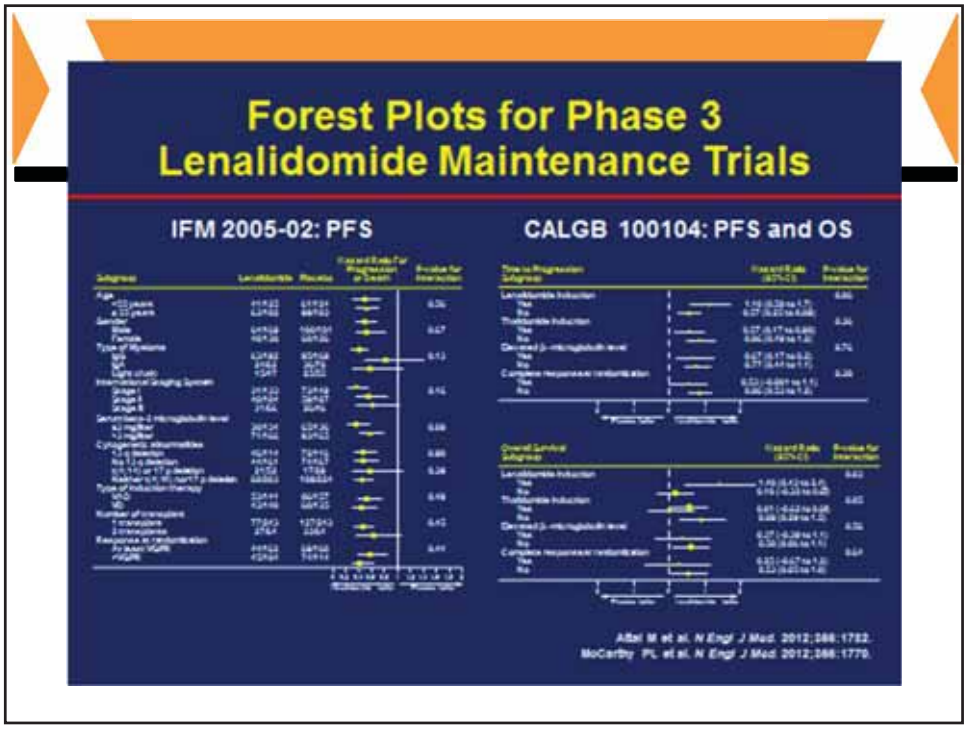
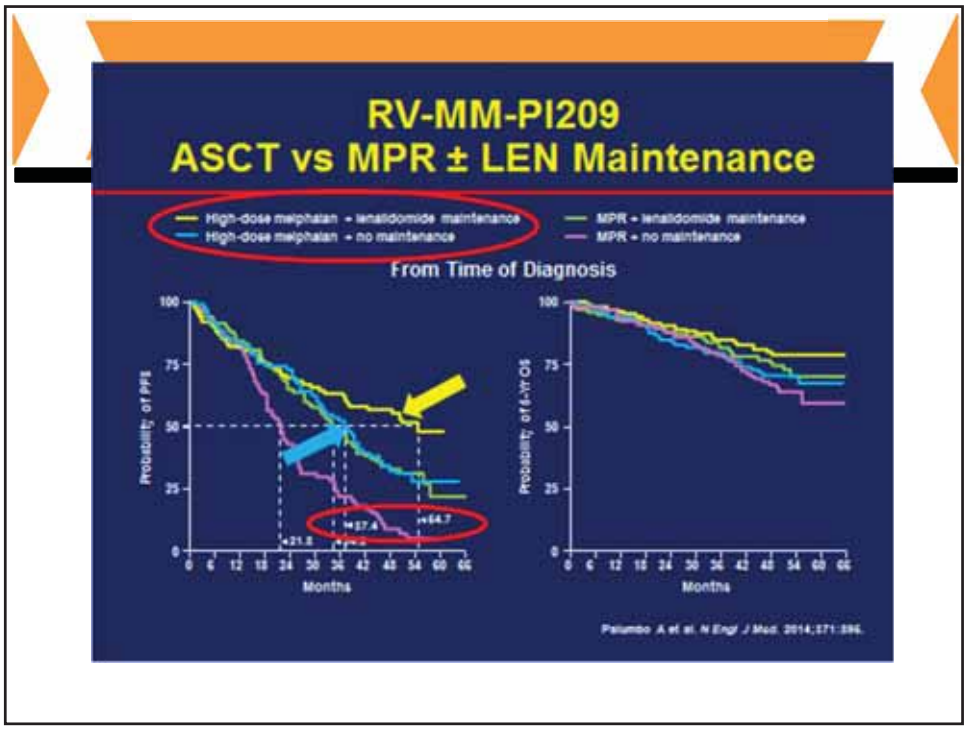


Figure 2. Survival outcomes of patients with high-risk disease. (a) Progression free survival among all patients (b) Progression free survival among patients with del 17p (c) Overall survival among all patients (d) Overall survival among patients with del 17p.

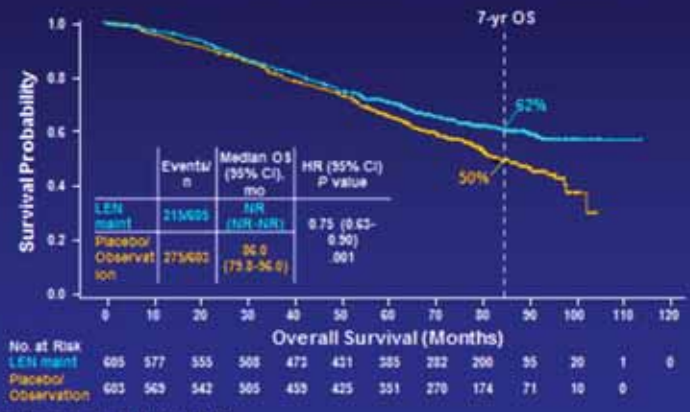
Nooka et al Leukemia (2014) 28, 690–693,


Forest Plots for Phase 3
Lenalidomide Maintenance Trials
IFM 2005-02: PFS
CALGB 100104: PFS and OS
Attal M et al. N Engl J Med. 2012;366:1782.
McCarthy PL et al. N Engl J Med. 2012;366:1770.


RV-MM-PI209
ASCT vs MPR ± LEN Maintenance
High-dose melphalan + lenalidomide maintenance
High-dose melphalan + no maintenance
MPR + lenalidomide maintenance
MPR + no maintenance
From Time of Diagnosis
Probability of PFS
Probability of 6-Yr OS
Months
Palumbo A et al. N Engl J Med. 2014;371:895.

Meta-Analysis Of Overall Survival

25% reduction in risk of death, representing an estimated 2.4-year increase in median survival



McCarthy et al IMW 2017

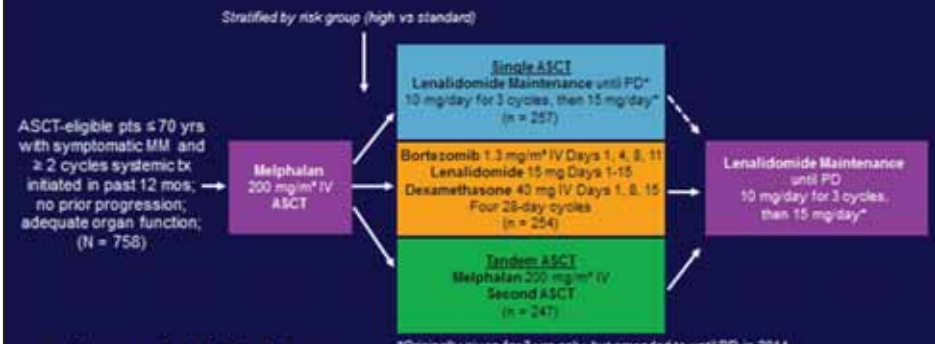
Post-ASCT Bortezomib Therapy

Study/ Year	Time Randomized	N	Bortezomib Regimen	Control Arm	Median PFS (mos)	Median OS (mos)
Sonneveld 2012[1]	At diagnosis	827	1.3 mg/m² Q 2 wks ×2 yrs	BTZ Thal	35* 28	61%* vs 55% at 5 yrs
Mellqvist 2013[2]	Post-ASCT	370	1.3 mg/m² ×20 doses (7 mos)	BTZ None	27* 20	NS (75–80% at 3 yrs)
Rosinol 2013[3]	Post-ASCT	266	1.3 mg/m² D 1,4,8,11 q 3 mo + thal 100 mg/d ×3 yrs	VT Thal IFN	~43* ~36 ~24	NS

*Statistically significant

1. Sonneveld P et al. J Clin Oncol. 2012;30:2946.
2. Mellqvist U-H et al. Blood. 2013;121:4647.
3. Rosinol L et al. Blood. 2012;120. Abstract 334.

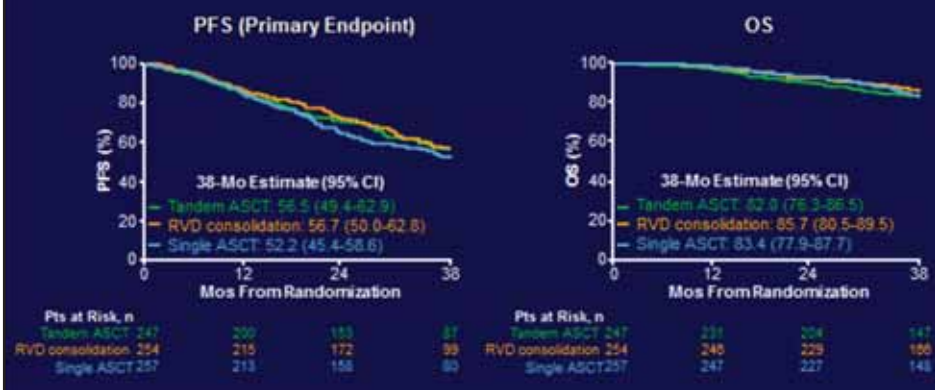
STaMINA: Phase III Study Design



- Primary endpoint: PFS at 38 mos
- Secondary endpoints: OS, ORR, CR conversion rate, safety, infections, tx-related mortality, QoL

Stadtmauer EA, et al. ASH 2016. Abstract LBA-1

STaMINA: PFS and OS for Overall Population



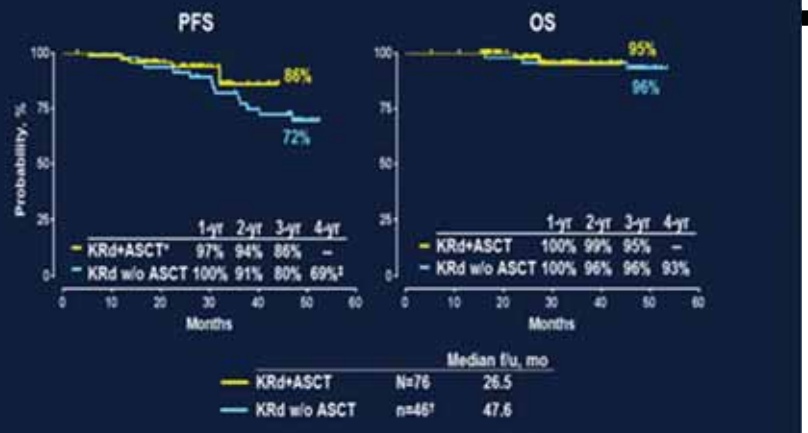
Stadtmauer EA, et al. ASH 2016. Abstract LBA-1.

Final Results of a Phase 2 Trial of Extended Treatment With Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Plus Autologous Stem Cell Transplant (ASCT) in Newly Diagnosed Multiple Myeloma

Todd M. Zimmerman, Noopur Raje, Ravi Vij, Donna Reece, Jesus G. Berdeja, Leonor Stephens, Kathryn McDonnell, Cara A. Rosenbaum, Jagoda K. Jasielec, Paul Richardson, Sandeep Gurbuxani, Jennifer Nam, Erica Severson, Brittany Wolfe, Shaun Rosebeck, Andrew Stefka, Dominik Dytfeld, Kent Griffith, Andrzej J. Jakubowiak

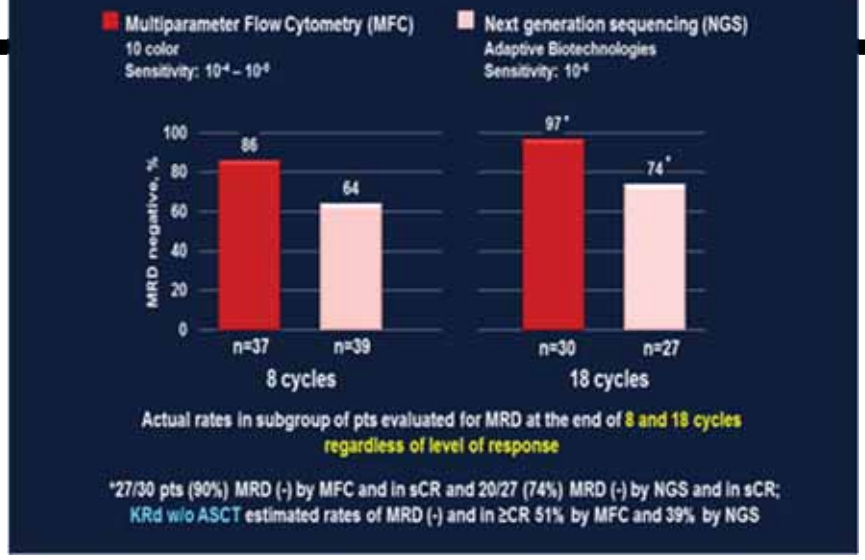
Abstract # 675

Treatment Outcomes



*6 patients progressed (2 post transplant; 1 after consolidation; 3 after EOT, during maintenance)
†Excludes 7 pts who discontinued to pursue ASCT; ‡ Intent-to-treat (N=53), 4-year PFS 64%
At cut-off date 10/1/2016

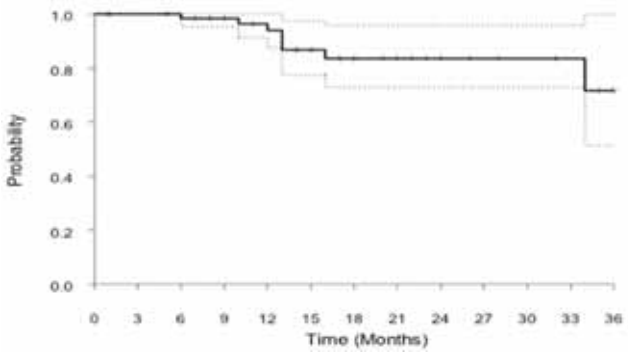
MRD Evaluation



Actual rates in subgroup of pts evaluated for MRD at the end of 8 and 18 cycles regardless of level of response

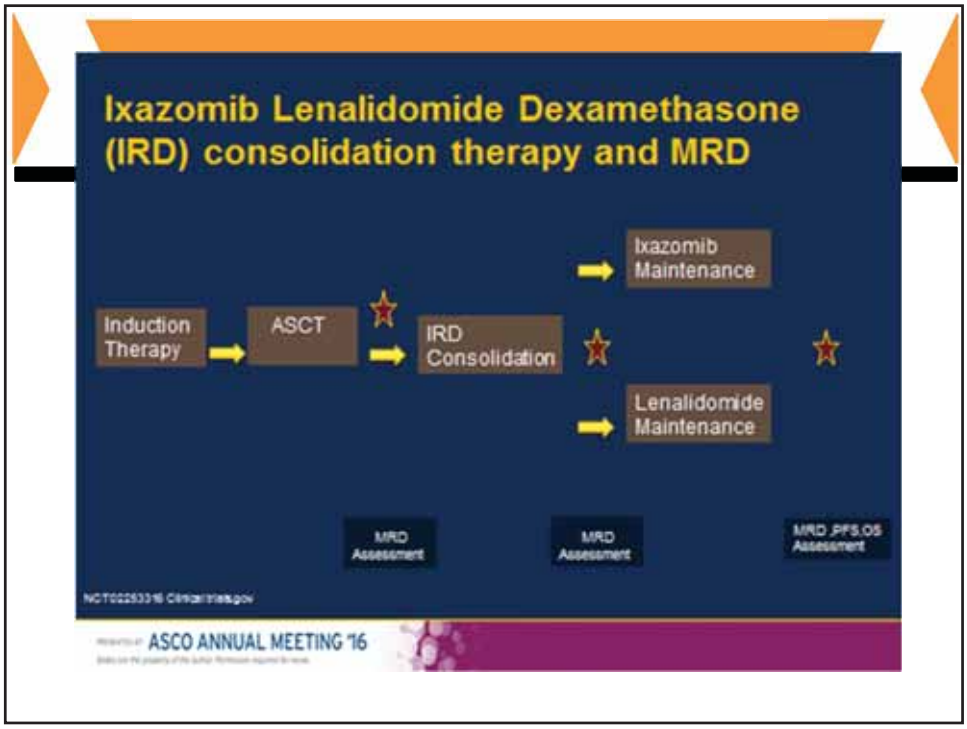
*27/30 pts (90%) MRD (-) by MFC and in sCR and 20/27 (74%) MRD (-) by NGS and in sCR; KRd w/o ASCT estimated rates of MRD (-) and in ≥CR 51% by MFC and 39% by NGS

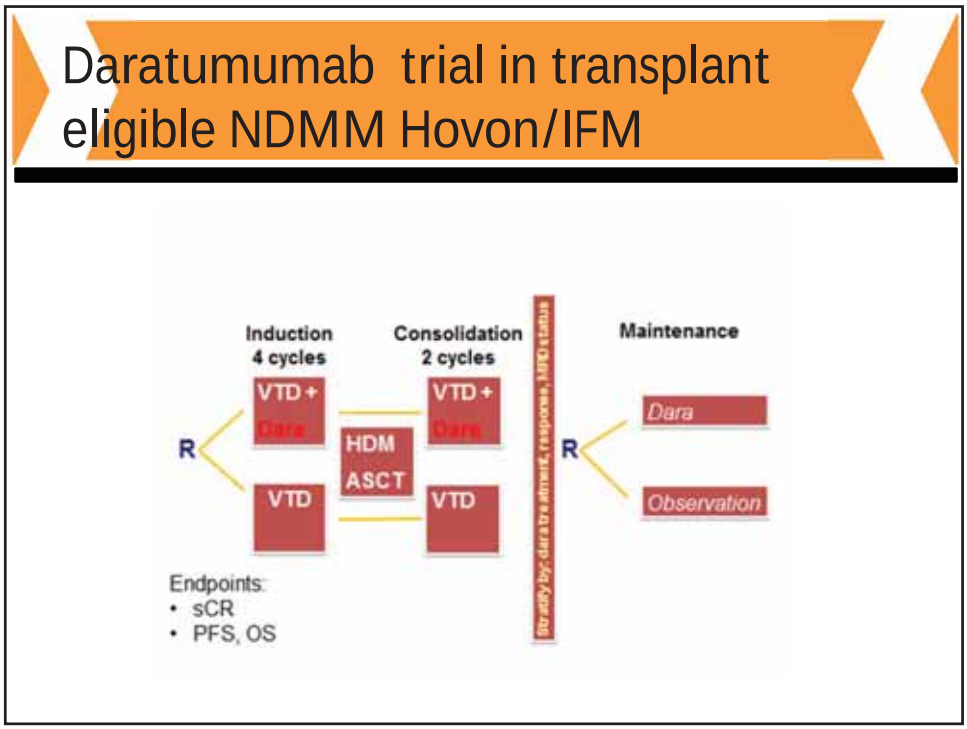
MDACC: Ixazomib +Lenalidomide Phase II



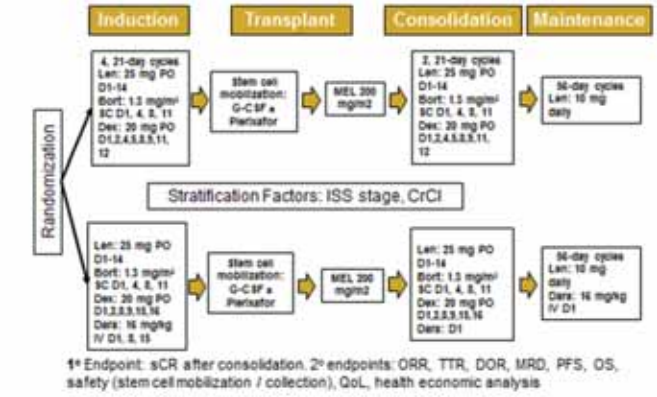
IXA 4mg D1,8,15 Len 10mg

Shah et al ASH 2015


Ixazomib Lenalidomide Dexamethasone (IRD) consolidation therapy and MRD
Induction Therapy
ASCT
IRD Consolidation
Ixazomib Maintenance
Lenalidomide Maintenance
MRD Assessment
MRD Assessment
MRD ,PFS,OS Assessment
ASCO ANNUAL MEETING '16


Daratumumab trial in transplant eligible NDMM Hovon/IFM
Induction 4 cycles
Consolidation 2 cycles
Maintenance
R
VTD + Dara
VTD
HDM ASCT
VTD + Dara
VTD
R
Dara
Observation
Endpoints:
• sCR
• PFS, OS

AFT-29 / MMY2004: randomized, phase II study of VRD +/-daratumumab



However…

- Myeloma is not one disease[1]
  - At least 7 subtypes based on cytogenetic and molecular features
  - Highest risk cytogenetic subtypes by FISH
    - t(4;14)
    - del 17p
    - t(14;16)
  - Likely that not all patients require continuous therapy

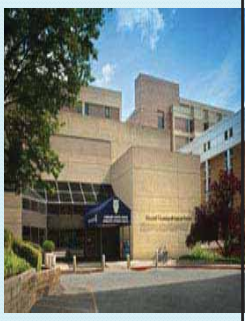
Conclusions

- Consolidation therapy currently remains an element of clinical trials aiming to minimize disease burden and improve patient outcomes.
- Long-term maintenance treatment is now widely accepted standard. However, the optimum agents, duration of maintenance and need for maintenance therapy for all patients remains an area for future research

Questions?

CELLULAR THERAPY IN MULTIPLE MYELOMA

David H. Vesole, MD, PhD
Professor of Medicine
Director, Myeloma Program
Georgetown University
Co-Director, Myeloma Division
Director, Myeloma Research
John Theurer Cancer Center
Hackensack UMC
david.vesole@hackensackmeridian.org



Allogeneic SCT

- Graft-vs-myeloma effect
- Tumor-free grafts
- Can potentially provide sustained disease control (ie, cure)
- High treatment-related mortality (10-20%)
- Morbidity from GVHD
- Debatable OS advantage vs autologous SCT in randomized trials
- Should be considered for high-risk pts in trials

Allogeneic Transplantation can cure some patients with MM

Vol. 325 No. 18 BONE MARROW TRANSPLANTATION IN MULTIPLE MYELOMA — GAHRTON ET AL. 1267

ALLOGENEIC BONE MARROW TRANSPLANTATION IN MULTIPLE MYELOMA

Gösta Gahrton, M.D., Sante Tura, M.D., Per Ljungman, M.D., Coralie Belanger, M.D., Lena Brandt, B.Sc., Michele Cavo, M.D., Thierry Facon, M.D., Alberto Granena, M.D., Martin Gore, M.D., Alois Gratwohl, M.D., Bob Löwenberg, M.D., Jukka Nikoskelainen, M.D., Josy J. Reiffers, M.D., Diana Samson, M.D., Leo Verdonck, M.D., and Liisa Volin, M.D., for the European Group for Bone Marrow Transplantation*

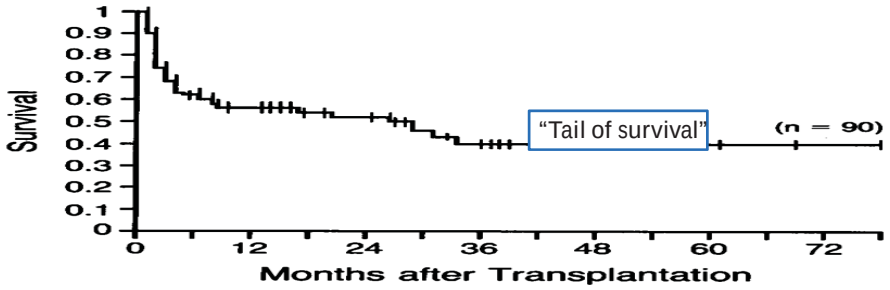
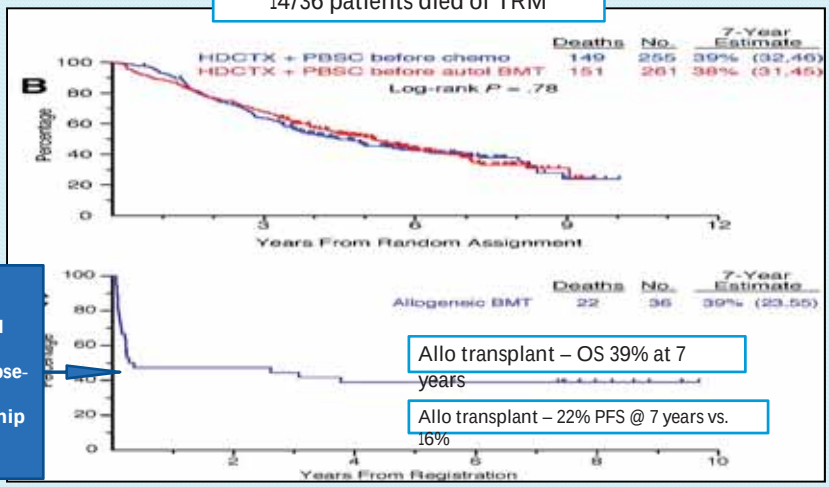


Figure 1. Kaplan—Meier Curve for Actuarial Survival after Bone Marrow Transplantation in All Patients.

Gahrton G et al N Engl J Med. 1991 Oct 31;325(18):1267

US Prospective Study S9321

Melphalan 140 + TBI 12 Gy
14/36 patients died of TRM



Early TRM (53%) but long relapse-free survivorship

Allo transplant – OS 39% at 7 years

Allo transplant – 22% PFS @ 7 years vs. 16%

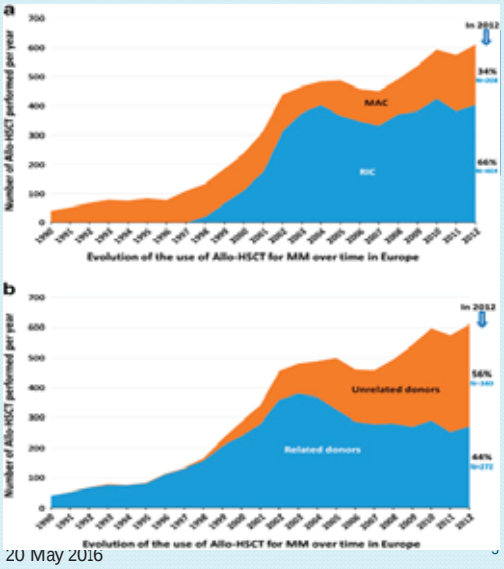
JOURNAL OF CLINICAL ONCOLOGY

Barlogie et al JCO 2006; 24:929

Technology has come a long way since 1991…

1980s

2010s



Sobh M et al Leukemia advance online publication 20 May 2016

Auto → Reduced Intensity Allo Transplant

Newly diagnosed patients

⇩

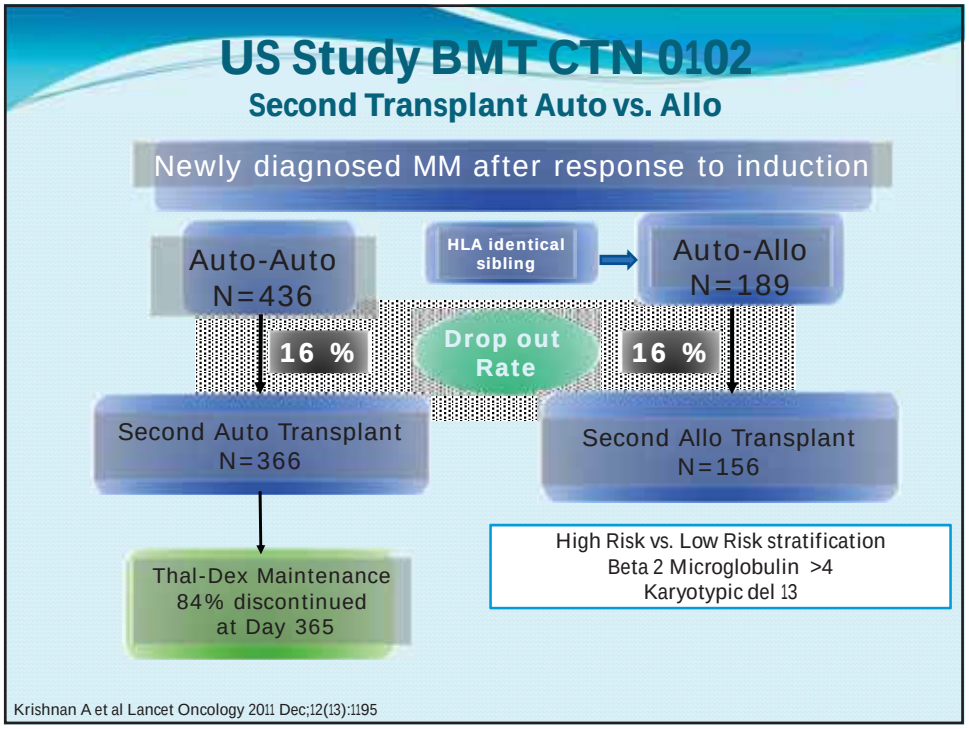
INDUCTION + AUTOLOGOUS TRANSPLANT

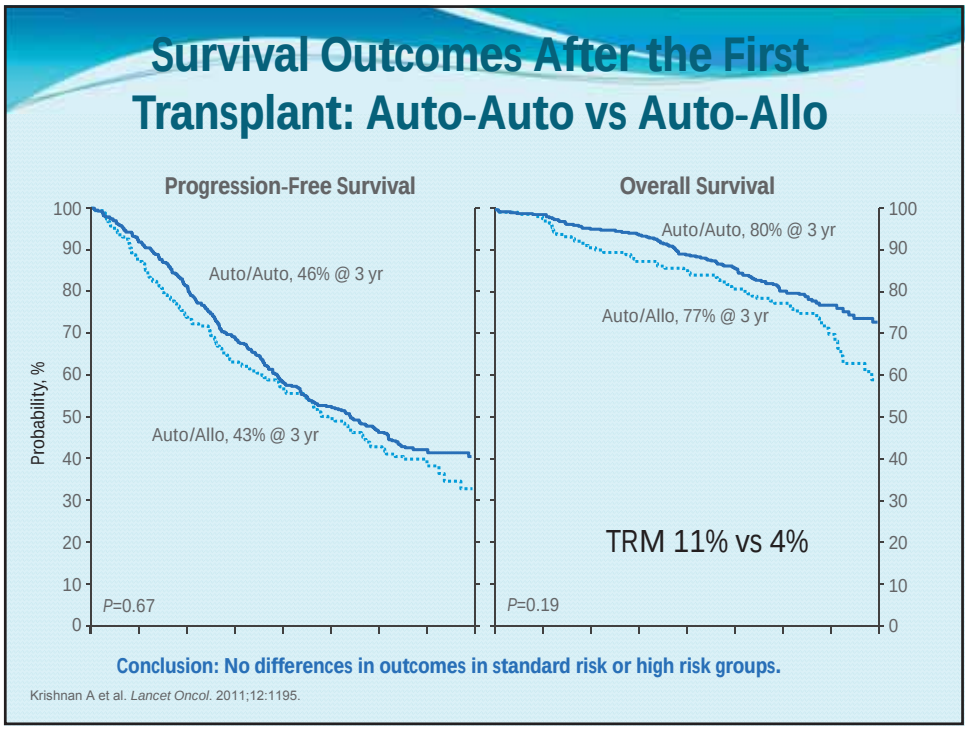
⇩ 3 to 6 mo later

Reduced Intensity Allogeneic Transplant

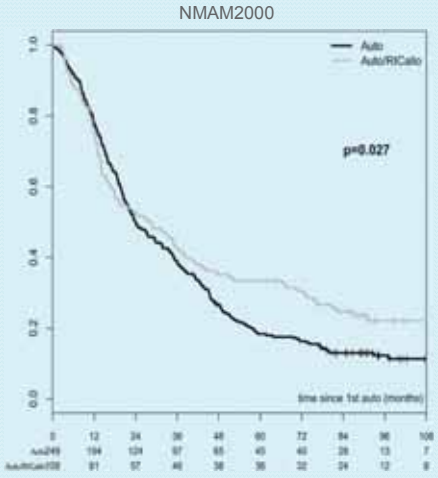
Post Allo transplant maintenance?

- Uncouples myeloablation and immune benefit
- Lower risk of TRM
- Allo as immune therapy


US Study BMT CTN 0102
Second Transplant Auto vs. Allo
Newly diagnosed MM after response to induction
Auto-Auto N=436
HLA identical sibling
Auto-Allo N=189
16 %
Drop out Rate
16 %
Second Auto Transplant N=366
Second Allo Transplant N=156
Thal-Dex Maintenance 84% discontinued at Day 365
High Risk vs. Low Risk stratification
Beta 2 Microglobulin >4
Karyotypic del 13
Krishnan A et al Lancet Oncology 2011 Dec;12(13):1195


Survival Outcomes After the First Transplant: Auto-Auto vs Auto-Allo
Progression-Free Survival
Overall Survival
Probability, %
Auto/Auto, 46% @ 3 yr
Auto/Allo, 43% @ 3 yr
P=0.67
Auto/Auto, 80% @ 3 yr
Auto/Allo, 77% @ 3 yr
TRM 11% vs 4%
P=0.19
Conclusion: No differences in outcomes in standard risk or high risk groups.
Krishnan A et al. Lancet Oncol. 2011;12:1195.

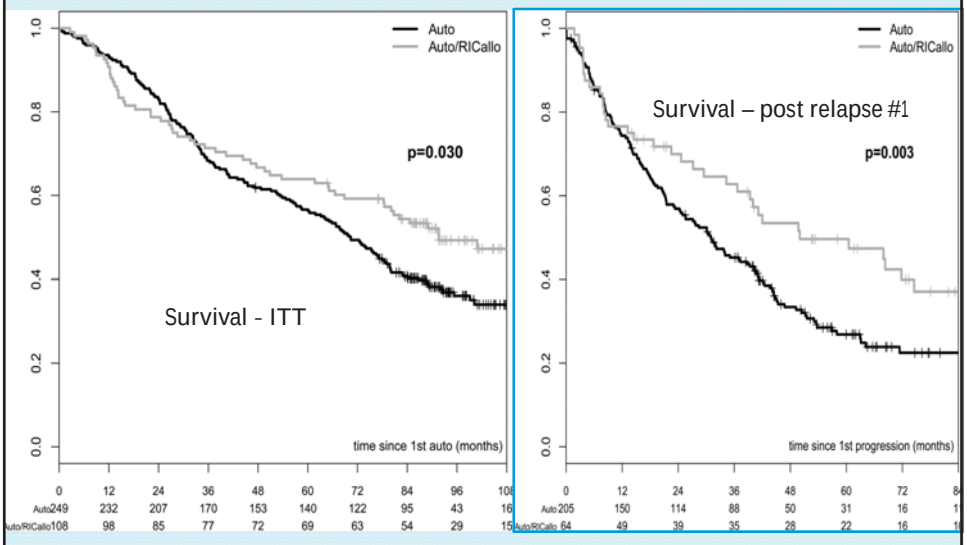
European Bone Marrow Transplant Study



- PFS was significantly better for the auto/allo group:
  - 22% vs 12% at 96 months, *P*=0.027
  - OS was significantly better in the auto/allo group
  - 49% vs 36% at 96 months, *P*=0.030
- Relapse/progression 50% vs 82%, *P*=0.0002
- Non-relapse mortality at 36 months
  - 13% vs 3%, *P*=0.0004

Gahrton G et al. *Blood*. 2013;121:5055.

Long Term – Relapse and Post Relapse Survival - EBMT NMAM 2000



Gahrton G et al. Blood 2013;121:5055-5063

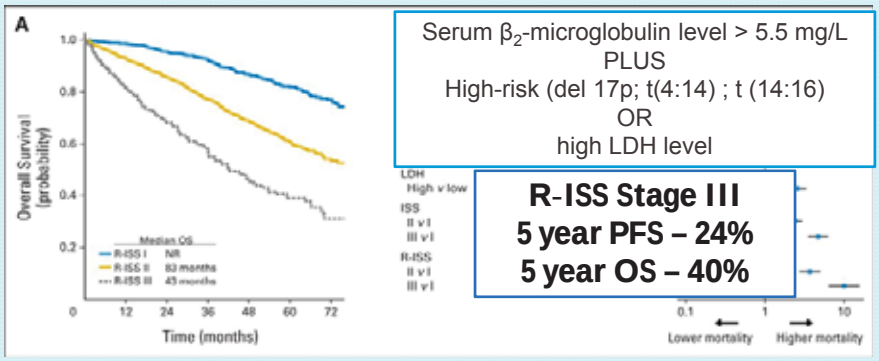
Myeloma HCT Comparison Trials

Randomized Trials Comparing Tandem Auto-HCT Allo-HCT vs. Tandem Auto HCT					
Author	**Population**	**Auto**	**Allo**	**PFS Allo/Auto**	**OS**
Bjorkstrand/Gahrton	<70yrs	Mel200/200	Flu+TBI200cGy 8yr	22% vs. 12%	49% vs. 39%
Garban	Del13 or B2>3mgIL	Mel200/220	Bu Flu ATG	No Diff PFS/OS	
Giaccone/Bruno	<65yrs	Mel200/100-200	TBI 200cGy	35mo/29mo	80/54mo
Krishnan	<70yrs	Mel200/200	TBI 200cGy	No Diff PFS/OS	

TRM 10-16%

Bjorkstrand J. et al. J Clin Oncol 2011;29(22):3016-22; Gahrton G. Blood 2013; 121(25):5055-63; Garban F. Blood 2006;107(9):3474-80. Giaccone L Blood 2011;117(24):6721-7; Krishnan A. Lancet Oncol 2011;13:1195-1203

Survival by R-ISS Stage III



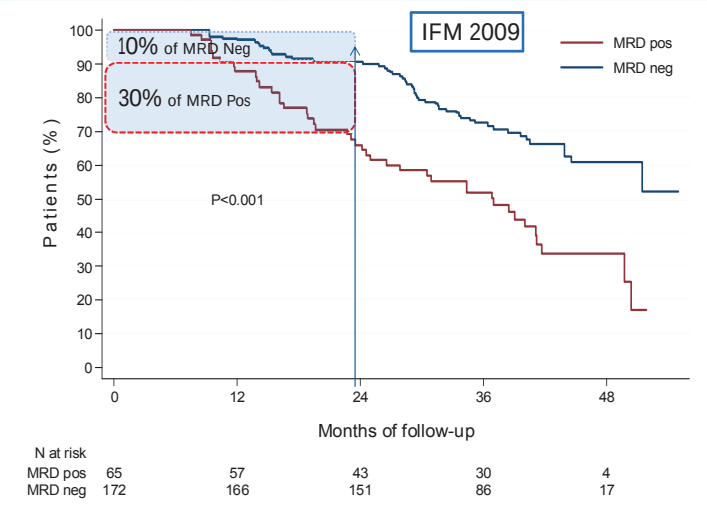
Serum β_2-microglobulin level > 5.5 mg/L
PLUS
High-risk (del 17p; t(4:14) ; t (14:16)
OR
high LDH level

R-ISS Stage III
5 year PFS – 24%
5 year OS – 40%

- Patients in clinical trials 2005-12
- Median age 62 years

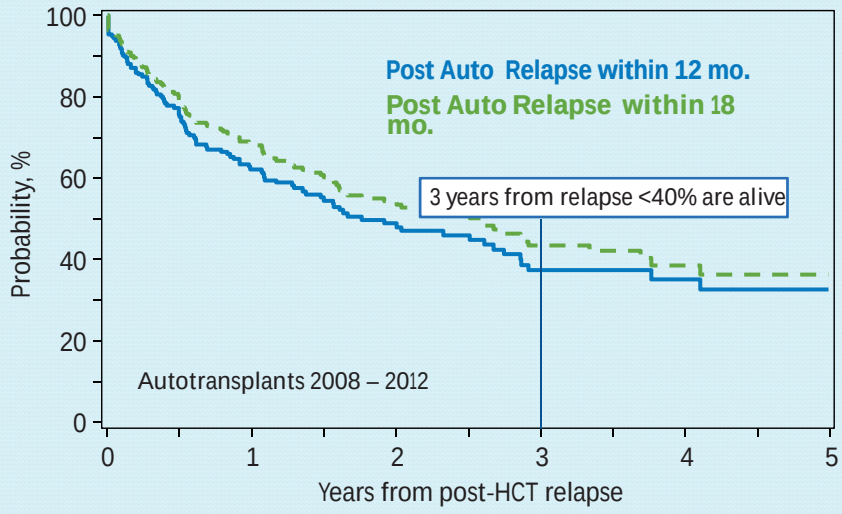
Antonio Palumbo et al. JCO 2015;33:2863-2869

How many pts relapse early?



Attal M et al Blood 2015 126:391

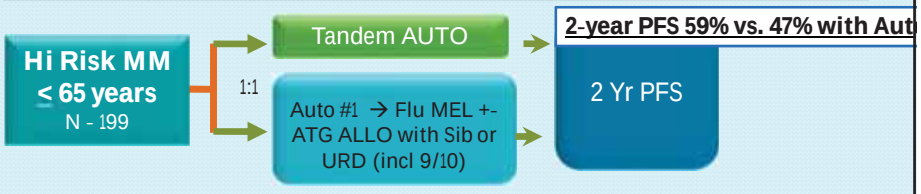
Early Relapse After Auto HCT – is a high risk group



Center for International Blood and Marrow Transplant Research

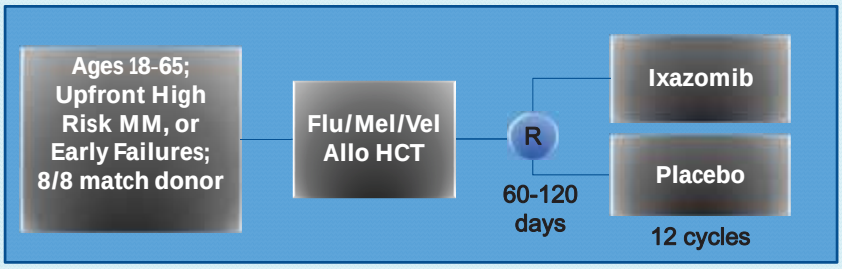
Can upfront Allotransplant "cure" high risk?

Author	N	HIGH RISK DEFINITION	High risk Allo vs. Auto
EBMT NMAM	92	Deletion 13 q	PFS - 8 years 21% vs. 5% OS - 8 years 47% vs. 31%
Knop	199	DEL 13q + DEL 17p	Median PFS NR vs. 6 mo Median OS NR vs. 23 mo



Knop S et al; ASH abstract 2014 Dec #43

BMT CTN 1302: Study Outline



Early failure of initial therapy defined as:

Relapsed pts eligible IF	- **Progression within 18 mo after an AutoHCT, or** - **High risk as above within 18 mo from initiation of therapy (no prior AutoHCT)**	**≥ VGPR**

- Primary end point: 18 months PFS
- Sample size: 138 patients

ASBMT-IMWG Expert Consensus

Allo HCT - appropriate for any eligible patient with

early relapse (< 24 months) after primary therapy that included an autologous HCT

or with high-risk features (ie, cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase)

provided that they responded favorably to salvage therapy before allogeneic HCT.

Whenever possible, in the context of a clinical trial.

Post allo HCT maintenance therapy needs to be further explored.

Giralt et al, BBMT 2015 Dec;21(12):2039

Allotransplant for MM: Summary

- Remains underutilized in the US
- Consider the option
- Patient Selection is key:
  - Young patients with highest risk upfront
  - Early relapse after auto
  - Do not wait till late relapse

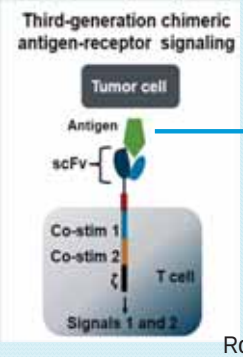
National Coverage Decision in the USA Centers for Medicare /Medicaid Services

- In January 2016, CMS expanded coverage for alloHCT to some beneficiaries with **Multiple Myeloma**, Sickle Cell Disease & Myelofibrosis under Coverage with Evidence Development (CED)
  - Reimbursement provided only if the patient is enrolled in a **CMS-approved clinical trial** designed to evaluate benefit in the Medicare population

19

Adoptive Cellular Therapy

- Donor Lymphocytes for relapse post Allo
- Autologous marrow derived myeloma Infiltrating Lymphocytes
- NK cell therapies (from donors or expanded)



Antigenic targets for CAR – T cells :
BCMA – B cell Maturation Antigen
NY ESO -1 / LAGE
SLAM F7
CD 56
NKG2L
Kappa Light Chain
CD19 / CD38 / CD70 / CD138

Rotolo A et al; Br. Journal of Haem. 2016;173: 350

Chimeric Antigen Receptor (CAR) T Cell Therapy in Multiple Myeloma

CASE PRESENTATION

- 47 year old female diagnosed with IgA kappa multiple myeloma, ISS 2, standard risk in 2006
  - IgA 5596 mg SPEP 4.3 g; 24 h TUP 5.5 g UPEP 3.04 g BJP
  - Bone marrow 90% with normal cytogenetics/FISH
  - Skeletal survey negative
  - Hb 10.4 Ca 10.1 albumin 3.4 B2M 1.7 mg LDH 113

TREATMENT HISTORY

1. Thalidomide/dexamethasone—CDEP—autoPBSCT
   33 month remission
2. Lenalidomide/dexamethaseone x 16 cycles
3. Bortezomib/lenalidomide/dex x 10 cycles
4. Bortezomib/cyclophosphamide/prednisone x 35 cycles
5. Carfilzomib/prednisone x 1 cycle (DC due SOB)
6. Pomalidomide/dex x 1 cycle
7. Isatuximab x 1.5 cycles
8. Carfilzomib/pomalidomide/dex x 6 cycles
9. Pomalidomide/vorinostat/dex x 1 cycle
10. Pomalidomide/carfilzomib/cyclophosphamide/dex x 3 cycles

TREATMENT HISTORY

11. Melphalan/bortezomib—autoPBSCT
    12 mo remission
12. Daratumumab/pomalidomide/pred x 1 cycle
13. Daratumumab/carfilzomib/dex x 2 cycles

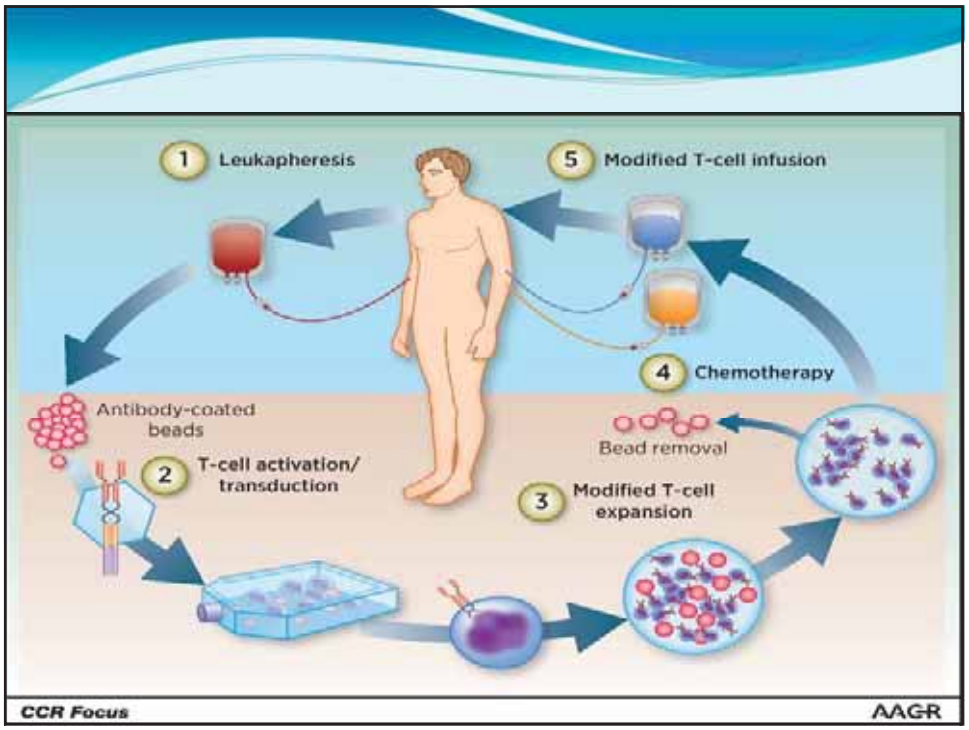
Daratumumab/Metronomic therapy (Mt. Sinai)

14. PACMED (cisplatin/ara-c/cyclophosphamide/melphalan/etoposide/dex with PBSCT) x 1 cycle
15. Bortezomib/nelfinavir/dex
16. CAR T cell

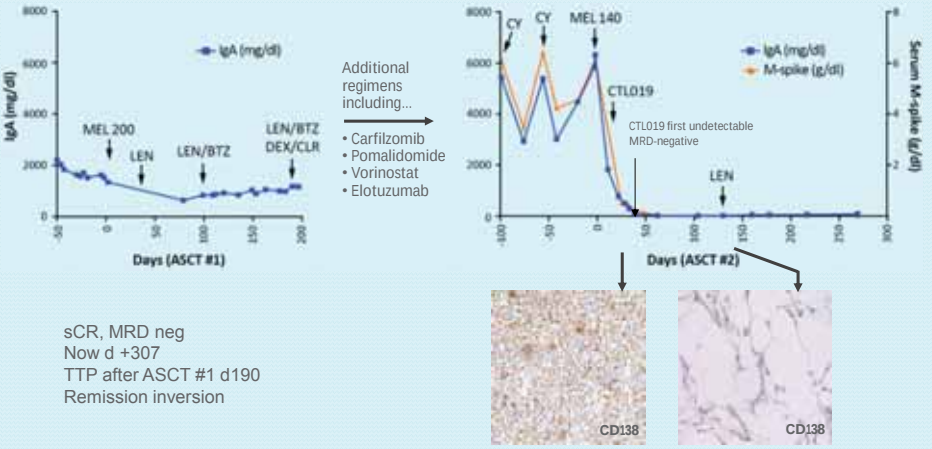
She has not had venetoclax, bendamustine

CLINICAL COURSE OF RELAPSED REFRACTORY POST CAR T CELL THERAPY

Date	3/24/17	6/13/17	7/25/17	10/18/17
Treatment	Pre-CAR T	2 mo post	3 mo post	6 mo post
SPEP				
M Spike 1 g/dl	0.39	0	0	0
M spike 2 g/dl	0.17	0	0	0
Serum Immunofixation	IgA kappa	Negative	Negative	Negative
Kappa Lambda Free Light Chain				
Kappa Free Light Chain mg/l	351.3	, 1	< 1	2.87
Lambda Free Light Chain mg/l	< 1	<1.3	<1.3	5.53
Kappa Lambda Ratio	UTD	UTD	UTD	0.52
Serum Immunoglobulins				
B2M	4.04	1.68	1.87	
IgA mg/dl	128	< 5	< 5	6
IgG mg/dl	681	229	130	109
IgM mg/dl	12	< 5	< 5	21
24 Hour Urine				
Protein	234	480	90	225
M Spike	15	0	0	0
Immunofixation	Free kappa	Negative	Negative	Negative
CMP				
Calcium mg/dl	9.3	8.6	8.5	9.7
Creatinine mg/dl	0.64	0.65	0.79	0.7
Albumin g/dl	4.4	4.4	4.0	4.2
BM	> 50% t(14;16)		Negative/MRD negative	Negative/MRD negative
PET CT	1. Right posterior ilium 4.5 2. Proximal left femur 2.9 3. Proximal right femur 1.9 4. Distal left femur 4.5 5. Distal right femur 4.8 6. Proximal left tibia 1.0	1. Right posterior ilium 4.5 2. Proximal left femur 3.1 3. Proximal right femur 3.1 4. Distal left femur 2.9 5. Distal right femur 3.2 6. Proximal left tibia 1.0	1. Right posterior ilium SUV equals 3.5. 2. Proximal left femur 2.1 3. Proximal right femur 2.4 4. Distal left femur 2.6 5. Distal right femur 2.0	Negative



MM Patient #1: Response to CD19 CAR Therapy



sCR, MRD neg
Now d +307
TTP after ASCT #1 d190
Remission inversion

Garfall AL et al. *N Engl J Med.* 2015;373:1040.

CAR-BCMA T Cells in MM: Study Design

- First-in-human phase 1 trial

Pts with advanced R/R MM; ≥3 prior lines of therapy; normal organ function; clear, uniform BCMA expression on MM cells (N=12)

→ **Cyclophosphamide 300 mg/m²**
Fludarabine 30 mg/m²
QD for 3 days

→ **CAR-BCMA T cells***
Single infusion

*Dose escalation of CAR+ T cells/kg
0.3×10^6
1.0×10^6
3.0×10^6
9.0×10^6

- CAR-BCMA expression determined by flow cytometry

Ali SA et al. *Blood.* 2015; 126: Abstract LBA-1.

CAR-BCMA T Cells in MM: Response

Pt	Myeloma Type	CAR-BCMA Dose (T cells/kg)	Response	Response Duration, Wks
1	κ light chain only	0.3×10^6	PR	2
2	IgA λ	0.3×10^6	SD	6
3	κ light chain only	0.3×10^6	SD	6
4	κ light chain only	1.0×10^6	SD	12
5	IgG κ	1.0×10^6	SD	4
6	IgG λ	1.0×10^6	SD	2
7	IgG λ	3.0×10^6	SD	7
8	κ light chain only	3.0×10^6	VGPR	8
9	κ light chain only	3.0×10^6	SD	16
10	IgA λ	9.0×10^6	sCR	12+
11	IgG λ	9.0×10^6	PR	6+
12	IgA λ	3.0×10^6	SD	2

Ali SA et al. *Blood*. 2015; 126: Abstract LBA-1.

Comparison of CART-BCMA trials (pre-ASCO)

	NCI	Penn (cohort 1)	Bluebird
Sites	Single	Single	Multi-center
scFv	Murine	Human	Murine
Vector	Gamma-retroviral	Lentiviral	Lentiviral
Domains	CD3/CD28	CD3/41BB	CD3/41BB
BCMA+ required	Yes (IHC) (52/85 (62%) +)	No	Yes (??)
Dosing	0.3 – 9x10⁶/kg 1 day	5 x 10⁸ 3 days	0.5 – 4.5 x10⁸ 1 day
Conditioning	Flu/Cy	-	Flu/Cy
Med # priors	7*	9	6
Responses (Longest)	4/12 (4.5+ mos)	4/9 (12+ mos)	7/9 (8+ mos)

*includes XRT

Ali et al, Blood 2016; Cohen et al, ASH 2016, #1147; Lin et al, EORTC-NCI-AACR Symposium 2016

Phase 1 bb2121 (anti-BCMA CAR T cells) in rel/ref MM

- CD3/41BB 2nd gen CAR
- Cytoxan/Fludarabine conditioning
- Requires >50% BCMA+ MM cells by IHC
- N=35 screened/ 24 collected / 21 treated

Demographics and Clinical Characteristics

Parameter	Statistic	N=21 Dosed Patients
Age years	Median (range)	58 (37-74)
Male gender	n (%)	13 (62%)
Time since diagnosis (years)	Median (range)	5 (1-16)
ECOG = 0	n (%)	10 (48%)
ISS Stage I II III	n (%)	6 (29%) 11 (52%) 4 (19%)
High-risk cytogenetics (del17p, t(4;14), t(14;16), 1q, del 13)	N\n (%)	14 (67%)

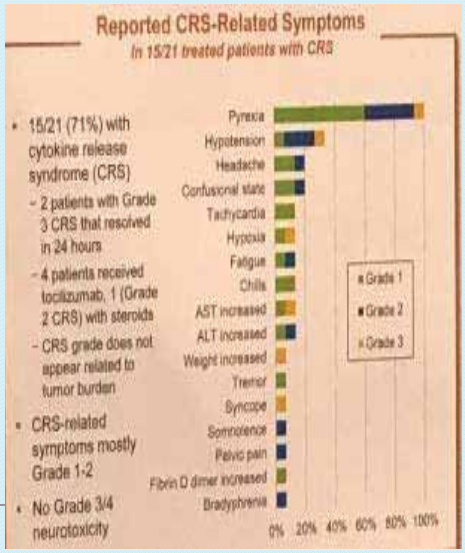
ECOG: Eastern Cooperative Oncology Group Performance Score
ISS: International Staging System
SCT: stem cell transplant

MM Treatment History

Parameter	Statistic	N=21 Dosed Patients
Prior lines of therapy	Median (range)	7 (3-14)
Prior autologous SCT	n (%)	21 (100%)
Prior therapies	**Exposed**	**Refractory**
Bortezomib	100%	67%
Carfilzomib	91%	57%
Lenalidomide	100%	86%
Pomalidomide	91%	71%
Daratumumab	71%	48%
Cumulative Exposure	**Exposed**	**Refractory**
Bort / Len	100%	67%
Bort / Len / Car	91%	48%
Bort / Len / Pom	91%	57%
Bort / Len / Car / Pom	86%	43%
Bort / Len / Car / Pom / Dara	71%	29%

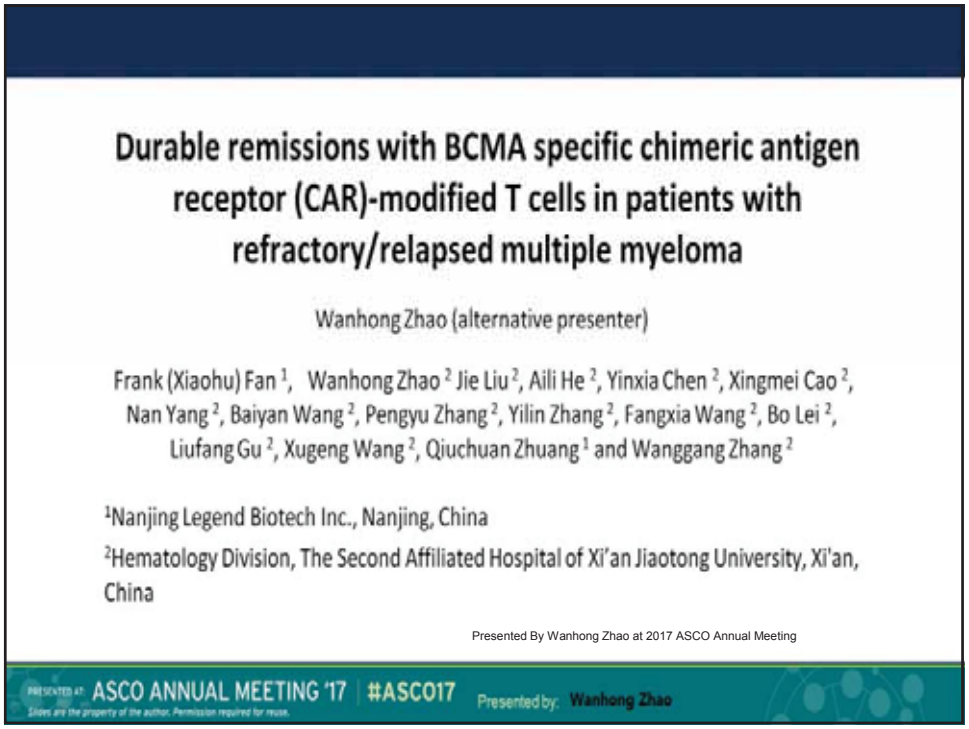
Berdeja et al ASCO 2017 Abstract 3010

Phase 1 bb2121 (anti-BCMA CAR T cells) in rel/ref MM



- 18/18 (100%) responses at higher doses, 27% CR

Berdeja et al ASCO 2017 Abstract 3010



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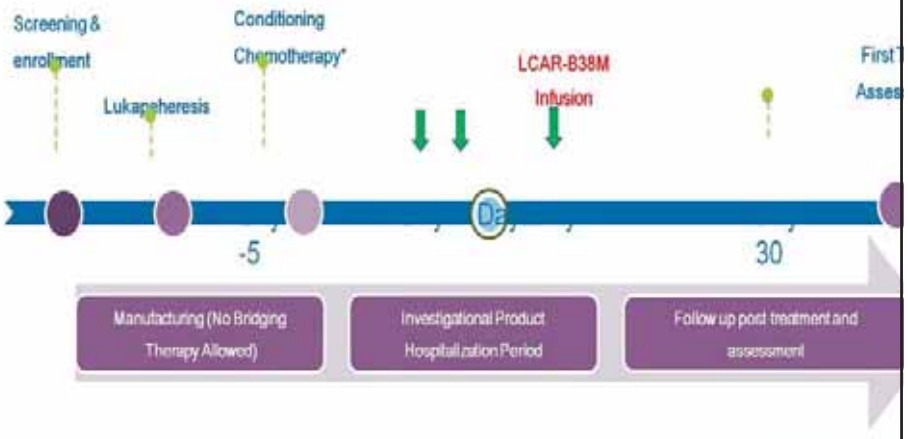
Legend LCAR-B38M Treatment Scheme

Clinicaltrials.gov/NCT03090659

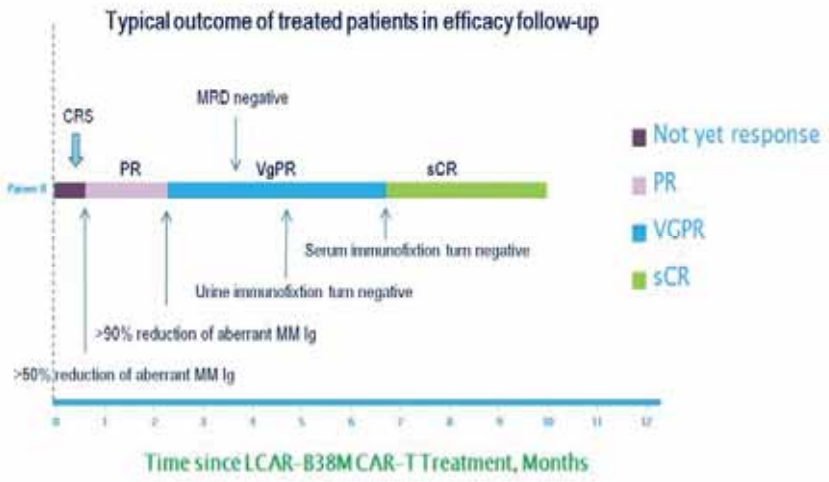


Summary of Patient Characteristics

Clinicaltrials.gov/NCT03090659

Characteristic	Cohort
r/r MM patient, total number enrolled	35
Median age (range), years	55 (43-72)
Male, n(%)	19(54)
Durie-Salmon stage, n(%) I/IIA/IIIA/IIIB	1(3)/4(11)/ 25 (71)/ 5 (14)
Number of prior lines of therapy, n(%) 3/4/≥5	14 (40)/ 16 (46)/ 5 (14)
Refractory subgroup, n(%) Refractory to ≥ 2nd line therapy	35(100)

Efficacy follow-up of LCAR-B38M CAR-T cells



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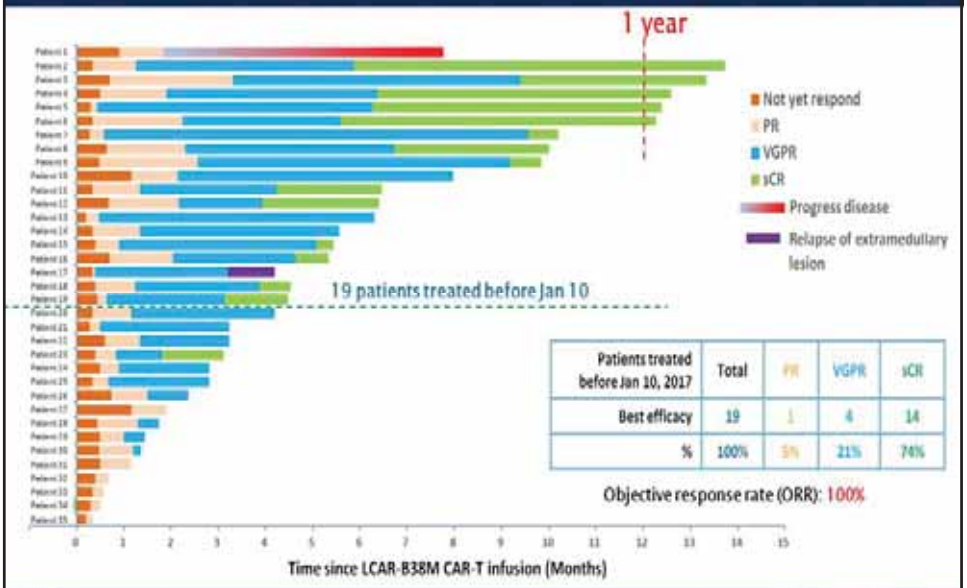
Efficacy follow-up of LCAR-B38M CAR-T cells



Patients treated before Jan 10, 2017	Total	PR	VGPR	sCR
Best efficacy	19	1	4	14
%	100%	5%	21%	74%

Objective response rate (ORR): 100%

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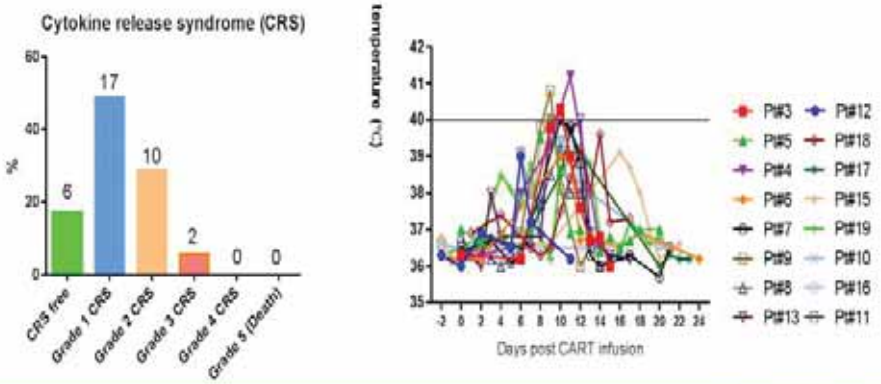
Safety: Major adverse events is cytokine release syndrome (CRS)

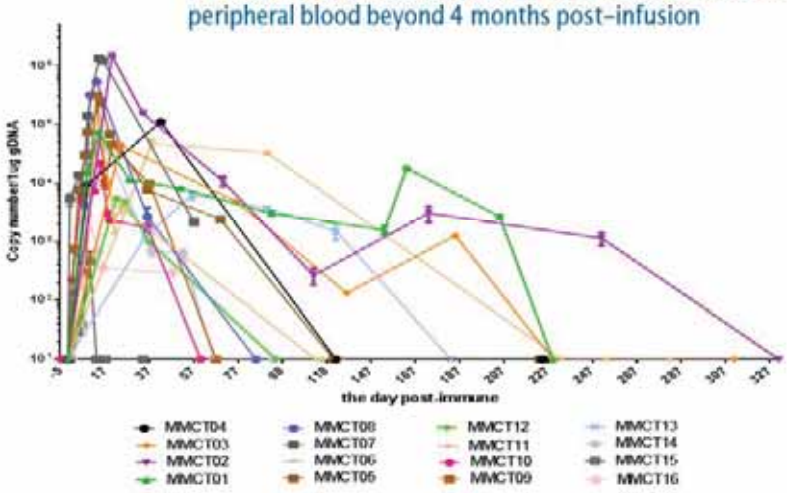
Adverse Event, n (%)	Patients (N=35)
Grade ≥3 adverse event	2 (5.7%)
Serious adverse event	0 (0)
Fatal events excluding disease progression	0 (0)



ASCO ANNUAL MEETING '17 | #ASCO17

Persistence of infused LCAR-B38M cells

For majority of patients, LCAR-B38M cells are undetectable in peripheral blood beyond 4 months post-infusion



ASCO ANNUAL MEETING '17 | #ASCO17 Presented by: Wanhong Zhao

Conclusions

- LCAR-B38M CAR-T technology exert quick and reproducible therapeutic effects in refractory and relapsed multiple myeloma patients.
- >12 months follow-up of early patients shows durable and stringent complete remission which raises hopes of cure.
- LCAR-B38M technology not only demonstrate outstanding efficacy, but also suggest a great safety profile.
- US clinical trial is under way and the technology will be fully validated under "American (FDA) standard".

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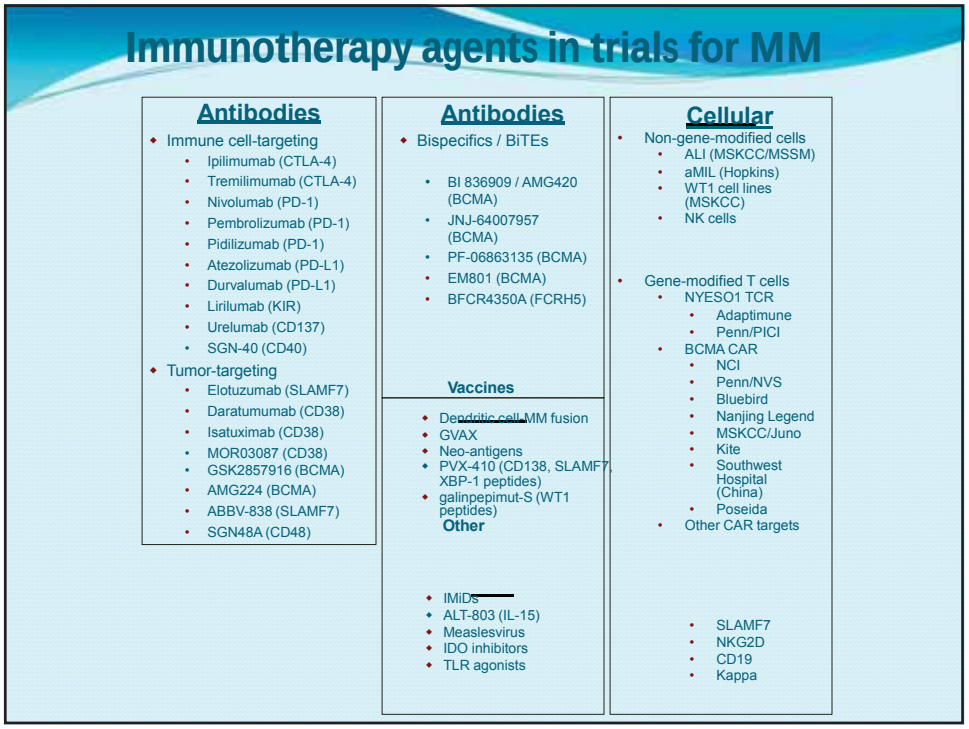
Myeloma CAR T Cell Therapy

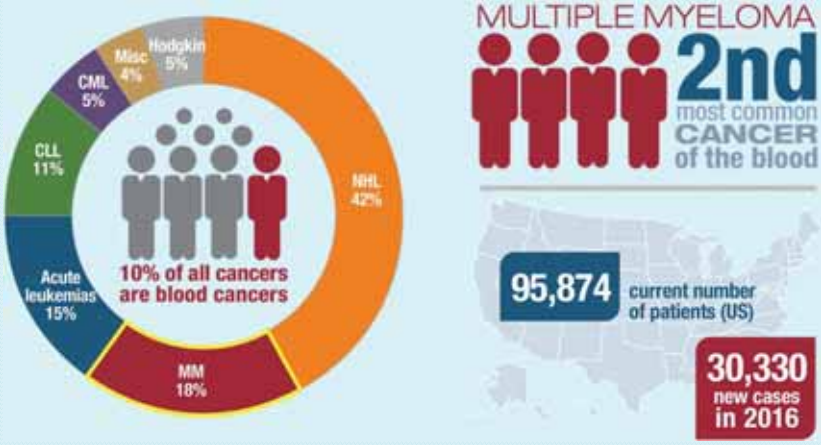
- Multiple promising targets:
  - CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1, BCMA
- Functional CAR T cells can be generated from MM patients
- CAR T and NK cells have in vitro and in vivo activity against MM
- Clinical trials under way
  - Anecdotal prolonged responses but no robust efficacy data available yet
- Many questions remain about CAR design:
  - Optimal co-stimulatory domains
  - Optimal vector
  - Optimal dose and schedule
  - Need for chemotherapy
  - Perhaps "cocktails" of multiple cars or cars + chemotherapy will be required for best outcomes

Garfall AL et al *N Engl J Med*. 2015;373:1040.



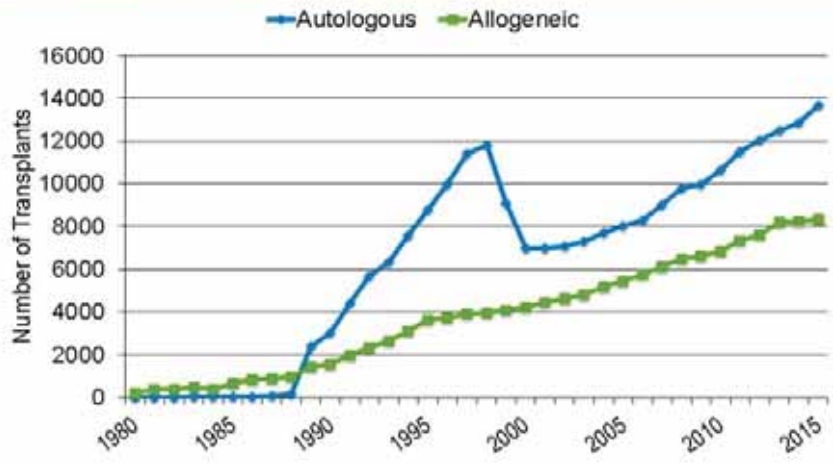
TRANSPLANT UTILIZATION

Multiple Myeloma Today



Available at: http://www.lls.org/#/resourcecenter/freeeducationmaterials/generalcancer/facts. Accessed April 6, 2015.
Siegel RL et al. *CA Cancer J Clin*. 2016;66:7.

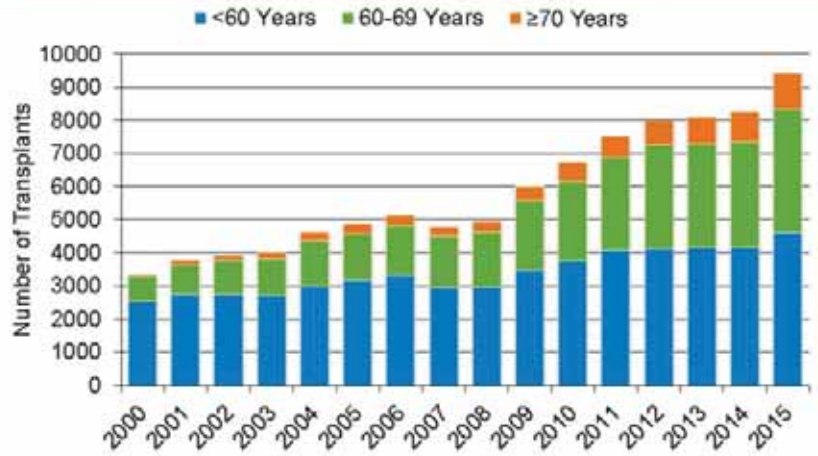
Annual Number of HCT Recipients in the US by Transplant Type



CIBMTR

D'Souza A, Zhu X. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2016. Available at: http://www.cibmtr.org 3

Trends in Autologous HCT by Recipient Age^

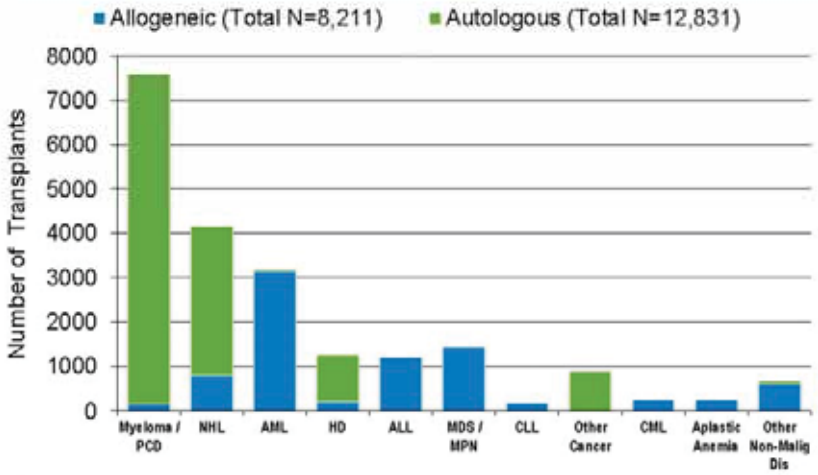


CIBMTR

^Transplants for NHL, Hodgkin Disease and Multiple Myeloma

11

Indications for Hematopoietic Cell Transplant in the US, 2014



CIBMTR

13

Trends in the Upfront Utilization of Autologous Hematopoietic Cell Transplantation in Multiple Myeloma by Age

Patient Characteristics	1995-1999	2000-2004	2005-2010
Median age at transplant (range)	54 years (27-73)	57 years (22-80)	57 years (22-80)
< 50 years	32%	21%	21%
50-64 years	60%	59%	59%
≥ 65 years	7%	20%	20%

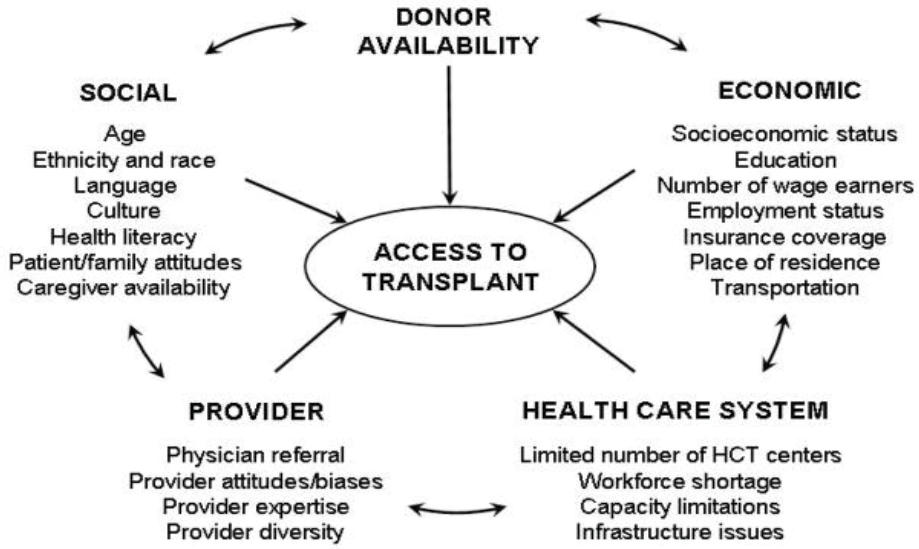
Costa et al Biol Blood Marrow Transplant. 2013; 19:1615-1624

Hematopoietic Stem Cell Transplantation Utilization Rates in the United States

Year	Hispanic	Non-Hispanic Black	Non-Hispanic White	Overall
2008	8.6	12.2	22.6	19.1
2009	9.8	13.2	26.6	21.9
2010	11.9	15.7	29.4	24.7
2011	11.4	18.2	34	27.8
2012	14.2	19	35.4	29.5
2013	16.9	20.5	37.8	30.8

CIBMTR statistics

Barriers to Transplantation Access in Multiple Myeloma



Majhail et al Biol Blood Marrow Transplant. 2010 ;16:1070-5

Recommendations for Addressing Barriers to Transplantation

Barriers	Recommendations
Delayed HCT referral	Improved education for referring HCPs
Lack of cells mobilized	Target minorities to become donors
Financial burden	Make search assistance funds available Advocate for patients for insurance appeals
Lack of social support and caregiver issues	Engage in advocacy efforts
Poor acces to health care, including geographic barriers	Research disparities in healthcare access Target at-risk populations for outreach
Barriers in language, culture, literacy	Use culturally sensitive patient education materials

Murphy et al Biol Blood Marrow Transplant. 2010; 16: 147-156

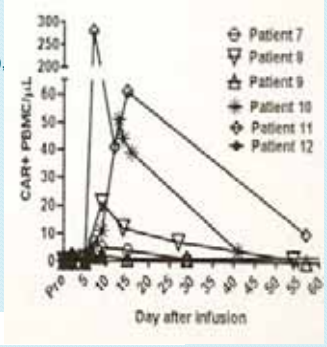
NCI BCMA-specific CAR in rel/ref MM

Cyclophosphamide 300 mg/m²
Fludarabine 30 mg/m²
QD for 3 days

→ CAR-BCMA T cells*
Single infusion

*Dose escalation of CAR+ T cells/kg 0.3 x 10^6
1.0 x 10^6
3.0 x 10^6
9.0 x 10^6

- **Responses in 4/12 pts.**
  - PR (2wks), VGPR (8wks), sCR (17wks), VGPR (26+ wks)
- **Associated with CART expansion**
- **Severe CRS and delirium**



Ali et al, ASH 2015, LBA #1; Blood 2016.

Asymptomatic Multiple Myeloma

To Treat or Not To Treat?

Ashraf Badros
Professor of Medicine
University of Maryland
Director of Myeloma Service

No Disclosures

What to do?

- We have seen 6 patients that met the criteria for the diagnosis of MM. But have not had a progressive course.
- Although no chemotherapy was given, their condition has remained stable for 5 or more years.
- We designate these cases "smoldering multiple myeloma".

Kyle R & Grieipp P. N Engl J Med 1980; 302:1347-1349

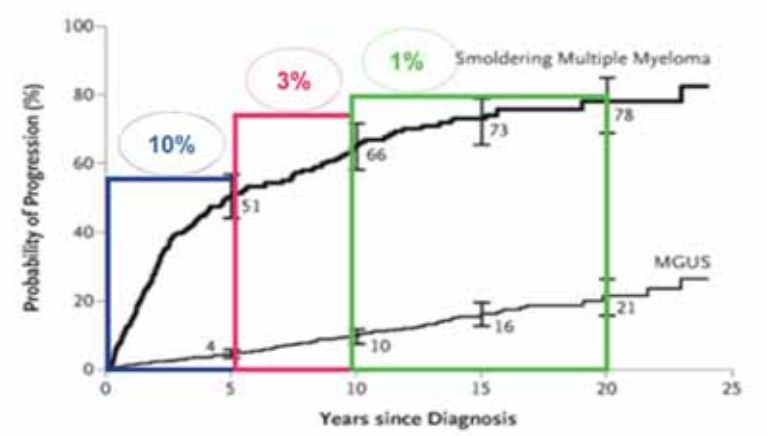
SMM

- We wish to call attention to this group because SMM should be recognized and treatment withheld.

- Although chemotherapy may prevent the complications of active myeloma,
- Therapy may lead to leukopenia, thrombocytopenia, refractory anemia, and acute leukemia.
- Furthermore, unnecessary chemotherapy causes unnecessary expense, and it is a source of concern to the patient.

Kyle R & Grieipp P. N Engl J Med 1980; 302:1347-1349

Natural History of MGUS & SMM

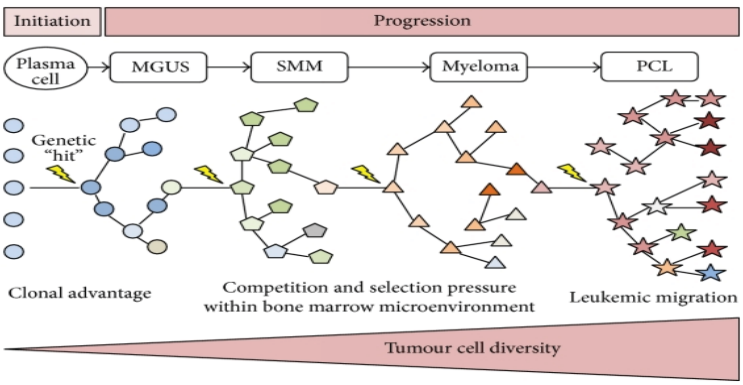


Kyle RA et al. N Engl J Med 2007;356:2582-2590

MGUS	SMM	MM
<3 g M spike & <10% PC	≥3 g M spike Or ≥10% PC	**Clonal PC + M spike +CRAB**
Asymptomatic		
Incidence		
• **3%-8%**	• **not defined**	• **6.6 cases per 100K**
• **Age/sex/race**	• **0.9 per 100K**	• **30,280 cases per yr**
	• **4 100 cases per yr**	

Angela Dispenzieri et al. Blood 2013;122:4172-4181
Ravindran A. et al. Blood cancer J. 2016 Oct; 6(10): e486
Irene M. Ghobrial, and Ola Landgren Blood 2014;124:3380-3388

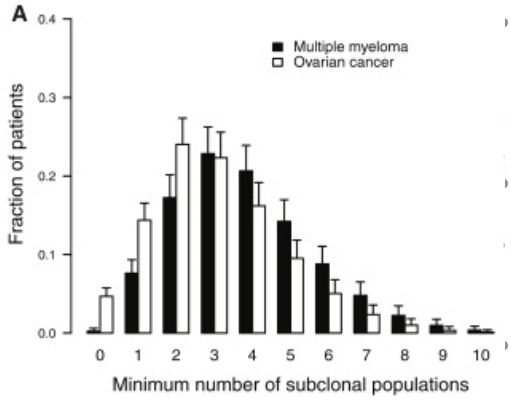
Initiation & Progression of MM



- Expansion of malignant clones already present in the MUGS stage
- Progression
  - Molecular events that lead to disease progression
  - Immune surveillance

Adopted from Morgan GJ, et al. Nat Rev Cancer. 2012;12:335

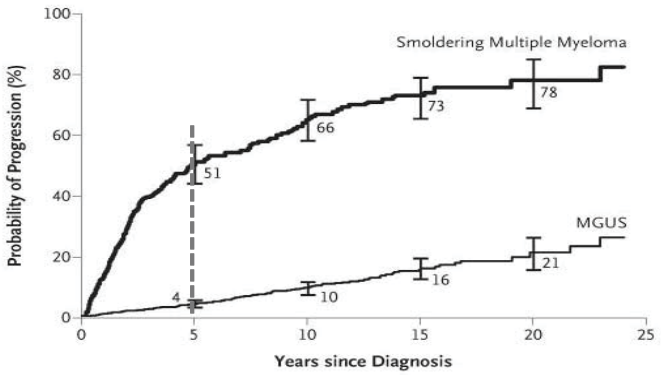
Clonal Heterogeneity in MM



- Genome sequencing of paired PC/normal samples from 203 MM pts
- Every patient has several parallel myeloma subclones at diagnosis
- Sub-clones respond differently to a given drug

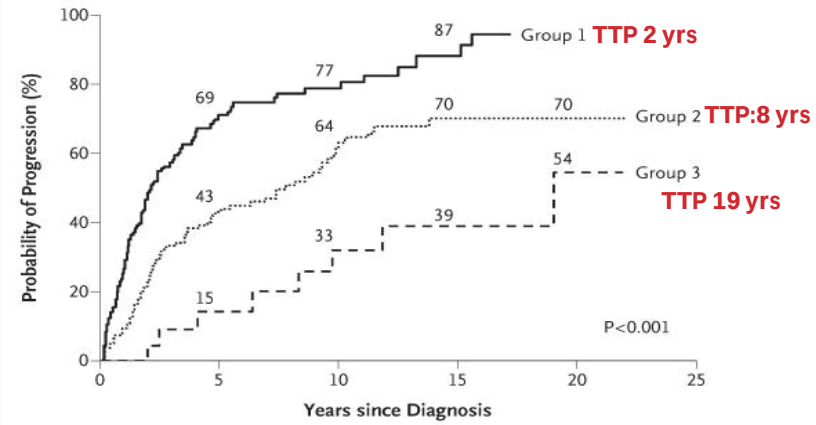
Lohr J, et al . Cancer Cell. 2014 Jan 13;25(1):91-101

SMM ---



Risk of Progression ---Mayo Model

By BMPC & M spike; n=276

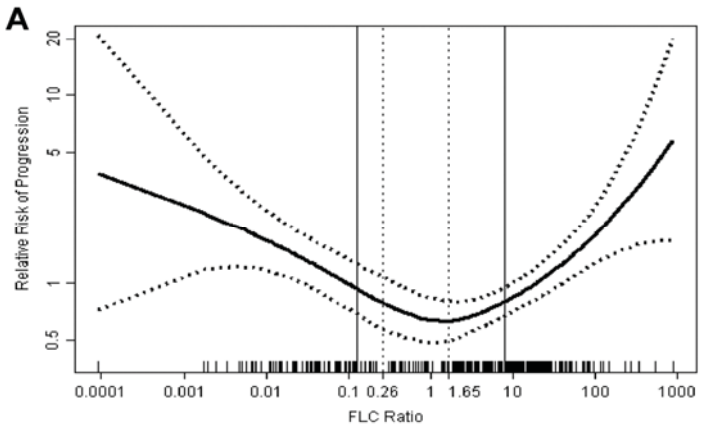


1. **PC > 10%, M spike > 3 g**
2. **PC > 10%, M spike < 3 g**
3. **PC < 10%, M spike > 3 g**

Kyle R, et al. N Engl J Med 2007; 356:2582-2590

Risk of Progression

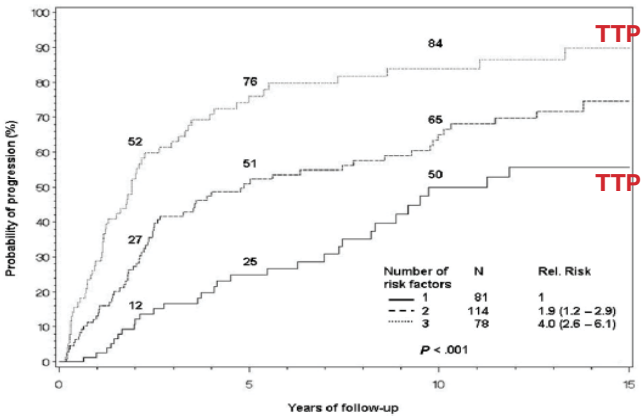
By Free Serum Light Chain (sFLC)



Angela Dispenzieri et al. Blood 2008;111:785-789

Risk of Progression

By BM PC, M spike, sFLC



TTP 1.9 yrs

TTP: 5.1 yrs

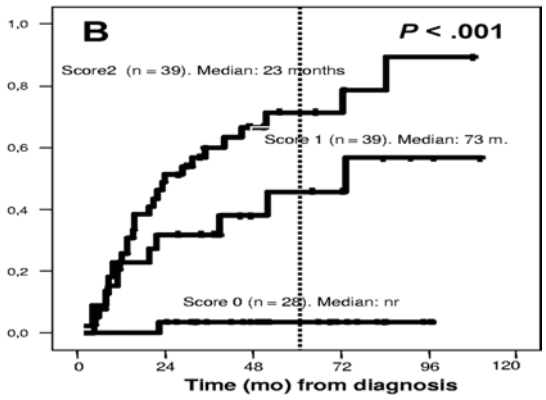
TTP 10 yrs

1.BMPCs ≥10%
2. M-protein ≥3 g/dL serum
3. FLC ratio <0.125 or >8

Angela Dispenzieri et al. Blood 2008;111:785-789

Risk of Progression---Spanish Model

by aberrant PC & Immunoparesis

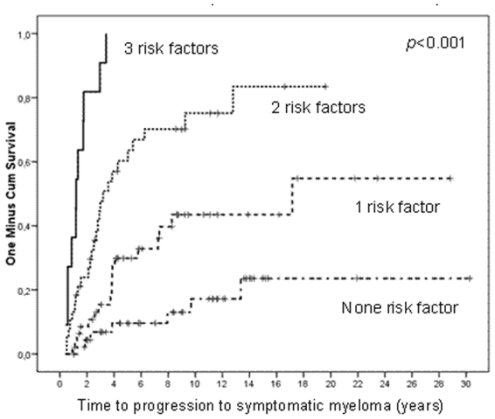


Score system:

- % of immunophenotypically aberrant PC/Normal: <95% = 0; ≥95% =1
- Immunoparesis: yes=1 or no=0

Ernesto Pérez-Persona et al. Blood 2007;110:2586-2592

Risk of Progression
by M spike change, Immunoparesis, BMPC>20%



- *At progression, anemia (52%); lytic lesions (40%); renal insufficiency (5.8%)*
- *The median survival after progression was 5 years (95% CI 3.8 to 6.2).*

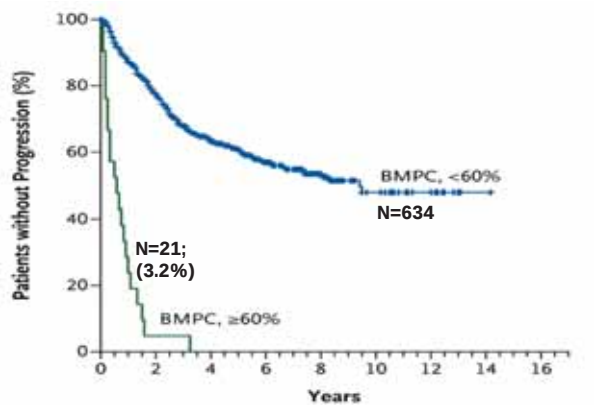
Fernandez de Larrea C, et al. Blood 2014 124:3363

SMM --- Risk of Progression

- Ultra high risk…Pending MM
  - TTP <2 years
- High risk …
  - 25% risk of progression per year
- Low risk …
  - 1-5% risk of progression per year (? MGUS)

Bone Marrow Plasmacytosis ≥ 60%

3-8% of SMM Pts, 90% progression in 2 yrs

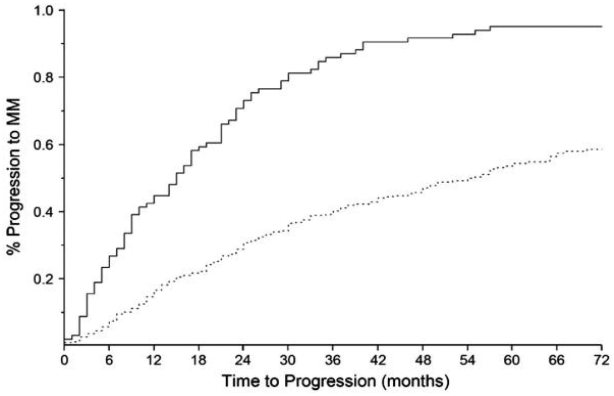


Median TTP was 7months

Rajkumar SV et al. N Engl J Med 2011; 365:474-475
Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53

Free-Light Chain (FLC) ratio ≥100

15% of SMM Pts, 80% progression in 2 yrs

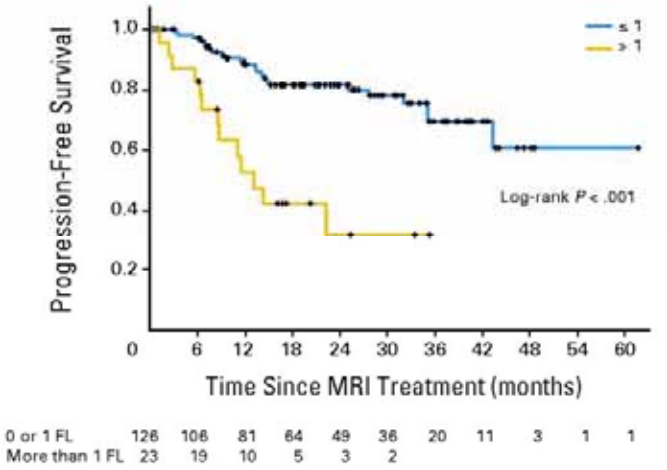


Median TTP was 15 m FLC ≥100 vs 55 m FLC ≤ 100

Larson JT, et al. Leukemia 2013: 27, (4): 941-946.
Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53

MRI with >1 focal lesion

15% of SMM pts, 70% progression in 2 yrs

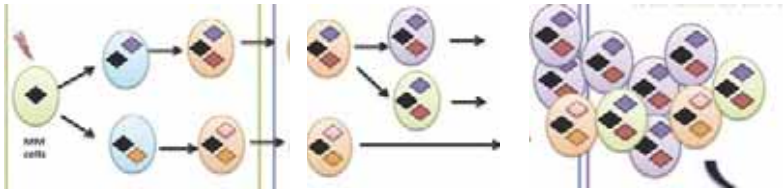


Median TTP 13 months

Hillengass J, et al. J Clin Oncol 2010;28:1606-1610
Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53

~~Ultra-high risk SMM~~--- MM

- 10-15% of SMM will be upstaged by
  - **BM PC ≥ 60%**
  - **Serum FLC ≥ 100**
  - **1 focal lesion ---MRI**
- **Risk of over treatment**
  - **20-30%**
- **Stage migration**
  - **Impact on clinical trials**

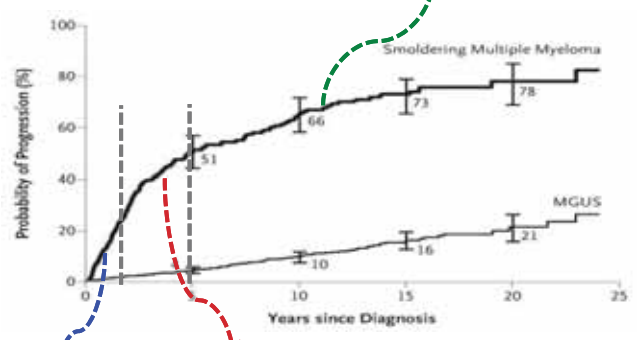


MGUS	SMM	MM
<3 g M spike & <10% PC	≥3 g M spike Or ≥10-60% PC	**Clonal PC + M spike** **+CRAB** + Myeloma defining events • **BM PC ≥ 60%** • **Serum FLC ≥ 100** • **> 1 focal lesion ---MRI**
Asymptomatic		

Angela Dispenzieri et al. Blood 2013;122:4172-4181
Ravindran A. et al. Blood cancer J. 2016 Oct; 6(10): e486
Irene M. Ghobrial, and Ola Landgren Blood 2014;124:3380-3388

What is left?

Low risk SMM ..1-5% risk of progression/yr



High risk SMM 25% risk of progression/yr

Redefined as MM

Definitions Of High Risk SMM

~50% risk of progression within 2 years

- Clonal BMPC ≥ 10% < 60% and any of the following:
  - Serum M protein ≥ 30 g/L
  - IgA isotype
  - Immunoparesis with decrease of 2 involved Ig isotype
  - Serum FLC ratio ≥ 8 but < 100
  - Increase in M protein by ≥ 25% in 6 months
  - Clonal BMPCs 50-60%
  - Abnormal BMPC phenotype & decrease ≥ 1 uninvolved Ig
  - t(4:14) or del 17p, or 1 q gain
  - Circulating PC
  - MRI with diffuse abnormality
  - PET/CT with focal uptake with no osteolytic lesions.

Rajkumar V, et al. Blood. 2015 May 14; 125(20): 3069–3075.

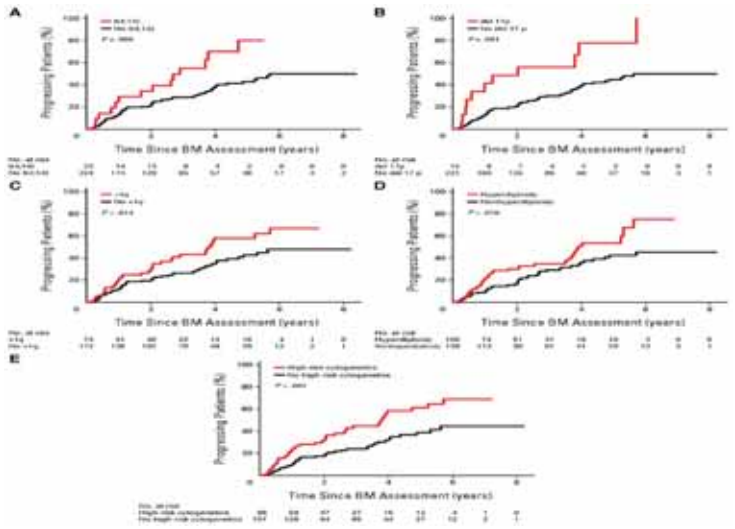
High-risk SMM

Risk (n=248)	TTP (Yrs)	P
Cytogenetics high vs low	3.7 vs N/A	.001
FISH		
+1q21 vs no gain of 1q21	3.9 vs N/A	.02
del(17p13) vs no del(17p13)	2.0 vs 5.6	.001
t(4;14) vs no t(4;14)	2.9 vs 5.7	.003
HD vs NHD	3.9 vs N/A	.016
Tumor mass low vs high	1.2 vs 9.03	< .001
aPC > 95% vs < 95%	1.2 vs 9.03	< .001
FLC ratio abnormal vs nl	2.7 vs N/A	. 001
Immunoparesis yes vs no	4.1 vs N/A	.003

Neben K, et al J Clin Oncol 2015, 31:4325-4332.
Inhye E. etal. J Clin Oncol **2015,** 33, 115-123.

High Risk SMM

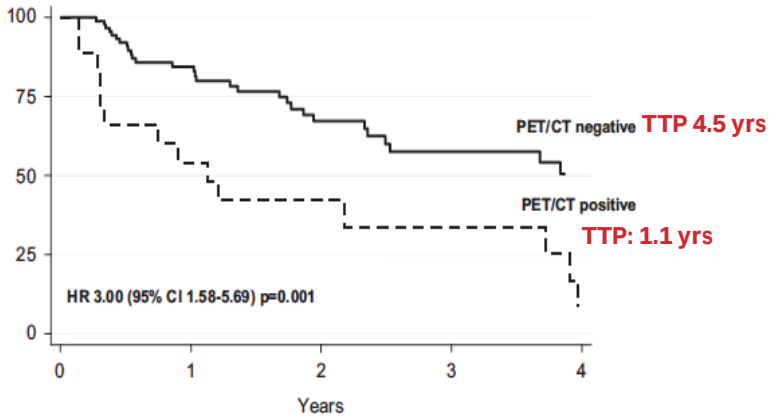
FISH



Neben K, et al J Clin Oncol 2015, 31:4325-4332.

PET/CT Focal Lesions

Predict Progression of SMM

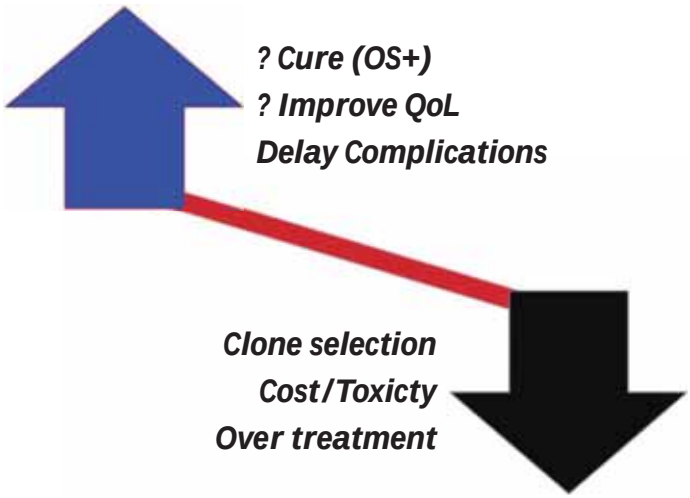


The probability of progression within 2 yrs was 58% for positive versus 33% for negative patients.

Zamagni et al, Leukemia (2016) 30, 417–422

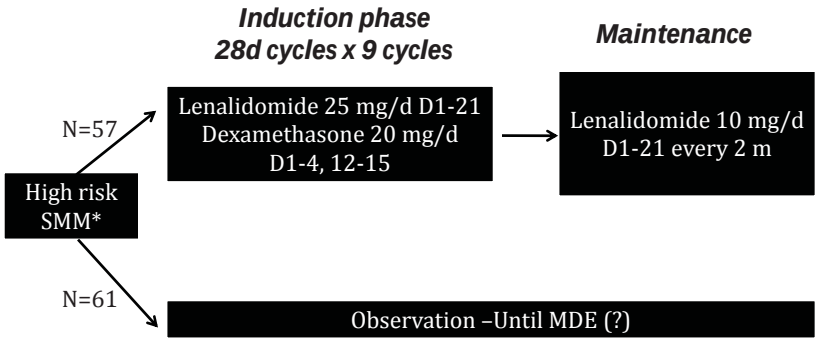
To Treat Or Not To Treat

We have better therapy



Lenalidomide & Dexamethasone

High-Risk SMM



High risk SMM defined as

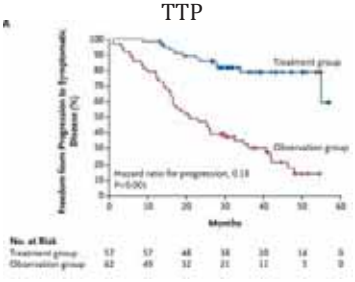
- *Both BMPC≥10% AND M-protein≥ 3 gm/dL*
- *Or one of the above plus aPC >95% and immunoparesis*

Mateos M et al. N Engl J Med 2013;369:438-447.

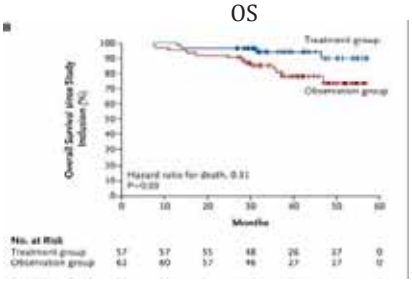
Lenalidomide & Dexamethasone
Outcomes

N=119; median follow up 32 months (range: 14-96)

TTP



OS



Median TTP 21 months vs not recahed
53 pts progressed (bone, renal events)

Mateos M et al. N Engl J Med 2013;369:438-447.

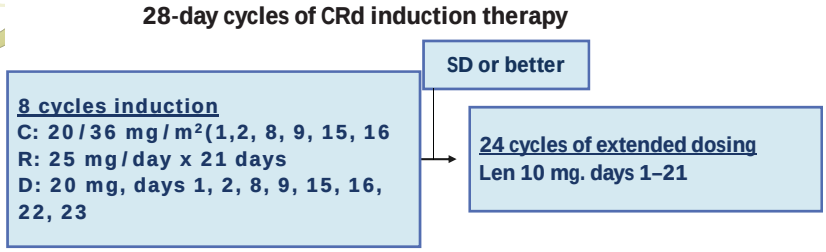
Lenalidomide & Dexamethasone
Adverse Events

	Grade 1	Grade 2	Grade 3
			number of patients (percent)
Induction phase			
Hematologic event			
Neutropenia	3 (5)	8 (13)	3 (5)
Thrombocytopenia	6 (10)	1 (2)	1 (2)
Anemia	11 (18)	4 (6)	1 (2)
Nonhematologic event			
Infection†	19 (31)	6 (10)	4 (6)
Rash	12 (19)	6 (10)	2 (3)
Asthenia	6 (10)	5 (8)	4 (6)
Constipation	4 (6)	6 (10)	0
Diarrhea	9 (15)	4 (6)	1 (2)
Deep-vein thrombosis	1 (2)	2 (3)	0

Mateos M et al. N Engl J Med 2013;369:438-447.

Carfilzomib/lenalidomide/Dex

Pilot trial (n=12) SMM



- **Endpoints**
  - **Primary:** ≥VGPR after 8 cycles of CRd
  - **Secondary:** PFS & safety
- **Results:**
  - All patients (100%) achieved nCR/CR after 8 cycles of CRd
  - After 8 cycles or achievement of a CR, 10 (83%) tested negative for MRD by next-generation sequencing (NGS)

Landgren O et al. *Proc ASH* 2014;Abstract 4746.w

Carfilzomib/lenalidomide/Dex

Adverse Events

	All events	Grade 3 or 4
Lymphopenia	100%	42%
Leukopenia	92%	8%
Thrombocytopenia	92%	25%
Electrolyte disturbances	92%	17%
Elevated liver function tests	92%	17%
Rash/pruritus	75%	25%
Anemia	67%	17%
Diarrhea	67%	17%
Neutropenia	42%	17%
Increased serum creatinine	17%	17%

Elotuzumab, Lenalidomide & Dex

High-Risk SMM

Primary Objective:

- To determine % of high risk SMM who are progression free at 2 years

Secondary Objectives:

- To assess ORR, TTP, DOR, OS
- To assess safety of the combination
- To determine minimal residual disease (MRD)

Elotuzumab, Lenalidomide & Dex

Patients Characteristics

	Total (n = 50)	
Characteristics	n	%
Median age, years (range)	62 (29–79)	
Male sex	18	36.0
Race		
White	41	82.0
Black	7	14.0
Heavy-chain type		
IgG	33	66.0
IgA	15	30.0
BM plasma (%)	20.0 (10.0–60.0)	BM plasma (%)
Cytogenetics (n=45)		
del 17p; p 53 mutation	5, 3	11, 6
t(4:14), t(14:16)	6, 3	13, 6
1q21 amp	11	24
t(11:14)	3	6
High Risk	20	44

Elotuzumab, Lenalidomide & Dex

Adverse Events > 10%

Toxicity category	Toxicity type	n (%)
Skin reactions	Rash maculo-papular	5 (10.0)
Hematological conditions	Anemia	6 (12.0)
	Neutropenia	10 (20.0)
	Thrombocytopenia	6 (12.0)
	Lymphopenia	11 (22.0)
	Leucopenia	5 (10.0)
Metabolism and laboratory conditions	Hyperglycemia	11 (22.0)
	Hypophosphatemia	17 (34.0)
Psychiatric disorders	Insomnia	5 (10.0)
Infections and infestations	Pulmonary infection	15 (30.0)
Cardiovascular disorders	Hypertension	5 (10.0)
Respiratory disorders	Dyspnea	5 (10.0)
Gastrointestinal disorders	Constipation	8 (16.0)
	Diarrhea	7 (14.0)

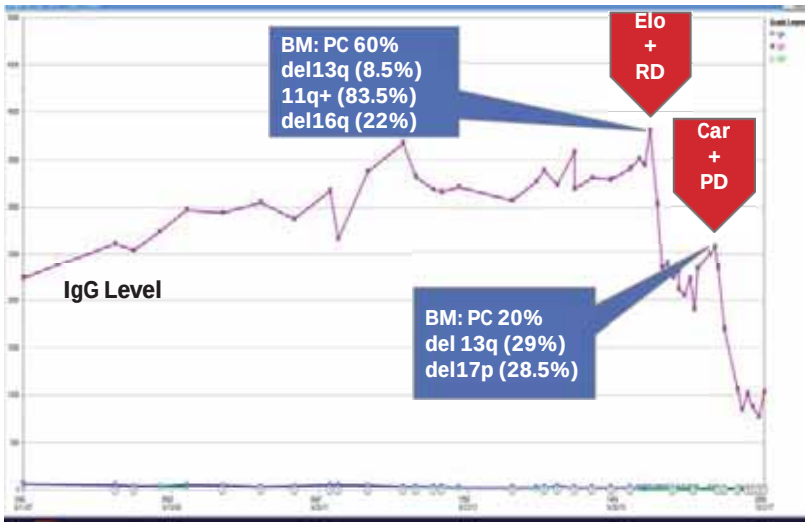
Elotuzumab, Lenalidomide & Dex

Response

Best response	n	%
CR	3	6
VGPR	13	26
PR	24	49
MR	7	14
SD	2	4
Clinical response benefit (≧MR)	47	100
Response rate (≧PR)	40	82

Elotuzumab, Lenalidomide & Dex

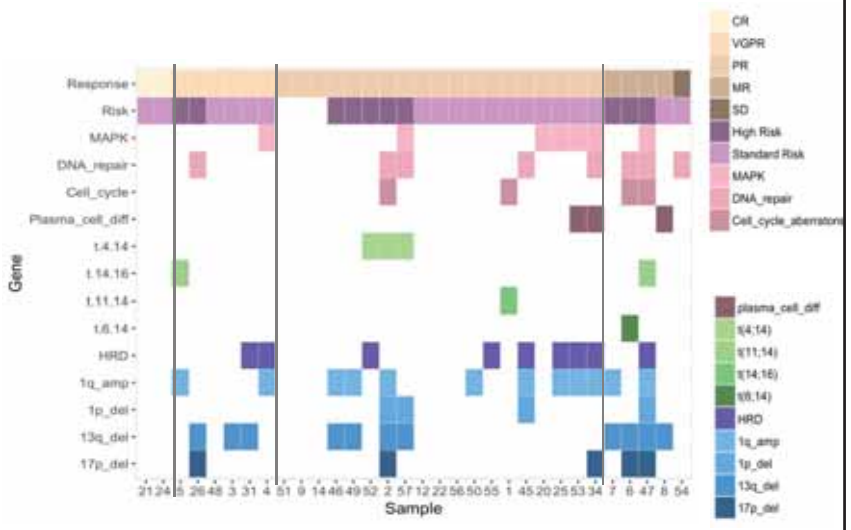
One patient progress



Bhatnagar V, Badros A. Leuk Lymphoma. 2014 Feb;55(2):464-6.

Whole Genome Sequencing

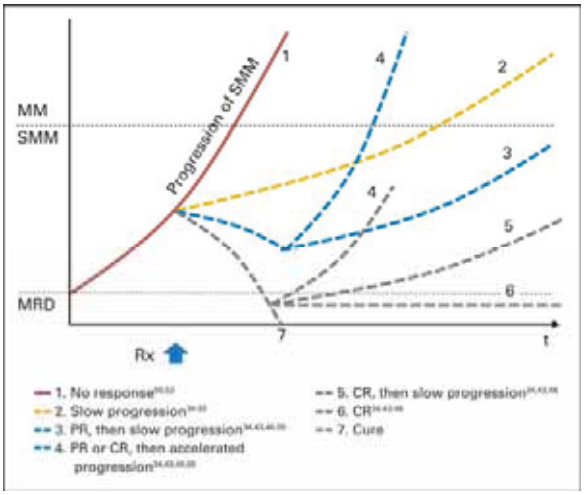
correlation with response and risk status



On Going Trials

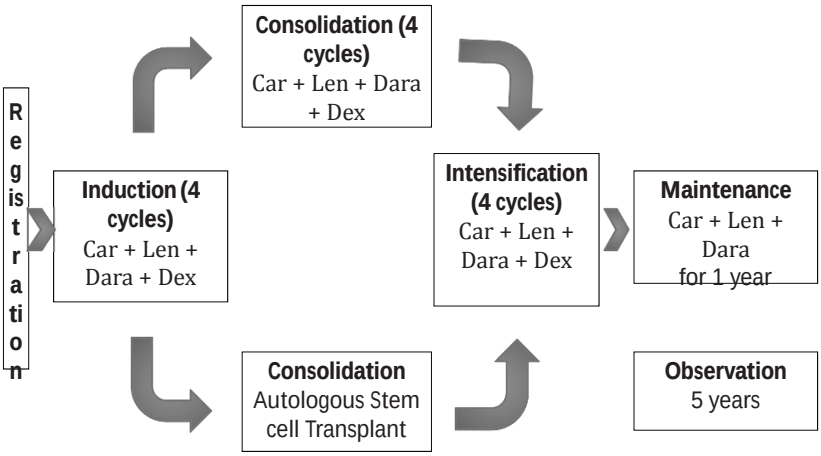
- 51 Trials on Clinicaltrials.gov
  - MM (IMiDs, PI, antibodies, SCT, etc…)
  - PD-1 inh
  - Statins
  - Ibrutinib
  - Anti-IL-6, IL-1 antibodies
  - Anti-KIR
  - Green tea extract

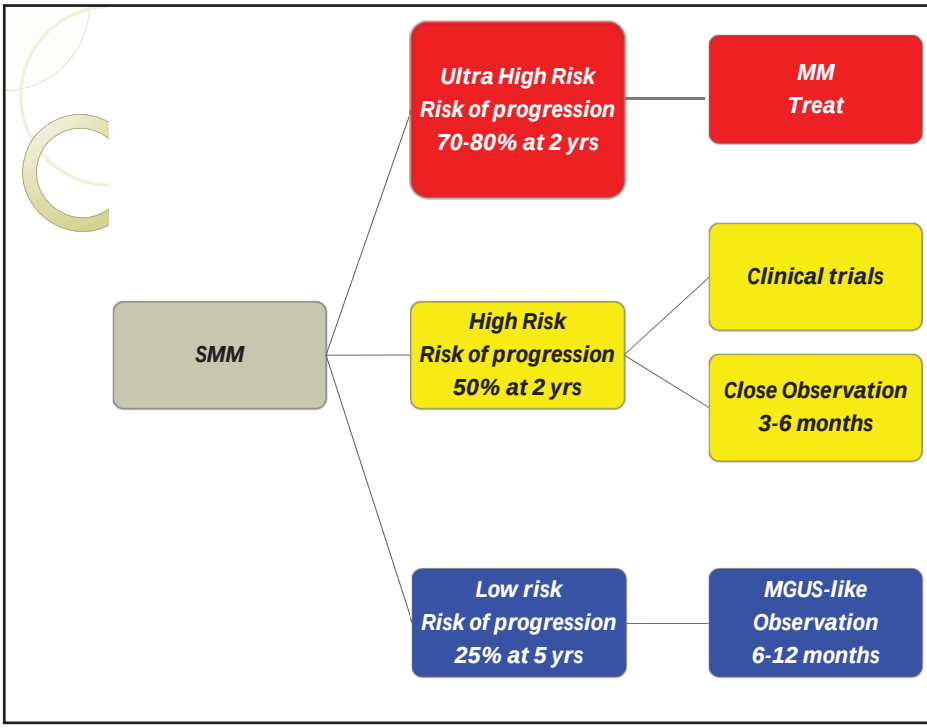
Trajectories Of Treatment In SMM



Inhye E. Ahn; Sham Mailankody; Neha Korde; Ola Landgren; *JCO* **2015,** 33, 115-123.

Aggressive Smoldering Curative Approach Evaluating Novel Therapies (ASCENT)





Comments

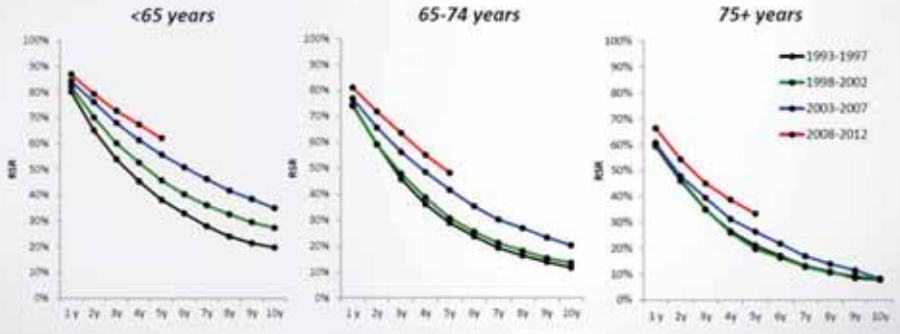
- What is the goal of therapy in SMM?
- Can early therapy provide cure?
- How about clonal selection?
- Cost and side effects ---

Treatment of Multiple Myeloma Complications

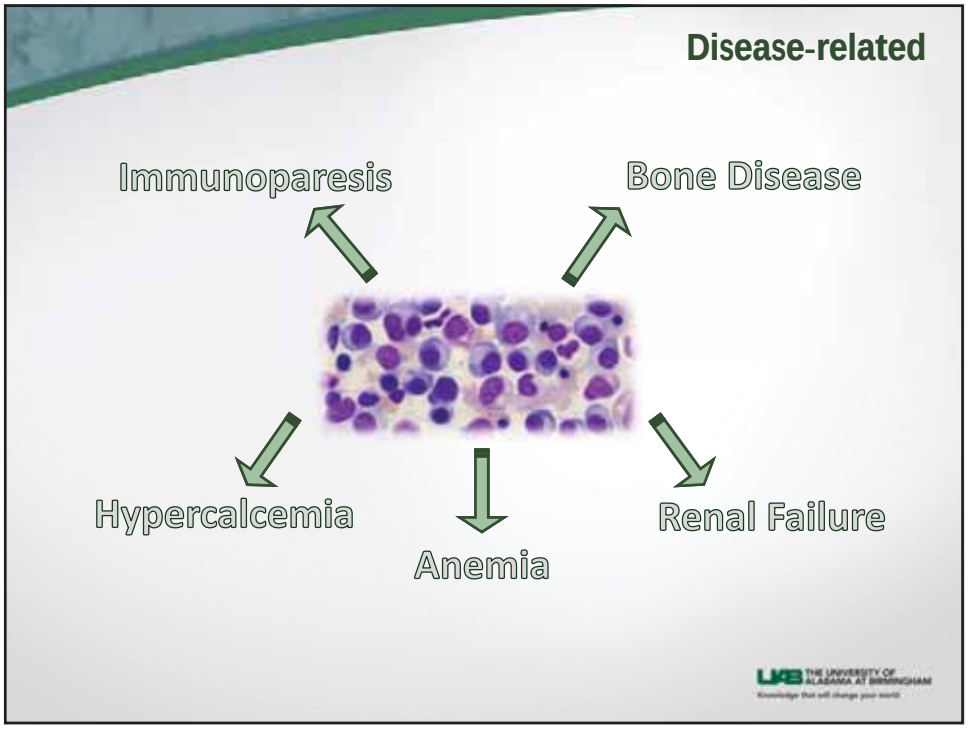
Luciano J Costa, MD, PhD
University of Alabama at Birmingham
Comprehensive Cancer Center

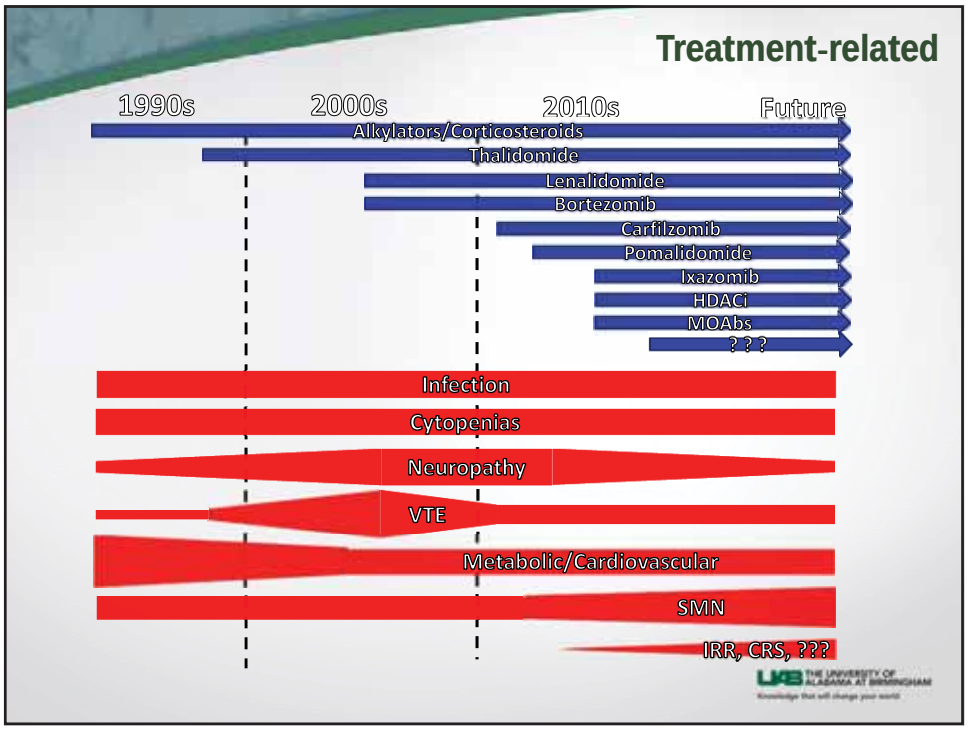
More therapy ⇒ Longer Survival ⇒ More @ risk of complications

Relative Survival of MM patients in US



Costa L et al. Blood Advances 2017, 1:282


Disease-related
Immunoparesis
Bone Disease
Hypercalcemia
Anemia
Renal Failure


Treatment-related
1990s
2000s
2010s
Future
Alkylators/Corticosteroids
Thalidomide
Lenalidomide
Bortezomib
Carfilzomib
Pomalidomide
Ixazomib
HDACi
MOAbs
???
Infection
Cytopenias
Neuropathy
VTE
Metabolic/Cardiovascular
SMN
IRR, CRS, ???

Key Principles

- Prevention always better than treatment.
- Consider comorbidities and residual toxicity when choosing next line of therapy.
- Clinical trials
  - Stick to protocol for structured parameters for dose omission, reduction or discontinuation
- Off trial
  - Monitor patients at least once per cycle for toxicities
  - Be aggressive with early management of complications
  - Balance efficacy vs. toxicity when deciding on dose and schedule.

Clinical Vignette

M.M., 72 yo man with HTN, Gleason 4 localized prostate cancer, osteoarthritis, is brought to primary care MD with 3 months worsening back pain, weight loss, 3 days somnolence, confused this AM.

Meds: HCTZ, multivitamins

Physical exam: dehydrated, BP 104 x 63, HR 108, confused.

Labs show Hgb 11.2 g/dL, Ca 13.7, Cr 2.8 (baseline 1.1), Total protein 11.3

Hypercalcemia

- Manifestation of disease, not therapy
- Initial presentation, relapse, or end-of-life.
- Often accompanied by bone disease and renal failure
- Golden principle of managing hypercalcemia of malignancy: If you can't treat the underlying malignancy, don't bother.
- Management
  - Hydration.
  - Prompt initiation of MM therapy/Corticosteroids
  - IV Biphosphonates as soon as safe (hydrated, renal function improved).
  - Consider denosumab if biphosphonate not feasible.

Clinical Vignette (cont)

M.M. is admitted to hospital, HCTZ discontinued, receives 2 L of normal saline overnight and one time dose of dexamethasone 40 mg, next morning he looks better.

Physical exam: Hydrated, BP 137 x 63, HR 92.

Labs show Hgb 9.9, Ca 10.9, Cr 2.3 (baseline 1.1), SPEP serum M spike 3.7 (IgG Kappa), FKLC 3574 mg/L, FLLC 78 mg/L, B2M 9.3.
Skeletal survey show multiple lytic lesions in pelvis, calvarium, ribs, lumbar spine, but no fracture.

What to do next?

Renal failure

- Deferred- **Nelson Leung** told you all you need to know.

(**Time is kidney**- Quick and aggressive disease control)

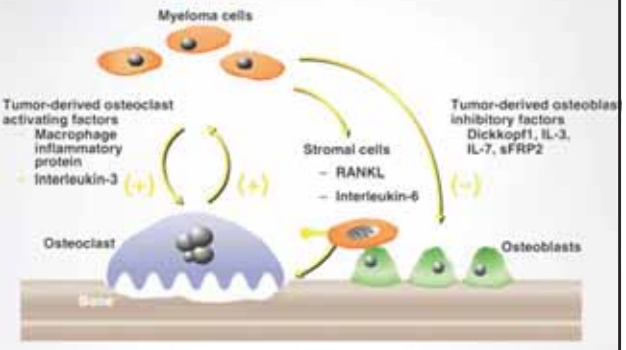
Clinical Vignette (cont)

M.M. has a bone marrow aspiration and biopsy, pathologist confirms with you two hours latter that is "full of plasma cells".

You start M.M. on Bortezomib (1.3 mg/m2 SQ days 1,4,8,11), Dexamethasone (40 mg on days 1,8,15)

What about his bone disease?

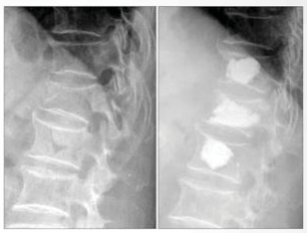
MM Bone Disease



- Present in the majority of patients at some point in the natural history of the disease.
- Major morbidity factor, contributes to mortality.
- Most important intervention is control of underlying disease.

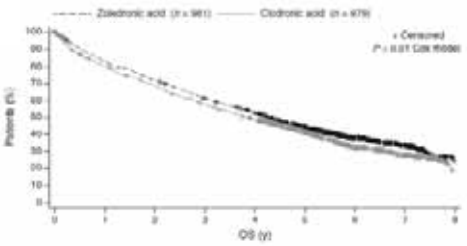
MM Bone Disease

- Surgery
  - Fracture
  - Unstable spine
  - Cord compression
  - Unknown diagnosis
- Balloon Kyphoplasty
  - Compression fractures
  - Acute pain relief
- Radiation
  - Pain control
  - Disease mostly localized
  - Palliative setting, systemic control not expected

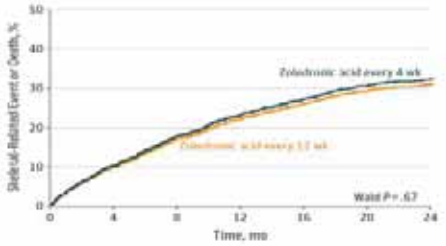


Look at the big picture. Don't delay systemic therapy !

MM Bone Disease



Morgan et al. Clin Cancer Res 19: 6030, 2013



Himelstein et al. JAMA 317: 48, 2017

- Management
  - Zoledronate is preferred agent.
  - Dental care. Discontinue if ONJ suspected.
  - Limit therapy to 2 years for patients in remission.
  - q12 weeks not inferior to q4weeks.
  - Calcium + VitD

Clinical Vignette (cont)

On day 4 of therapy M.M. feels better, pain is improved, he is walking the hospital halls and eating full meals and wants to go home.

Labs show: Hgb 9.7, Ca 9.3, Cr 1.5

You administer his day 4 bortezomib, IV zoledronate and discharge the patient to continue therapy as outpatient.

What are the discharge prescriptions?

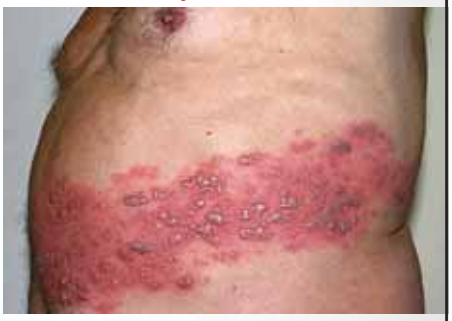
Infection

- 7 fold increase in risk of bacterial infection, 10 fold viral infection.
- Predisposition factors
  - Hypogammaglobinemia
  - Corticosteroid use.
  - Neutropenia
  - "Functional impairment".
- Immunize
  - Seasonal influenza
  - Pneumococcal (PCV13, 8 weeks latter PPSV23), Haemophilus influenzae
  - Other appropriate non-live vaccine

Infection- Prevention

- **Universal** prophylaxis for Zoster!
- Consider prophylaxis for invasive pneumococcal infection
  - PenVK/ doxycycline/ quinolone
  - Hypogammaglobulenemia
  - Elderly
  - Pulmonary disease
  - Prior infection

Don't let this be your reminder!



Clinical Vignette (cont)

M.M. Receives *Pneumococcus* and *Haemophillus influenzae* immunization before leaving the hospital. He goes home on Acyclovir and PenVK and completes the cycle outpatient.

For cycle 2 you add lenalidomide 25 mg days 1-14 of each cycle.

Any new prescription?

VTE

- Disease + Treatment factors.
- Greater risk with Thal and high dose dexamethasone (~ 25%).
- Risk-based approach for prophylaxis when on IMIDs
  - Risk factors: Thal , prior VTE, high-dose Dex, obesity, diabetes, immobility, strong family history of VTE, anthracyclines, ESA, hormonal therapy.
  - 0-1 factor: ASA 100 mg/day
  - 2+ factors: LMHW, warfarin.
  - Use clinical judgement
  - Limited data for direct thrombin inhibitors

Clinical Vignette (cont)

You subsequently learn that M.M's marrow showed 60% PC with monosomy 13 by FISH.

You added ASA 100 mg, Calcium + VitD, along with lenalidomide from onset of cycle 2.

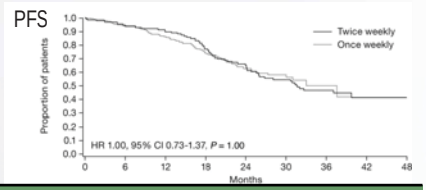
After 2 cycles (Vd + RVd) he feels a bit tired, pain is better. Wife complaints that he is getting "mean" and can't sleep well. Physical exam shows bilateral symmetric minimal peripheral edema.

Labs: Hgb 12.9, Plt 78 K, ANC 1,100, Cr 1.1, Glu 175 (fasting), M spike 0.8, FKLC 377 mg/L, FLLC 15 mg/L. He complaints of tingling and numbeness on toes, restless legs at night, unconfortable , but does not interfere on ADL.

Any changes in Plan?

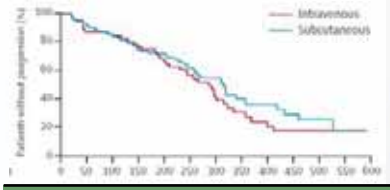
Neuropathy

- At risk:
  - Pre existing PN, elderly, DM(?)
  - Therapy with thalidomide, bortezomib (up to 50% patients)



	weekly	2x-weekly
Cum. planned dose (mg/m^2)	46.8	67.6
Cum. delivered dose(mg/m^2)	39.4	40.1
Neuropathy	8%	38%

Bringhem et al. Blood 116:4745, 2010



	IV	Subcut
Cum. delivered dose(mg/m^2)	31.4	33.7
Neuropathy	49%	35%
Neuropathy (Gr ¾)	15%	5%

Moreau et al. Lancet Oncol 12:431, 2011

Neuropathy

- Management
  - Early schedule change, dose reduction (> grade 1)
  - Discontinue agent if >grade 2
  - Limit dose of thalidomide
  - Bortezomib subcutaneous route, consider weekly dosing.
  - Gapabentin, pregabalin
  - Duloxetin
  - (Fill in with your favorite anecdote)

Cytopenias- Anemia – some tips

- Anemia almost always a disease manifestation, rarely a treatment toxicity in MM.
- I rarely (if ever) use ESA in MM patients.
- Always be aware of other causes
  - GI bleeding (corticosteroids, VTE prophylaxis/therapy)
  - Other malignancy
  - CKD
  - Iron/B12 deficiency

Cytopenias- Neutropenia – some tips

- Neutropenia almost always a toxicity of therapy, rarely a disease manifestation.
- Most regimens can be continued with ANC > 500.
- Think lenalidomide, pomalidomide, daratumumab, then others.
- For IMIDs, consider changing the schedule (e.g. 21/28 in maintenance) or reducing dose. There is hardly any data that more is better.
- Ad hoc use of G-CSF.

Cytopenias- Thrombocypenia – some tips

- Thrombocytopenia often a toxicity of therapy, occasionally disease manifestation.
- 50 K is safe for most.
- For IMIDs, consider changing the schedule (e.g. 21/28 in maintenance) or reducing dose. There is hardly any data that more is better.
- For Bortezomib, carfilzomib consider changing schedule

Metabolic/Cardiovascular

- At risk: high doses of Dexamethasone, Carfilzomib therapy.
- New onset DM, worsening DM, hypertension, CVA, coronary event, CHF.
- Prevention/ Management
  - Smoking cessation
  - Exercise
  - Once a week dexamethasone.
  - Limit Dex dose to 20 mg/week for >75, DM, CHF, severe hypertension.
  - Aggressively reduce Dex dose, omit from subsequent cycles.
  - Lipid control
  - Aggressive hypertension control.
  - Input from cardiologist/ cardio-oncologist.

Other toxicities/ Random management tips

- Rash from IMIDs : Hold, rechallenge.
- Blepharitis, chalazion on bortezomib: Antibiotic ointment, ophthalmologist input.
- Diarrhea on Lenalidomide maintenance: change schedule, reduce dose.
- Cough/ upper respiratory symptoms on daratumumab: montelukast.
- IRE on daratumumab: Consider “split” first dose. Stop, treat, resume at lower rate. Very unlikely after first dose.
- SMN: Alkylators, Prolonged use of lenalidomide. Age-appropriate cancer screening.

Clinical Vignette (cont)

You change M.M.'s regimen to Bortezomib 1.3 mg/m2 days 1,8,15, Lenalidomide 15 mg days 1-21, Dexamethasone 20 mg days 1,8,15,22 (28-day cycles).

He completes 3 more cycles of RVd without additional toxicities or dose changes. He feels better and is no longer "mean" (took Mrs. M. on a cruise). He obtains VGPR, successfully undergo AHCT reaching a sCR.

He completes 8 doses of zoledronate, 12 weeks apart.

3 years after initial diagnosis he is well, in remission and on lenalidomide maintenance, ASA, Acyclovir, Calcium+ Vit D.

THANK YOU!

ljcosta@uabmc.edu

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Knowledge that will change your world

25-year-old female presented to ER with worsening back pain, weight loss and fatigue.

1

WBC 13.4 k/mcl (N 60%, L 24%, M 12%)

Hb 10.6 g/dl

Plt 85 K/mcl

Cr 1.7 mg/dl

Ca 14.5

2

- SPEP: discrete band in the gamma region.
- Immunofixation: Free lambda light chains monoclonal protein.
- Estimated monoclonal protein: 0.19 g/dL
- Lamda LC 5481 mg/L
- Kappa LC 0.00
- Beta-2 microglobulin 6.5 mg/L
- Ig A 39 mg/dl
- Ig G 883 mg/dl
- Ig M 10 mg/dl

3

- Peripheral blood smear: Circulating plasma cells 3-5%
- Bone marrow aspirate smears: 80% cells are plasma cells.
- Flow cytometry on whole bone marrow specimen: population of plasma cells (23% of the leukocytes in the flow cytometry preparation) which are lambda restricted.
- Inadequate core biopsy

4

PET CT:

- heterogeneous activity in the liver (SUV = 8.9) without discrete lesion on the localizing CT.
- heterogeneous activity in the spleen (SUV = 6).
- increased metabolic activity involving the bone marrow of the axial and appendicular skeleton. multiple FDG avid osteolytic lesions with the following SUV:

-Focal activity in the skull (SUV = 16)

-Bilateral humeral heads more so on the left side (SUV = 10)

-Through out the sternum (SUV = 7)

-Through out the cervical, thoracic, lumbar spine (SUV = 7)

-posterior aspect of the thoracic ribs (SUV =8)

-sacral lesions (SUV = 12.5)

-bilateral femoral head and neck (SUV = 9)

-lytic lesion in the right medial femoral condyle with SUV=9

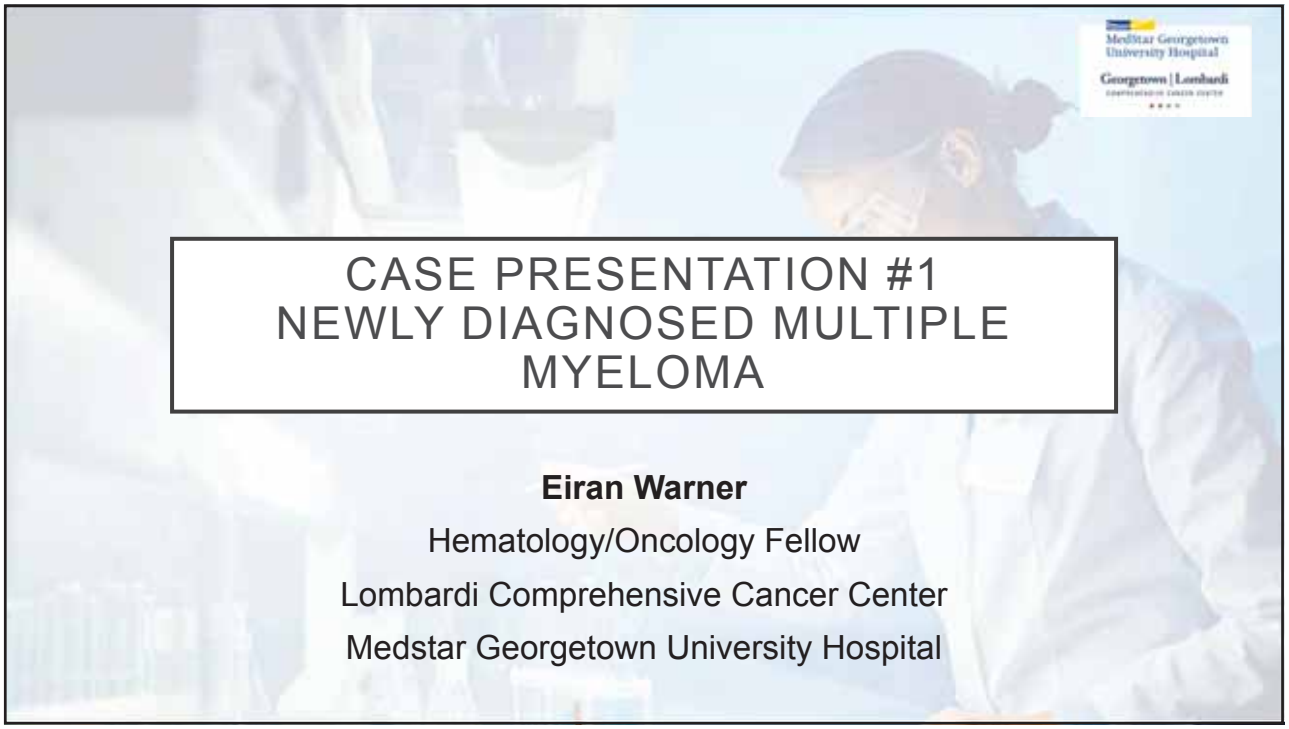
-lytic lesion in left proximal fibula SUV=19.4

5

Hospital course complicated by severe inflammatory response: hypotension requiring pressors, worsening LDH (1181 units/L) and elevated IL-6 (200 pg/ml) necessitating ICU transfer. Started on dexamethasone with significant improvement in hemodynamics.

6

7



CASE PRESENTATION #1
NEWLY DIAGNOSED MULTIPLE MYELOMA

Eiran Warner
Hematology/Oncology Fellow
Lombardi Comprehensive Cancer Center
Medstar Georgetown University Hospital

Case #1

Presenting History

- 53 year old Gentleman
- Several months of lower back pain
- Found with mild pancytopenia (Hb 11.4, platelets 123,000, MCV 104, ANC 1.58)

Case #1

Initial Workup - Labs

Lab Work

- CBC: WBC 3.9 k/uL, Hb 11.4 gm/dl, Platelets 136,000 k/uL
- BUN 14 mg/dl, Cr 0.91 mg/dl
- Ca 10.1 mg/dl
- Albumin 3.5. gm/dl
- Beta-2 microglobulin 3.7 mg
- Quantitative immunoglobulins:
  - IgG 431 mg
  - IgA 4005 mg
  - IgM 13 mg

- SPEP: 2.5 g/ dl
- Immunofixation: IgA Kappa Monoclonal Protein
- Serum Free Light Chain Assay:
- kappa 474.4 mg
- lambda 8 mg
- kappa/lambda 59.3

Case #1

Bone Marrow Biopsy

- Hypercellular with 90% plasma cells
- + for CD138 and CD 56 but no expression of CD38 is noted
- Cytogenetics (FISH): 17P deletion, gain 1q

Case #1

Imaging

- Skeletal survey : 2 small lucencies in the skull
- MRI of the lumbar spine showed a "cystic lesion" at S1-S2 and heterogeneous marrow signal with innumerable small lesions on 6/26/17
- PET CT: Recommended but not done

Case #1

Treatment Plan

- KRD
  - Carfilzomib: days 1, 2, 8, 9, 15, and 16
    - Starting dose, 20 mg/m2 on days 1 and 2 of cycle 1; target dose, 36 mg/m2 thereafter
  - Lenalidomide: 25 mg PO on days 1 through 21
  - Dexamethasone: 40 mg PO days 1,2,8,9,15,16

Case #1

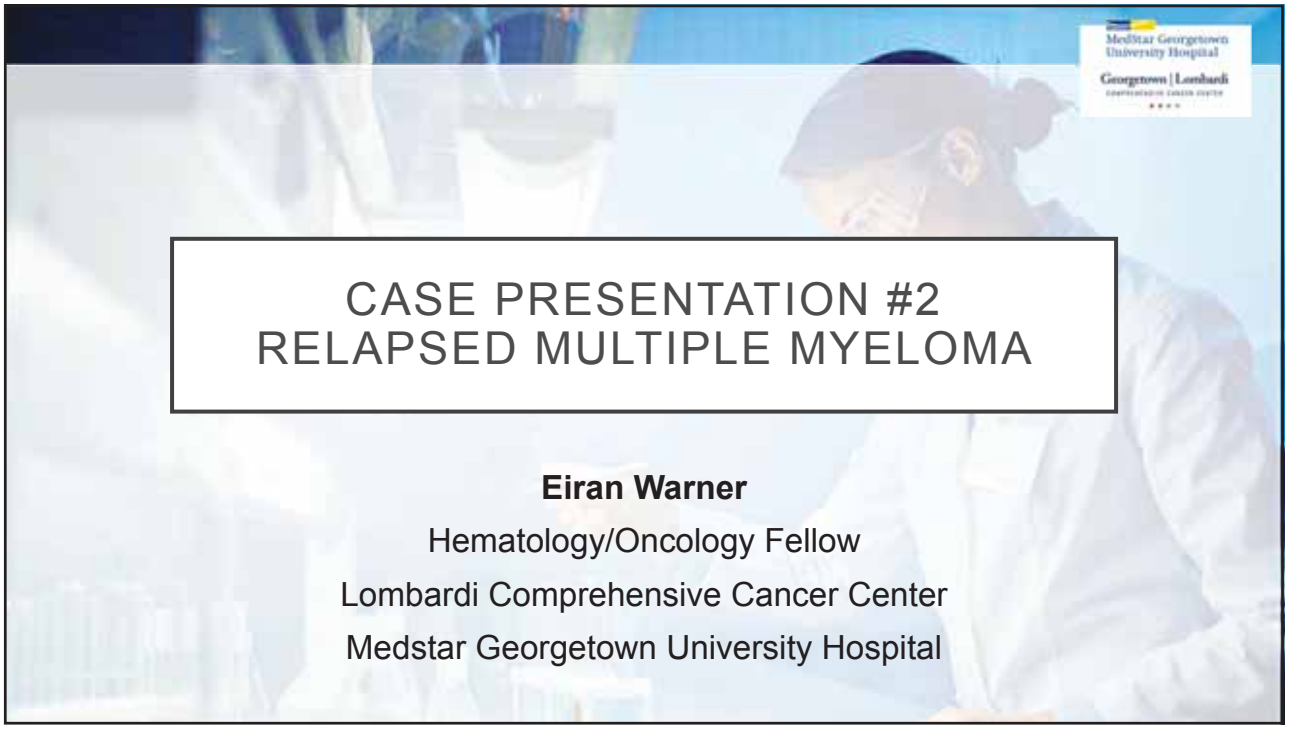
After 1 Cycle

- Partial remission
- SPEP from 2.8 g to 0.8 g
- Serum free kappa from 474 mg to 35.4 mg

Case #1

Question

How would you treat high risk Multiple Myeloma?



CASE PRESENTATION #2
RELAPSED MULTIPLE MYELOMA

Eiran Warner
Hematology/Oncology Fellow
Lombardi Comprehensive Cancer Center
Medstar Georgetown University Hospital

Case #2

Presenting History

- 77 AA woman
- Hx of MGUS; evolved to stage III IgG Lambda MM in 2010
- FISH positive 14q32 deletion, but no 13q deletion or other cytogenetic abnormalities

Case #2

Induction Treatment

Nine 6-week cycles of VMPT-VT:

A. Bortezomib 1.3 mg/m2, d 1, 8, 15, 22
B. Melphalan 9 mg/m2 d 1-4
C. Prednisone 60 mg/m2, d 1-4
D. Thalidomide 50 mg d 1-42

Case #2

Progression

- Velcade/Thal maintenance weekly
  - 11/2011- 2/2015 (DC'd due to progressive disease)
- Carfilzomib: 03/2015-02/2016
  - Developed progressive disease on single agent Carflizomib
- KRd: 02/2016-9/22/16
  - DC'd due to progressive disease
- KRCd: September 2016
  - Progressive disease after 1 cycle of KRCd
- Initiated ixazomib/pomalidomide/dexamethasone November 2016
  - Progressive disease after 1 cycle

Case #2

Progression Continued

- Dara/Pom: Dec 2016-March 2017
  - Progressive disease after weekly Dara completed
- Dara/Pom/Carfilz/Dex: March 2017-August 2017 (Dara changed back to weekly)
- Carfilzomib/Bendamustine: September 12, 2017
  - Progressive disease after 1 cycle
- Cyclophosphamide 1 g/m^2/etoposide 200 mg/m^2
  - Progressive disease after 1 cycle

Case #2

Question

How would you treat relapsed refractory Multiple Myeloma?

Case 1

IMS educational workshop, Washington D.C.

Arjun Lakshman
Research Fellow, Hematology
Mayo Clinic, Rochester.

Initial presentation

- 63 years/ male with hypothyroidism and hyperlipidemia
- Back pain- May 2013

Hemoglobin	**8.1** g/dL	M-protein	7.9 (**IgA-kappa**)
Calcium	9.5 mg/dL	Kappa/Lambda/FLCr (mg/dL)	9.1/0.3/32.4
Creatinine	1.5 mg/dL	Urine M-protein	27 mg/ 24 hours
PET-CT	Compression **fractures** involving multiple vertebrae and rib lesions	Albumin	3.2 g/dL
Bone marrow biopsy	80% (kappa-restricted)	Beta-2-microglobulin	**8.1** mg/dL
Cytogenetics	Normal male karyotype	LDH	125
FISH	**t(4;14), del(17p), monosomy 13**	ECOG PS	1

Diagnosis

- Multiple myeloma (high-risk)
  - ISS/ R-ISS stage III
  - Durie-Salmon stage IIIA
- ECOG 1

Initial therapy

- Received Bortezomib-Lenalidomide-dexamethasone (VRd) with IV zoledronic acid.
- Attained PR after 4 cycles.
- December 2013- Underwent ASCT after carfilzomib-melphalan conditioning and attained a VGPR.
- Received CYBORD consolidation x 12 cycles (VGPR) followed by bortezomib maintenance.

Follow-up

- August 2015- Biochemical relapse while he was off therapy for 5 months (off therapy due to autoimmune encephalopathy).

What are the therapeutic options that can be considered at first relapse in this patient?

Follow-up

- August 2015- Restarted on CYBORD, but biochemical progression after 3 cycles.
- October 2015- Switched to carfilzomib-pomalidomide-dexamethasone to which he was refractory.
- January 2016- Started daratumumab-pomalidomide-dexamethasone in to which he did not have a response.

What treatment choices are available for this patient with high-risk RRMM?

Follow-up

- March 2016- D-PACE x4 cycles- attained PR
- October 2016- Flu/Cy/TBI conditioning followed by allogeneic SCT from a haploidentical donor- no further deepening of response.
- March 2017- Progression and FISH showed persistence of original clone.

What therapeutic options are available?

Follow-up

- Contemplated pembrolizumab-pomalidomide dexamethasone (could not be started due to restrictions in insurance).
- April 2017- Started elotuzumab-pomalidomide-dexamethasone on which he progressed after 2 cycles.
- He failed bendamustine-lenalidomide-dexamethasone, and ixazomib-lenalidomide-dexamethasone.
- Not deemed a candidate for clinical trials.
- Currently admitted in hospital with pneumonia.
- Will pursue hospice after discharge.

Future Targets and Therapy in Myeloma

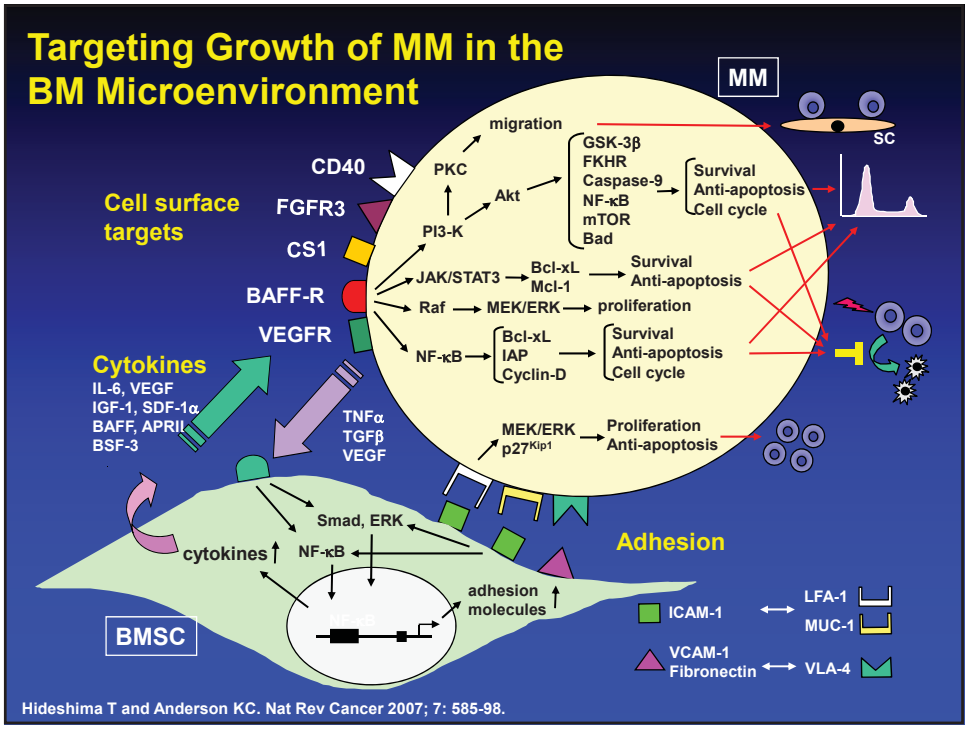
Kenneth C. Anderson, M.D.

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

Disclosure

Kenneth C. Anderson, MD

- Advisory Board: Millennium-Takeda, and Gilead
- Scientific Founder: Oncopep, C4 Therapeutics



Hideshima T and Anderson KC. Nat Rev Cancer 2007; 7: 585-98.

Integration of Novel Therapy Into Myeloma Management

Proteasome inhibitors: Bortezomib, carfilzomib, ixazomib; **immunomodulatory drugs:** thalidomide, lenalidomide, pomalidomide; **HDAC inhibitor:** panobinostat; **monoclonal antibodies:** elotuzumab and daratumumab

Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

20 FDA approvals and median patient survival prolonged 3-4 fold, from 3 to 8-10 years.

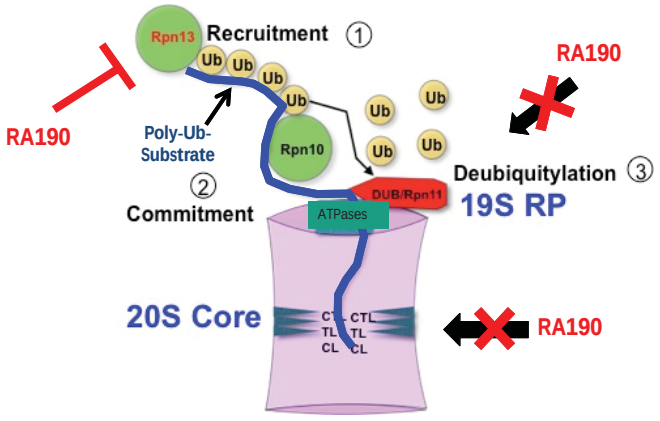
Targetting Hallmark Vulnerabilities (Achilles Heels) in MM

Modulate Protein Homeostasis:
Target protein degradation
Trigger selective protein degradation

Immune Suppression:
Restore host anti-MM immunity

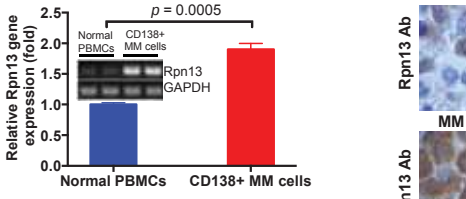
Genomic abnormalities:
Target and overcome mechanisms of genomic instability, target genomic abnormalities and their sequelae

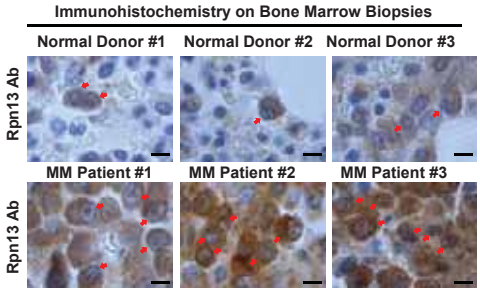
Targeting Ubiquitin Receptor Rpn13

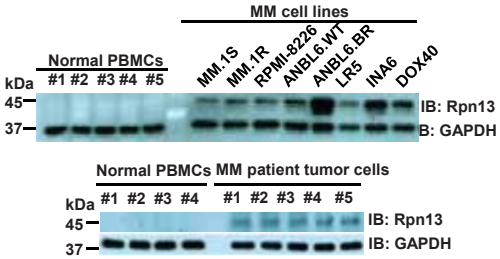


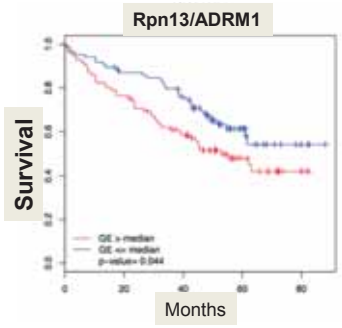
Song et al, Leukemia 2016; 30:1877-86.

Rpn13 is Upregulated in Myeloma and Associated with Decreased Survival

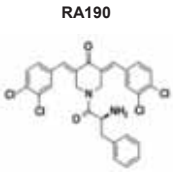


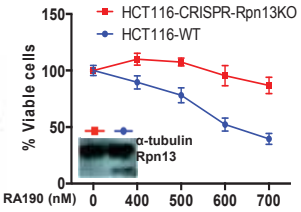


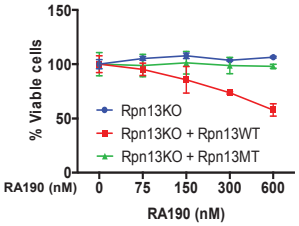




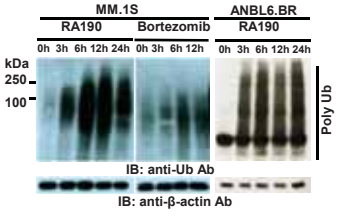
Biochemical Characterization of POC Rpn13 Inhibitor RA190

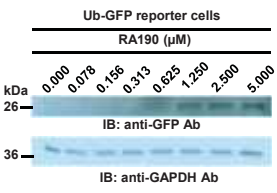


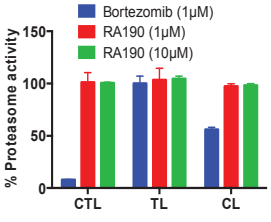




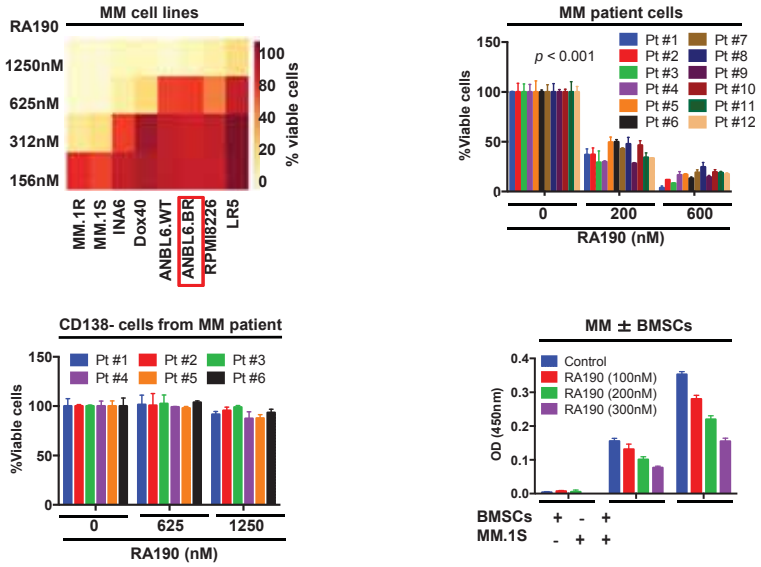
Cellular Proteasome function



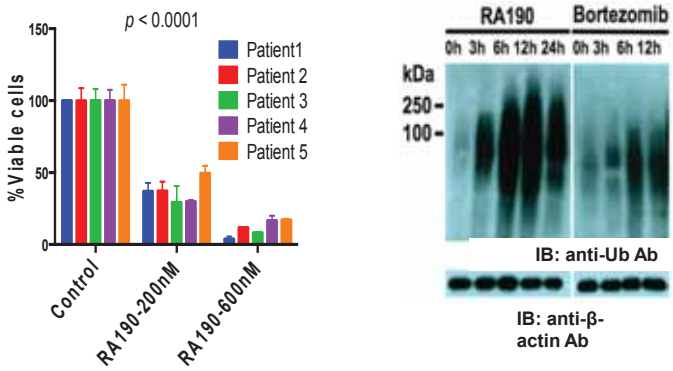




Rpn13 Inhibition via RA190 Decreases MM cell Viability without affecting Normal Cells and Overcome Bone Marrow Stromal Cells-induced Tumor Growth

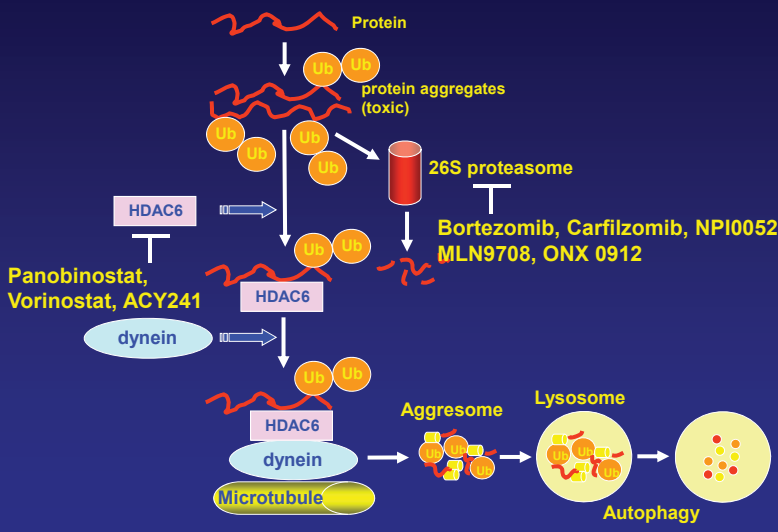


Blockade of Ubiquitin Receptor Rpn13 with RA190 Inhibits Myeloma Cell Growth and Induces Polyubiquitination



Song et al., Leukemia, 2016: 30:1877-86.

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



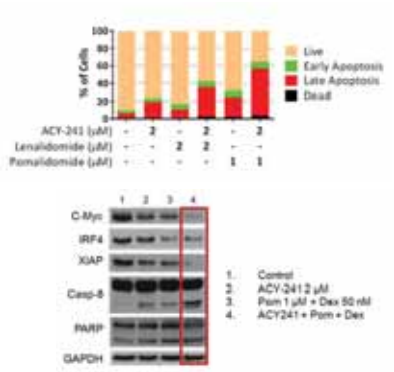
Hideshima et al. Clin Cancer Res. 2005;11:8530.Catley et al. Blood. 2006;108:3441-9.
Hideshima et al PNAS 2016; 113: 13162-7.

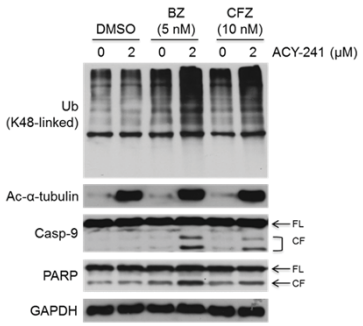
Selective Histone Deacetylase 6 Inhibitors Ricolinostat and ACY 241

- **Synthesized and validated at DFCI**
- **Well tolerated daily oral medication**
- **Achieves durable responses when combined with either bortezomib, lenalidomide or pomalidomide in relapsed refractory myeloma**
- **ACY 241 pom dex achieves improved PK/PD, tolerability, response and PFS in RRMM**

Raje et al Blood 2012, Hideshima et al PNAS 2016, Yee et al Lancet Oncol 2016, Vogl et al CCR 2017

HDAC6 Inhibitor 241 Enhances Apoptosis Triggered by Immunomodulatory Drugs and Proteasome Inhibitors

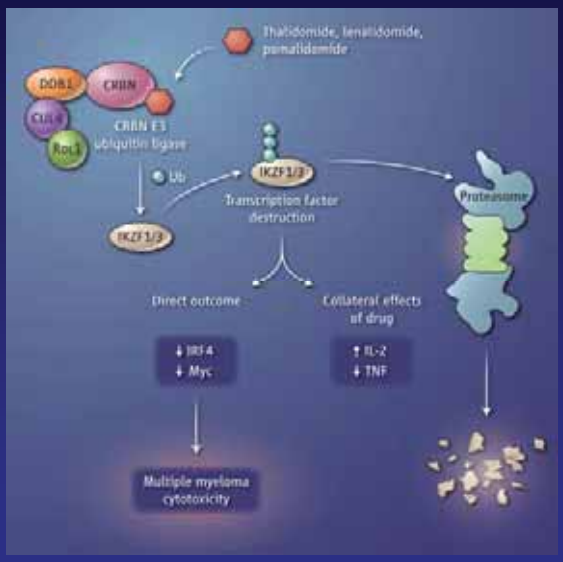




- ACY-241 with IMiDs downregulates c-Myc and IRF-4, and increases apoptosis
- ACY-241 with Pis enhances cell death markers and increases polyubiquitinated proteins

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Mechanism of Action of Immunomodulatory Drugs



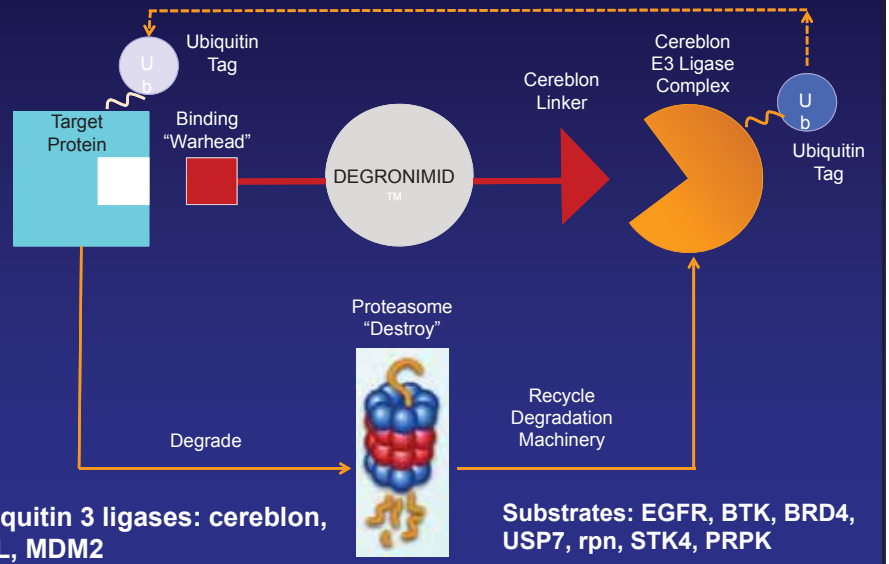
Degronimids: Link to ubiquitin 3 ligase complexes

Kronke et al, Science, 2014

Lu et al, Science, 2014

Degronimids Trigger Degradation of Selective Substrates

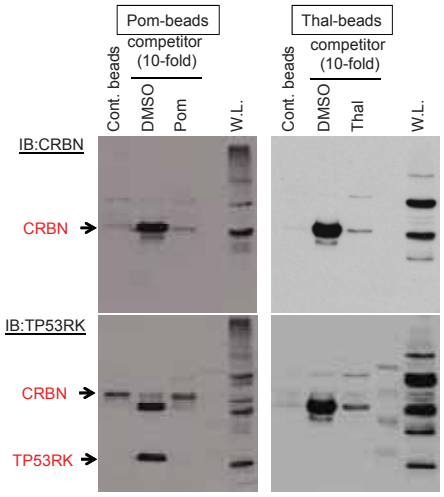
Bradner et al, Science, 2015



Ubiquitin 3 ligases: cereblon, VHL, MDM2

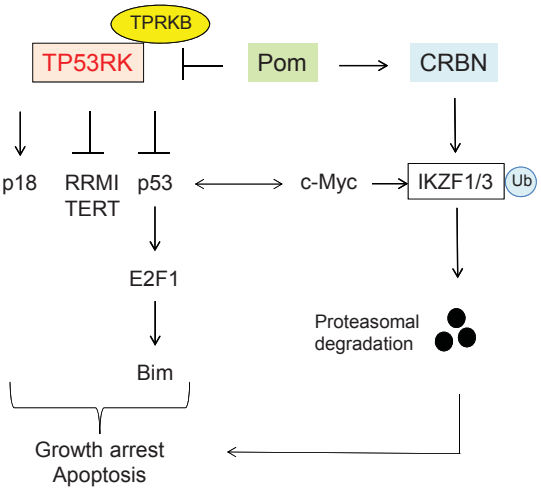
Substrates: EGFR, BTK, BRD4, USP7, rpn, STK4, PRPK

Pom-beads, but not Thal-beads, pull-down TP53RK



Hideshima T et al. Blood 2017; 129: 1308-19.

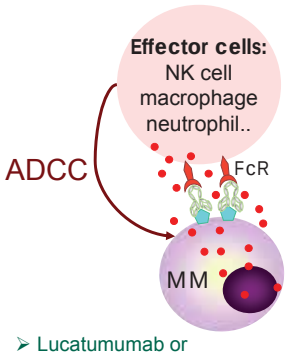
IMiDs bind and inhibit TP53RK: a cereblon independent mechanism of MM growth inhibition



Hideshima T et al. Blood 2017; 129: 1308-19.

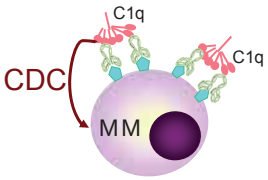
MAb Based Therapeutic Targeting of MM

Antibody-dependent Cellular Cytotoxicity (ADCC)



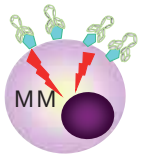
- Lucatumumab or Dacetuzumab (CD40)
- **Elotuzumab (CS1)**
- **Daratumumab (CD38)**
- XmAb®5592 (HM1.24)
- **SAR650984 (CD38)**

Complement-dependent Cytotoxicity (CDC)



- **Daratumumab (CD38)**
- **SAR650984 (CD38)**

Apoptosis/growth arrest via intracellular signaling pathways



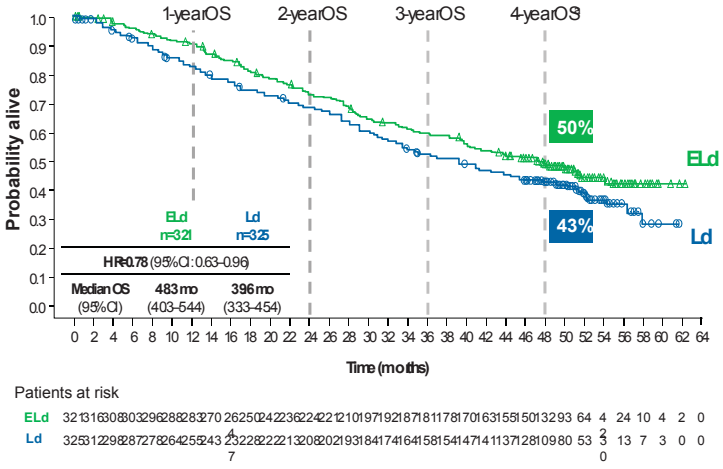
- **huN901-DM1* (CD56)**
- **nBT062-maytansinoid /DM4* (CD138)**
- 1339 (IL-6)
- BHQ880 (DKK)
- RAP-011 (activin A)
- **Daratumumab (CD38)**
- **SAR650984 (CD38)**
- **J6M0-MMAF* (BCMA)**

*** Ab drug conjugate**

Updated from
Tai & Anderson Bone Marrow Research 2011

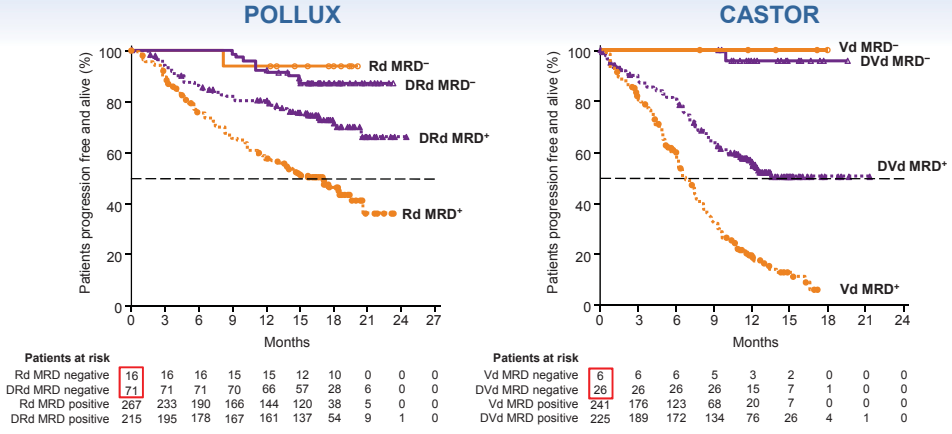
ELOQUENT-2: 4-Year Follow-up

Overall Survival: Elotuzumab (Targetting SLAMF-7) Rd vs Rd



Dimopoulos et al, EHA 2017

Daratumumab Len Dex and Dara Velcade Dex: PFS According to MRD Status at 10^{-5}



- Lower risk of progression in MRD-negative patients
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

Avet-Loiseau al ASH 2016

Daratumumab Pom Dex for Rel/Ref MM

- ORR 60% in 103 patients with median 4 prior therapies
- Of the CR, 29% were MRD negative
- ORR 58% in double refractory patients
- Median PFS of 8.8 months
- Other than increased neutropenia, safety profile consistent with individual therapies

Chari et al, Blood 2017; 130: 974-81.

21

Immune Effects of HDAC6 Inhibitor ACY 241 in MM Therapy

Augments HLA, CD38 on MM cells

Augments autologous MM cell cytotoxicity alone, which is enhanced by pomalidomide, CD38 Ab and/or PD-1/PD-L1 Abs, even in the presence of MDSCs or pDCs

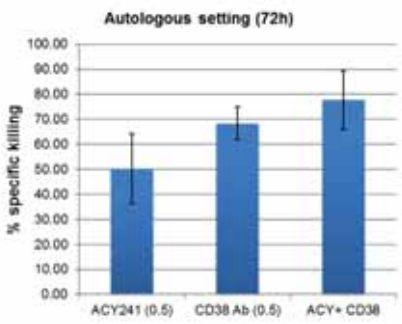
Augments NK cell function, alone and with PD-L1 Ab

Augments autologous central and effector memory MM specific immunity

22

Teru Hideshima, Ken Anderson

ACY-241 HDAC 6 Inhibitor Enhances αCD38-Mediated ADCC in Primary MM Samples

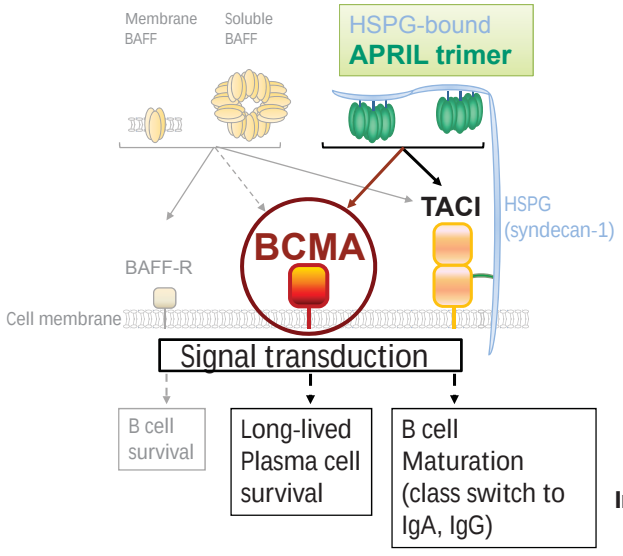


Bone marrow mononuclear cells
(n=6)
+
ACY-241
+
αCD38 Ab

- αCD38 antibody induces ADCC in primary MM samples
- ACY-241 treatment enhances αCD38-mediated ADCC

23

BCMA Is A Selective Plasma Cell Antigen



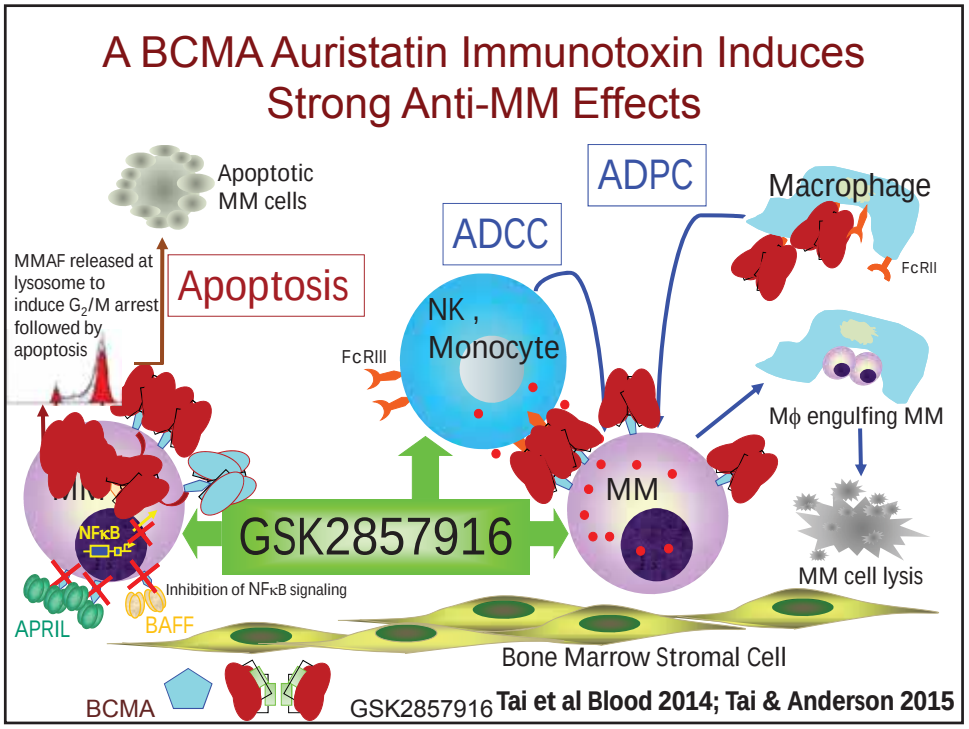
Ligands
by neutrophil, myeloid cell, DC, osteoclasts, tumor cell

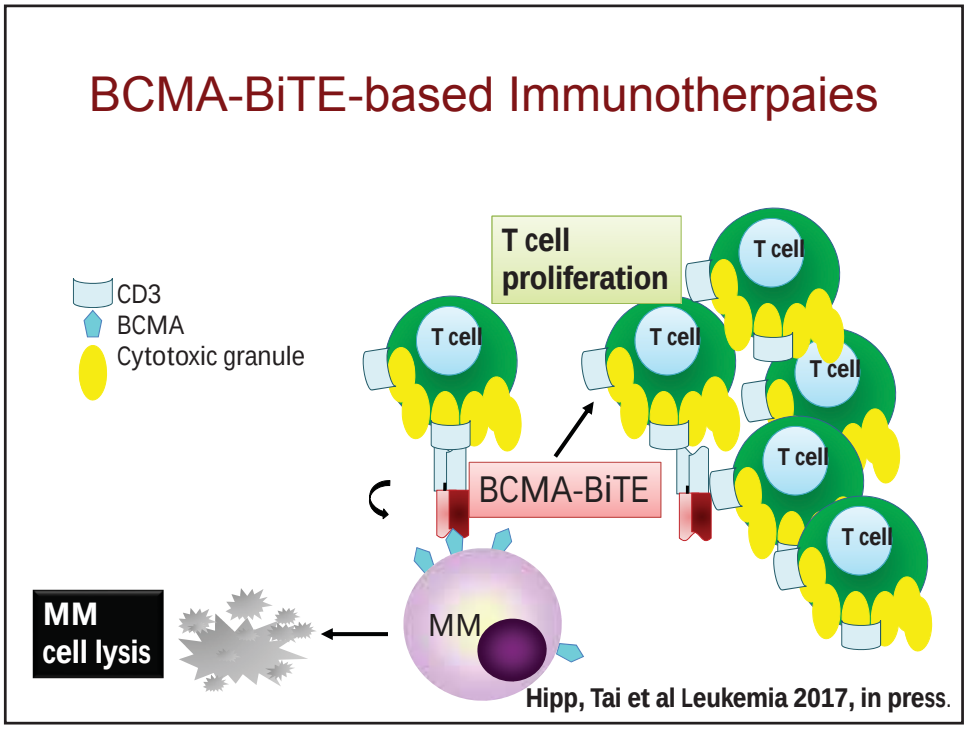
Affinity to BCMA:
APRIL (nM) >> BAFF (μM)
Elevated in sera of MM patients

Receptors
on B cells

BCMA >> TACI
by ~2-100-fold in MM
(loss of BAFF-R in MM)

Tai & Anderson
Immunotherapy 2015; 7: 1187-99.


A BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects
Apoptotic MM cells
MMAF released at lysosome to induce G2/M arrest followed by apoptosis
Apoptosis
ADCC
ADPC
Macrophage
FcRII
NK , Monocyte
FcRIII
Mϕ engulfing MM
MM
GSK2857916
NFκB
Inhibition of NFκB signaling
APRIL
BAFF
MM cell lysis
Bone Marrow Stromal Cell
BCMA
GSK2857916
Tai et al Blood 2014; Tai & Anderson 2015

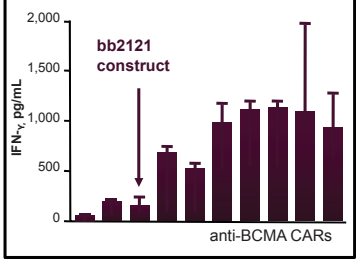

BCMA-BiTE-based Immunotherpaies
CD3
BCMA
Cytotoxic granule
T cell proliferation
T cell
BCMA-BiTE
MM
MM cell lysis
Hipp, Tai et al Leukemia 2017, in press.

bb2121: Anti-BCMA Chimeric Antigen Receptor T-Cell Product Candidate[1,2]

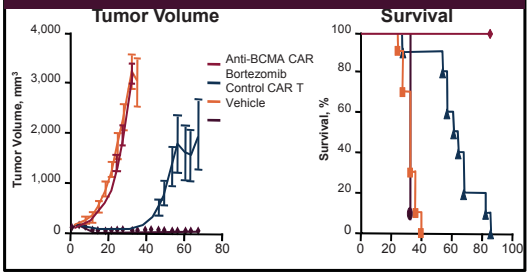
anti-BCMA CAR design

- Autologous T cells transduced with a lentiviral vector encoding a novel anti-BCMA CAR
- 4-1BB co-signaling motif selected to promote proliferation and persistence
- Construct demonstrated potent preclinical in vivo activity with low tonic signaling

bb2121 demonstrates low antigen-independent signaling



bb2121 improves survival and drives tumor clearance in MM mice[2]



1. Berdeja J, et al EORTC-AACR-NCI 2016.
2. Morgan et al. 24th Anniversary Congress of the European Society of Gene & Cell Therapy (ESGCT 2016).

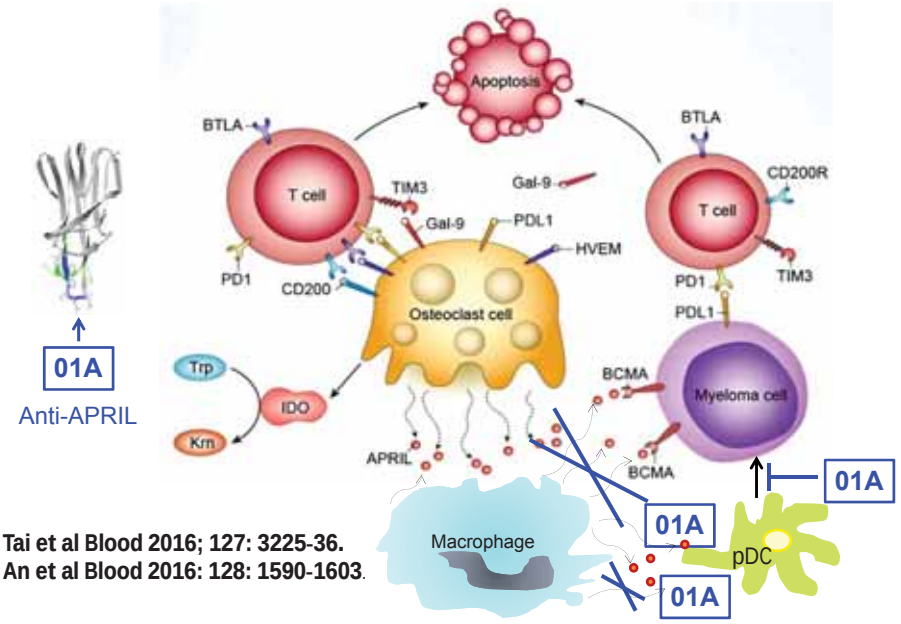
@PeerView

Summary of BCMA Car T Cell Studies Reported

Group	CoStim	Lympho Dep	Cell Dose X 10^6	No	ORR	≥CR	≥Gr 3 CRS / Neuro	Death	FU mo
NIH	CD28	Y	0.3-9*	12	4/12	1/12	2/0	0	nr
UP-Novartis	41bb	N	180-500#	9	4/9	1/9	3/2	1	0.5-12
Bluebird	41bb	Y	50-800	18+	15/18	3/18	2/0	2	0.5-11
Legend	41bb	Y	0.6-7*#*	19+	19/19	14/19	2/0	0	0.5-14

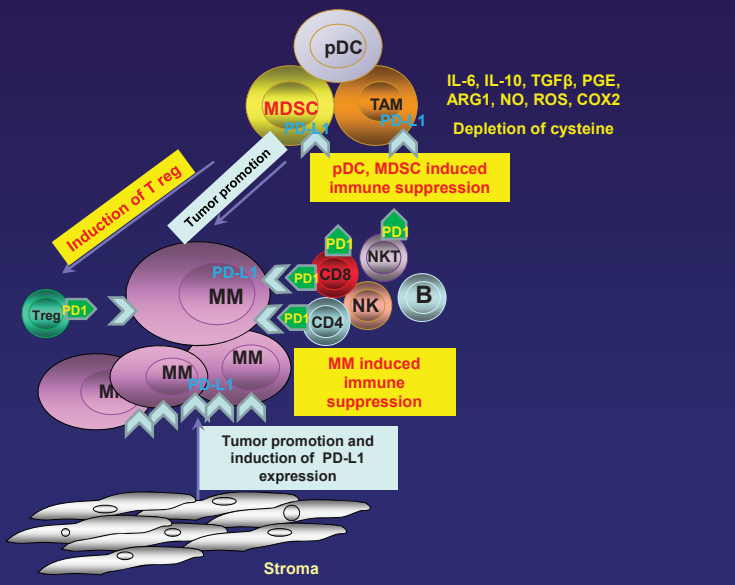
*per kg, # split dosing, * dual BCMA targeting

Targeting APRIL in MM



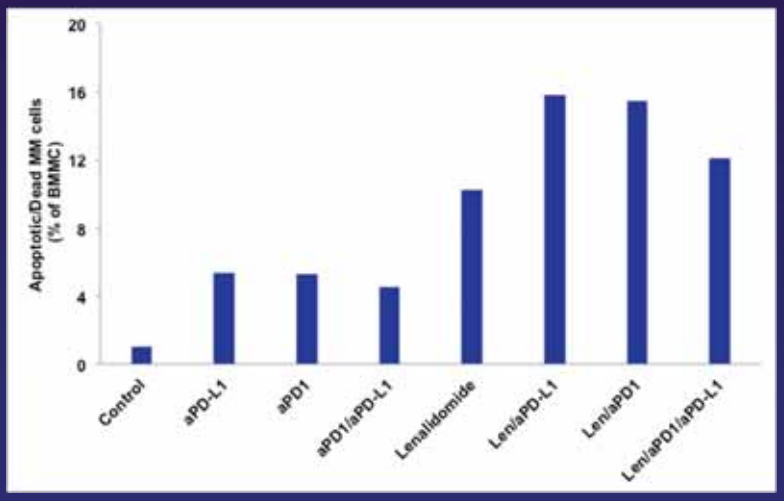
Tai et al Blood 2016; 127: 3225-36.
An et al Blood 2016: 128: 1590-1603.

Immune Suppressive Microenvironment in MM



Görgün GT, et al. Blood 2013;121:2975-87

Enhanced MM Cytotoxiciy of Combination Immune Therapies



Görgün G. et al. Clin Cancer Res 2015; 21: 4607-18.

Pembrolizumab, Lenalidomide/Dex in RR MM

- Heavily pretreated RRMM (median 4 prior therapies); Acceptable safety profile
- ORR 50% and disease control (CR, PR, or SD) was 98%
- Phase 3 trials now underway

Pembroluzumab Pomalidomide/Dex in RR MM

- Heavily pretreated RRMM (median of 3 prior therapies)
- ORR 56%; sCR 8%; VGPR 13%; PR 29%
- Median DOR: 8.8 months
- Double refractory ORR: 55%
- TRIALS ON HOLD BY FDA

Mateos et al, Badros et al ASH 2016.
NCT02036502

Vaccines Targeting MM Specific Peptides in Smoldering Multiple Myeloma

Goal is to prevent evolution of smoldering to active myeloma

- **Cocktails of immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses**

Clinical trials (LLS TAP Program):

Immune responses to vaccine in all patients including tetramer positive cells and type I cytokines

Lenalidomide with vaccine augments these immune response

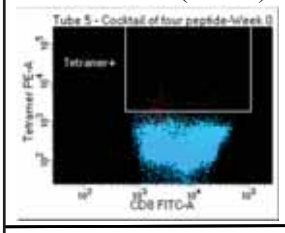
Lenalidomide and PDL-1, HDAC 6i 241 with vaccine to induce memory Immune response against myeloma

Bae et al, Leukemia 2011; 25:1610-9.
Bae et al, Brit J Hematol 2011; 155: 349-61.
Bae et al, Brit J Hematol 2012; 157: 687-701.
Bae et al, Clin Can Res 2012; 17:4850-60.
Bae et al, Leukemia 2015

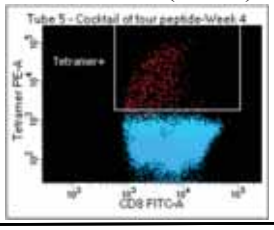
Vaccine Gradually Induces XBP1/CD138/CS1-Specific CTL in SMM patient

Stimulator: XBP1us / XBP1sp / CD138 / CS1 Peptides

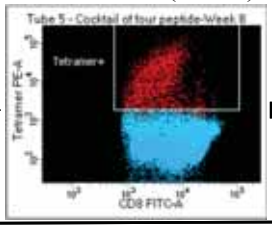
Baseline (Wk 0)



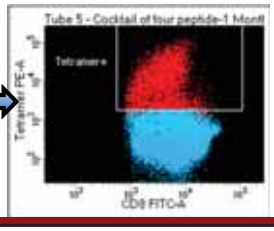
Post-2 Vac (Wk 4)



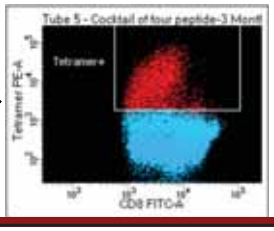
Post-4 Vac (Wk 8)



Post- 6 Vac (1M FW)



Post- 6 Vac (3M FW)

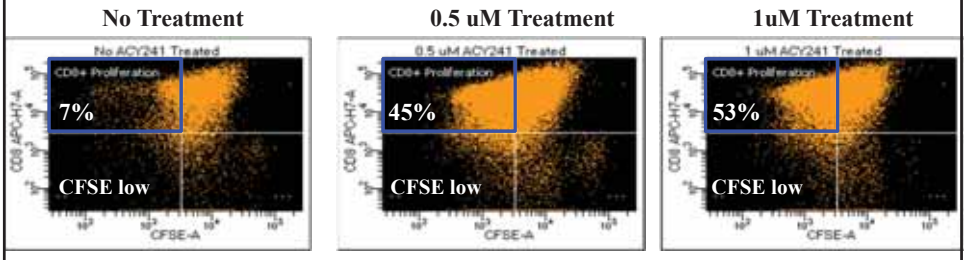


SUMMARY

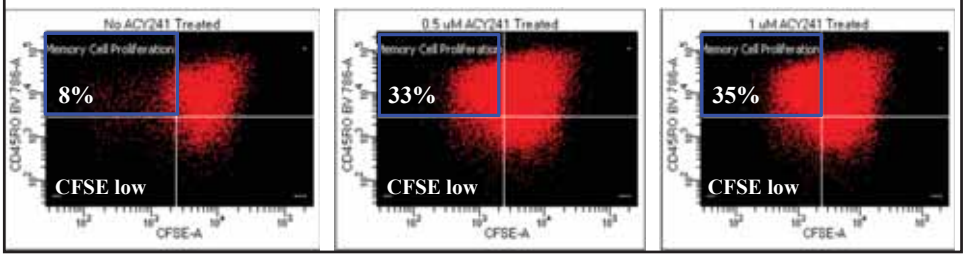
Induction of XBP1/CD138/CS1 Peptides-Specific CTL by Vaccine

ACY241 HDAC 6 Inhibitor Increases CD8+ and Memory CTL Proliferation to XBP1 Peptide Stimulation

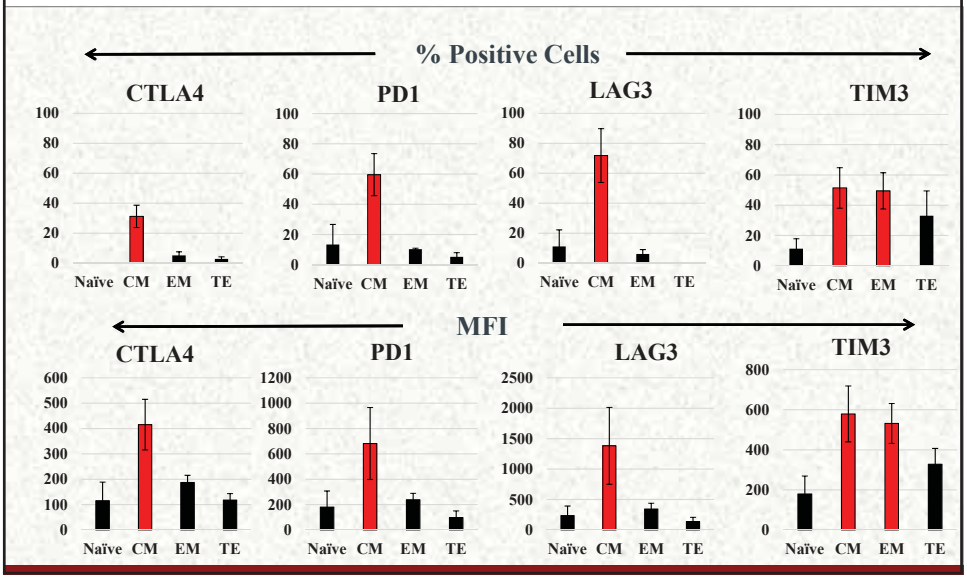
Increased Total CD8+ CTL Proliferation Following ACY241 Treatment



Increased Memory CTL (CD45RO+/CD8+) Proliferation Following ACY241 Trt

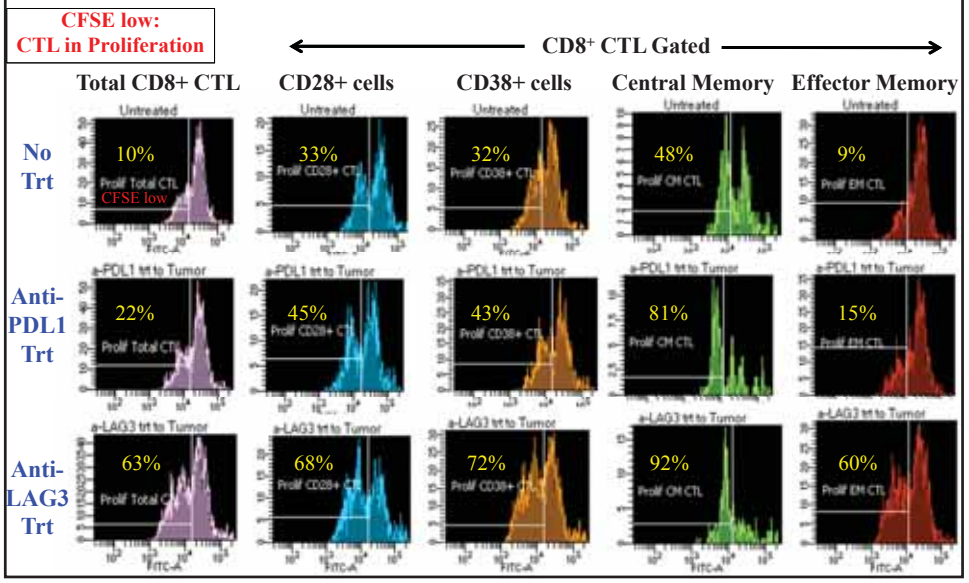


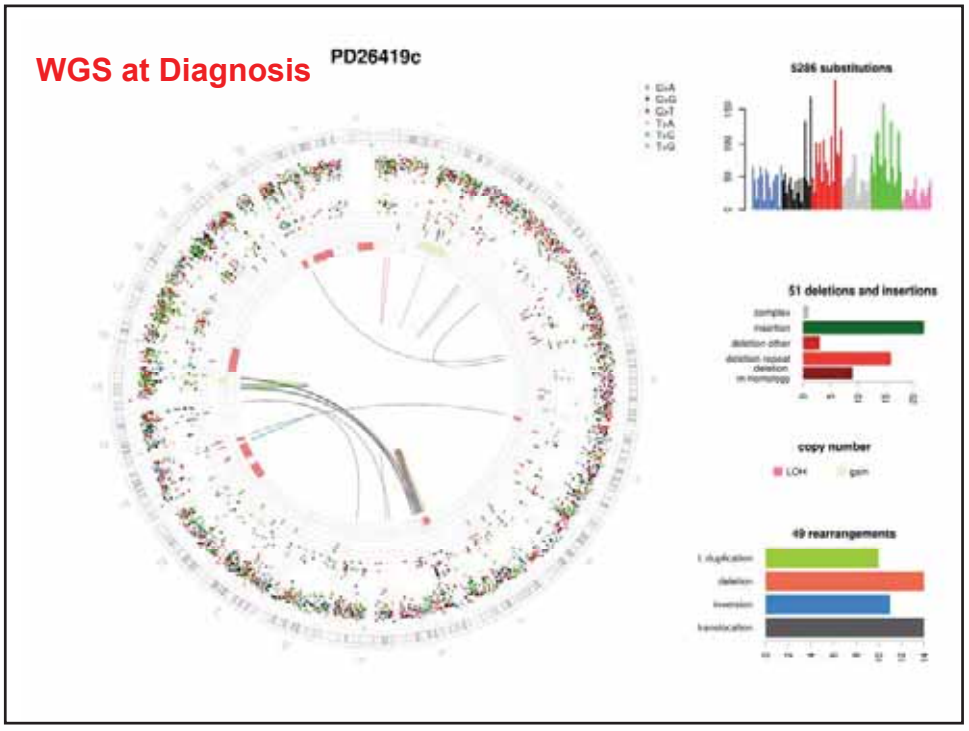
Enhanced Expression of Checkpoint Inhibitors on Memory CTL generated



Anti-PDL-1 or LAG3 Enhances Proliferation of XBP1 Peptide-CD8+CTL Subsets

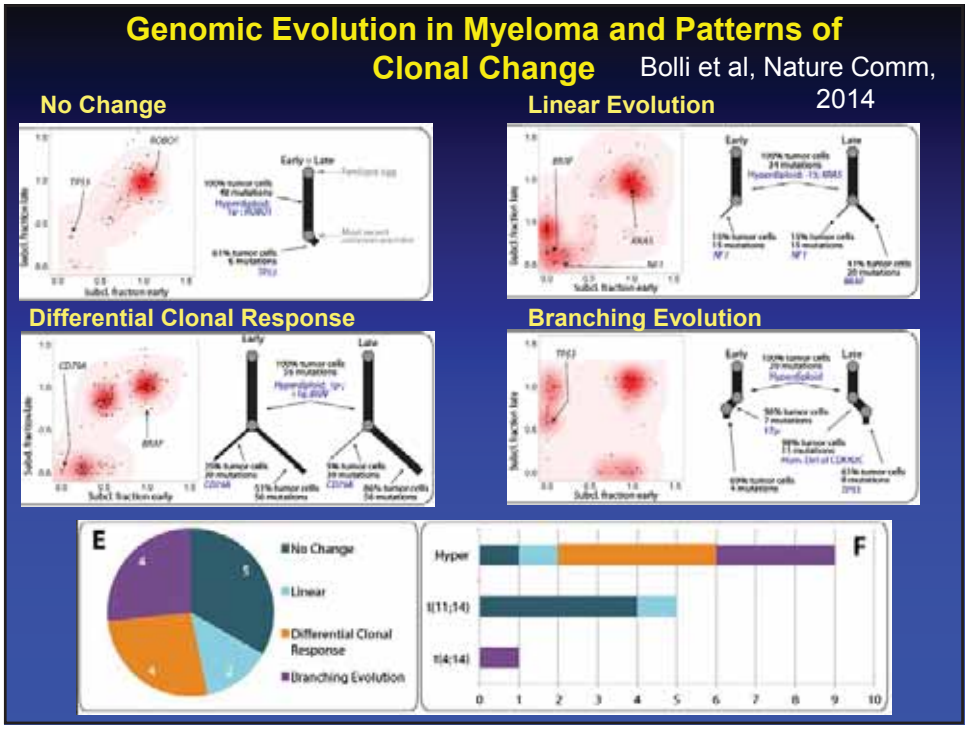
: Checkpoint Inhibition on U266 Myeloma cells





Genomic Evolution in Myeloma and Patterns of Clonal Change

Bolli et al, Nature Comm, 2014



Targets to Inhibit Genomic Instability

1. Homologous recombination (HR)
2. APEX nuclease activity
3. Pan nuclease activity
4. APOBEC activity

- Developed in vitro assays to measure HR, APEX, nuclease and APOBEC activity
- Ability to use this assays in HT screen

Shammas, Munshi, et al 2016

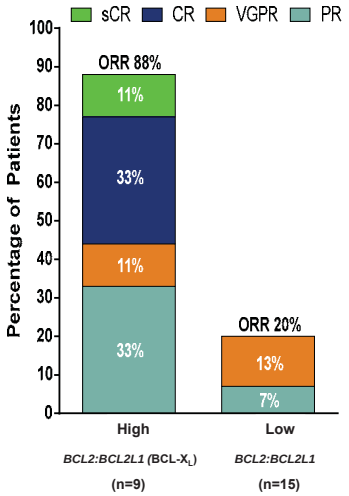
ASH Meeting on Hematologic Malignancies

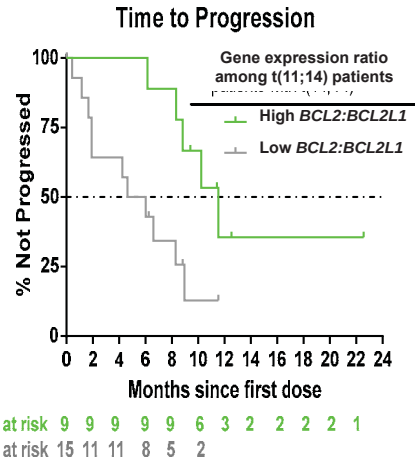
Mutational Landscape or Cloud of Myeloma

Therapies Targeting Ras Raf MAPK Pathway Achieve Transient Responses

Morgan GJ, Walker BA and Davies FE. Nature Reviews Cancer. 2012 Chapman *et al* Nature Genetics 2011, Walker et al 2012 Blood, Lohr et al Cancer Cell 2014, Bolli et al Nat Comm 2014, Walker BA et al Nat Comms 2015

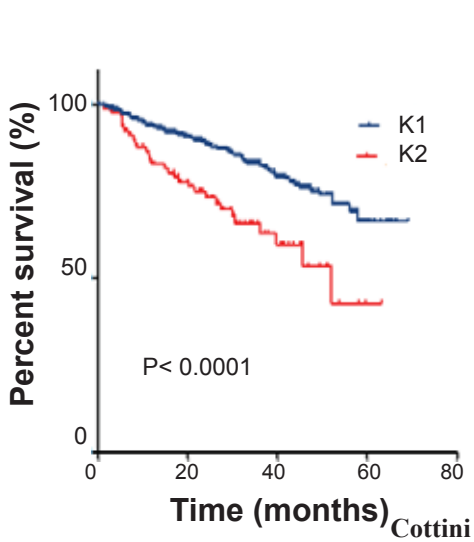
Responses to Venetoclax (Target BCL-2) by *BCL2:BCL2L1* Ratio Among t(11;14)-Positive Patients with RRMM

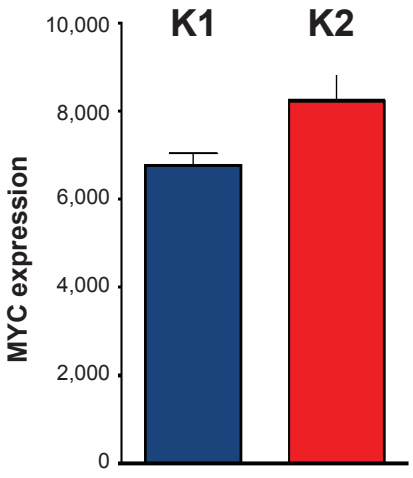




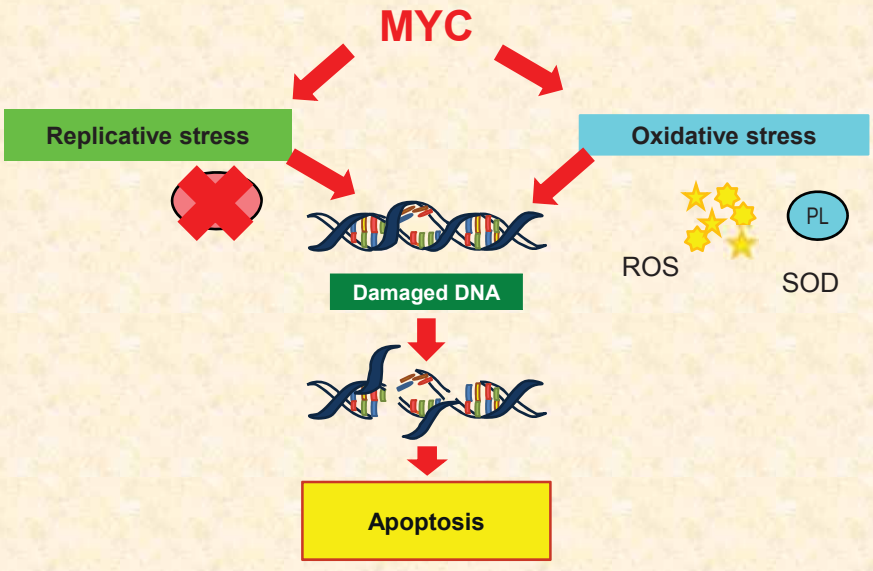
Kumar et al, ASH 2016

Achilles Heal: c-MYC Amplification is Associated with Poor Prognosis



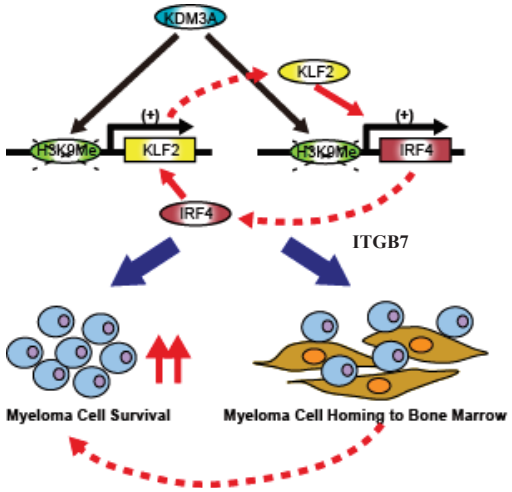


Cottini et al, Cancer Discovery 2015; 5:972-87.



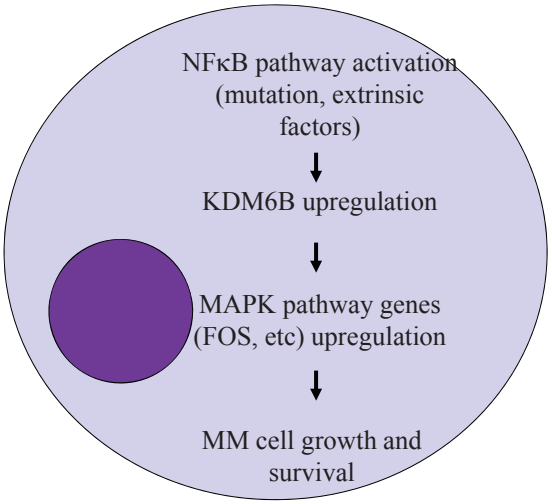
Model of KDM3A-KLF2-IRF4 Axis in MM cells

KDM3A catalyses removal of H3K9 mono- and di-methylation in MM



Ohguchi et al Nat Comm 2016; 7:10258

NFκB-KDM6B-MAPK signaling in MM cells



Ohguchi et al. Leukema. 2017 in press

DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

Targetting Hallmark Vulnerabilities (Achilles Heels) in MM

Modulate Protein Homeostasis:
Target protein degradation
Trigger selective protein degradation

Immune Suppression:
Restore host anti-MM immunity

Genomic abnormalities:
Target and overcome mechanisms of genomic instability, target genomic abnormalities and their sequelae

Conclusions and Future Directions

Combination therapies defined in preclinical studies will be used to treat subsets of patients, defined by profiling and informed by biomarkers

Collaborative effort of academia, biotech/pharma, NIH/NCI, FDA, and advocacy- International Myeloma Society-will facilitate continued advances.

Long term disease free survival and potential cure of MM will require both 1. achieving minimal residual disease negativity, and 2. combined immune therapies to restore host immunity.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Approaches To Newly Diagnosed MM In Transplant Ineligible Patients

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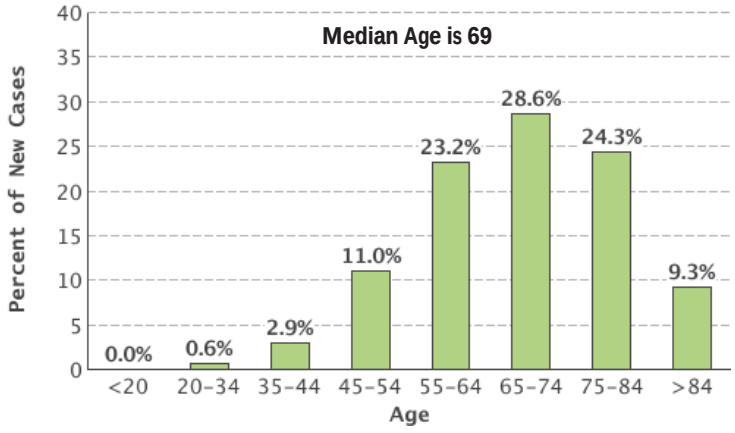
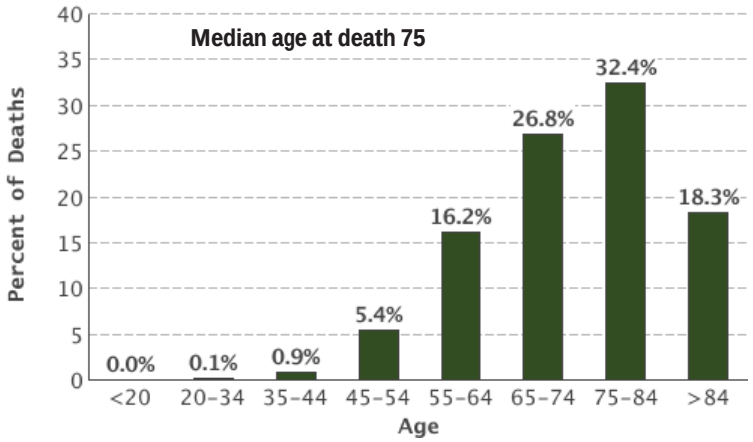
MAYO CLINIC

Myeloma: Age distribution



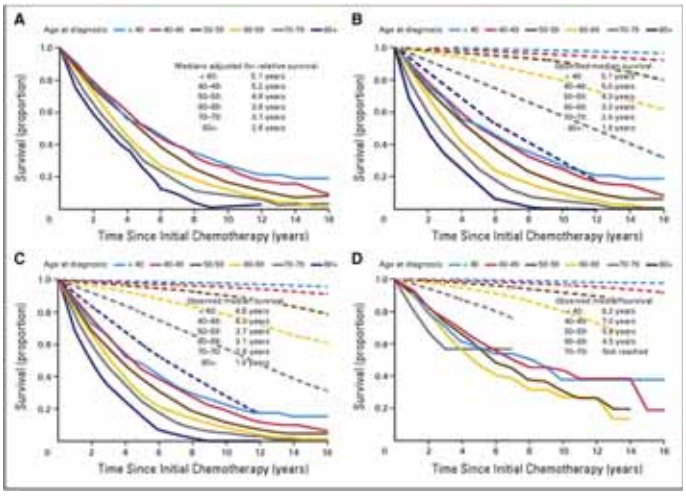
SEER Data, 2016

Age at death



The percent of myeloma deaths is highest among people aged 75-84

Impact of age

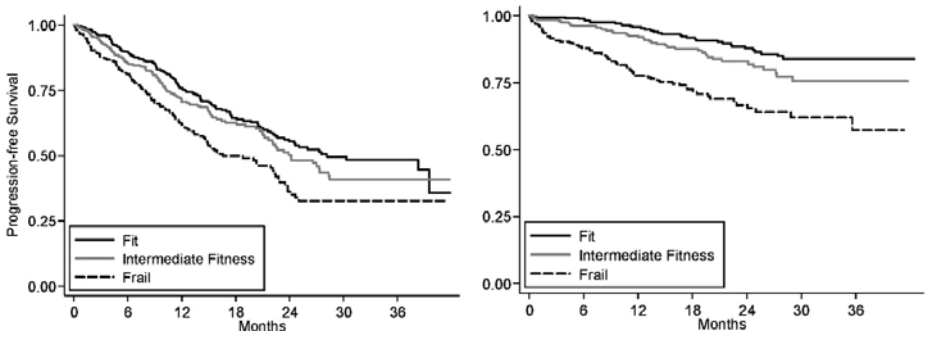


Ludwig et al. JCO 2010;28:1599-1605

Why is age an important issue?

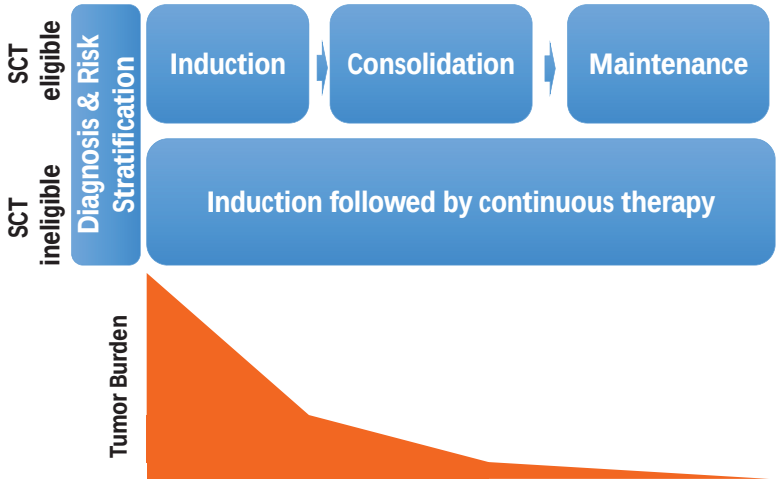
- Co-morbidities
  - Hypertension, Ischemic heart disease, Diabetes
  - Renal insufficiency
  - Osteoporosis
  - Psychological issues
- Frailty
- Altered drug metabolism
- Limited social support, financial issues
- Limited independence/ mobility

Impact of frailty



Antonio Palumbo et al. Blood 2015;125:2068-2074

Myeloma treatment paradigm

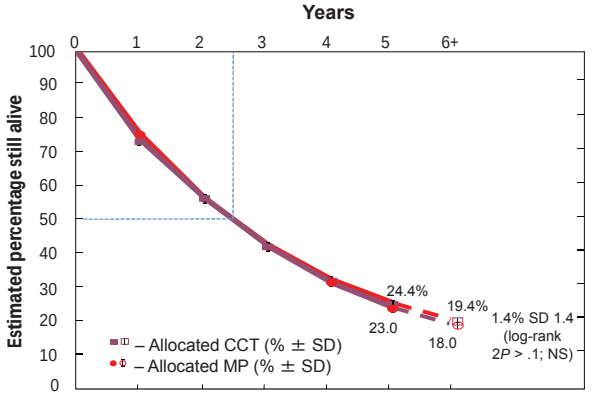


Drug options

- Immunomodulatory drugs
  - Thalidomide, lenalidomide
- Proteasome inhibitors
  - Bortezomib, Carfilzomib, Ixazomib
- Traditional chemotherapy
  - Cyclophosphamide, adriamycin/doxil
- Monoclonal antibodies
  - Daratumumab, elotuzumab

In clinical trials

The start: Melphalan + Prednisone



27 randomized trials

Myeloma Trialists' Collaborative Group. *J Clin Oncol.* 1998;16;12:3832

MP vs MPT

	GIMEMA[1,2]	IFM 99-06[3]	IFM 01-01[4]	Nordic[5]	HOVON[6]
Median PFS, months					
MP	15	18	19	14	10*
MPT	22	28	24	16	13
p value	0.0004	< 0.0001	0.001	TTP‡	< 0.001
Median OS, months					
MP	48	33	29	39	30
MPT	45	52	44	29	37
p value	NS	0.0006	0.028	NS	NS

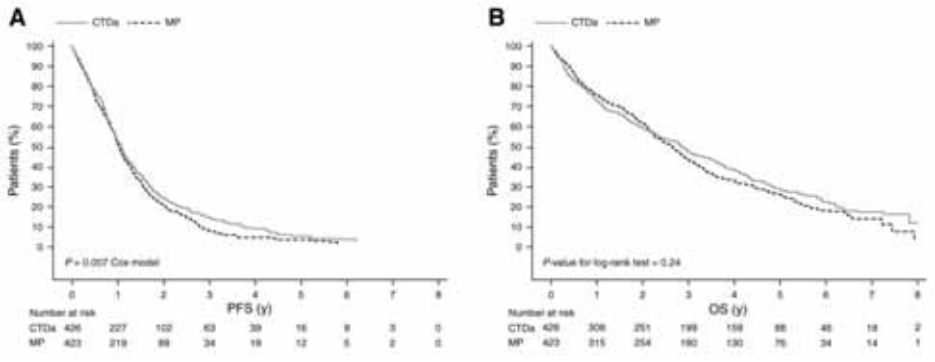
* Event-free survival.
‡ Significant.

In 5 of 5 studies, MPT was superior to MP in terms of PFS or TTP (or both)

In 2 of 5 studies, MPT was superior to MP in terms of OS

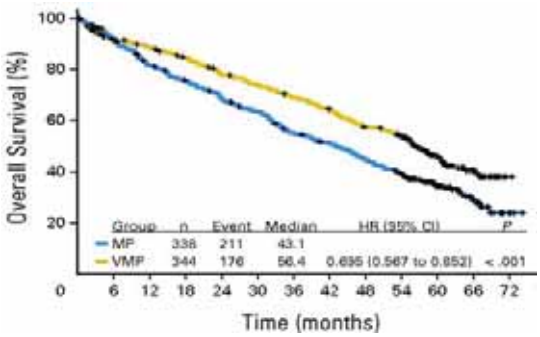
1. Palumbo A, et al. Lancet. 2006;111:825-31. 2. Palumbo A, et al. Blood. 2008;112:3107-14. 3. Facon T, et al. Lancet. 2007;370:1209-18.
4. Hulin C, et al. J Clin Oncol. 2009; in press. 5. Waage A, et al. Blood. 2007;110:[abstract 78].
6. Wijermans P, et al. Blood. 2008;112:[abstract 241]; updated data presented at ASH, 2008.

CTDa: MRCIX trial



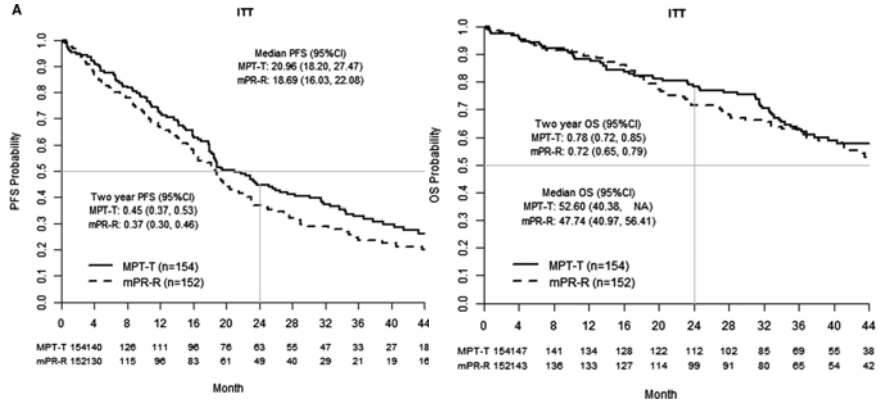
Morgan et al, Clin Cancer Res November 1, 2013 19; 6030

VISTA trial: MPV vs. MP



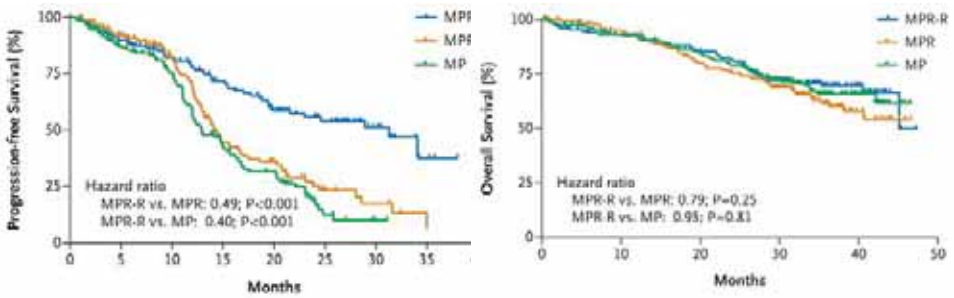
San Miguel et al. JCO 2013;31:448-455

MPT vs. MPR



A. Keith Stewart et al. Blood 2015;126:1294-1301

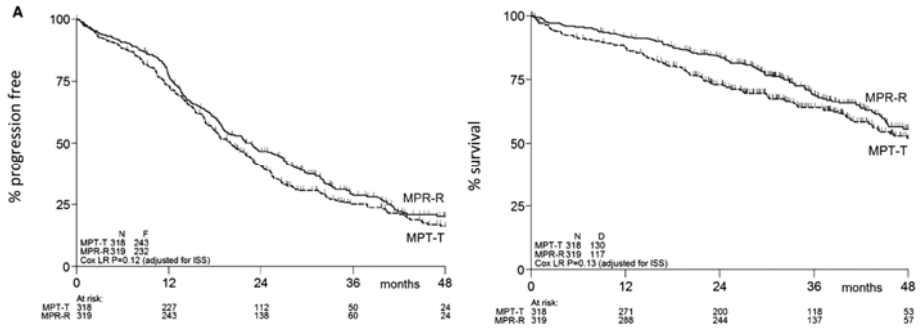
MP vs. MPR vs. MPR-R



Variable	MPR-R (N=152)	MPR (N=153)	MP (N=154)
Best response			
Complete or partial response — no. (%)	117 (77.0)†	104 (68.0)‡	77 (50.0)
Complete response	15 (9.9)	5 (3.3)	5 (3.2)
Partial response§	102 (67.1)	99 (64.7)	72 (46.8)
Very good partial response¶	35 (23.0)	45 (29.4)	14 (9.1)

Palumbo A et al. N Engl J Med 2012;366:1759-1769.

MPR-R vs. MPT-T



Sonja Zweegman et al. Blood 2016;127:1109-1116

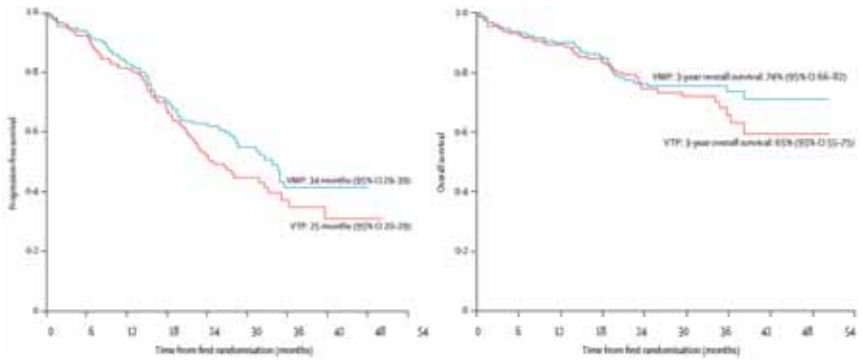
Bendamustine/prednisone (BP) vs MP

Efficacy	BP (n=68)		MP (n=63)		p
ORR (%)	75		70		ns
CR (%)	32		13		0.007
PR (%)	43		57		ns
PFS in >65 years (months)*	18		11		0.0017
Adverse events	**Gr 3**	**Gr 4**	**Gr 3**	**Gr 4**	
Neutropenia (%)	28	12	25	6	n/a
Thrombocytopenia (%)	6	4	10	5	n/a
Anemia (%)	21	3	21	3	n/a
Infection (%)	10	2	10	2	n/a
Mucositis (%)	4	0	2	0	n/a
Nauseas (%)	12	0	0	0	n/a

- No significant difference in OS between arms
- Significantly higher QoL scores on BP arm

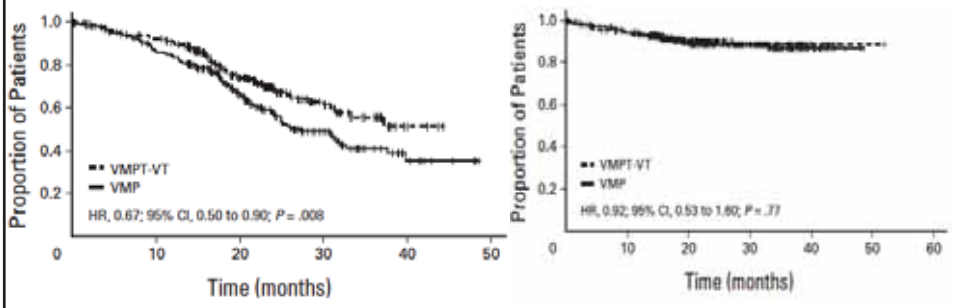
Pönisch et al. J Cancer Res Clin Oncol 2006;132(4):205-12

VMP vs. VTP



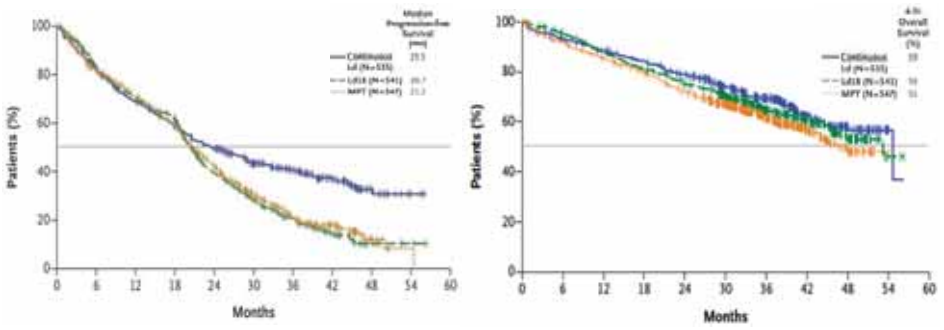
Mateos, et al., The Lancet Oncology , Volume 11 , Issue 10 , 934 - 941

VMPT-VT vs. VMP



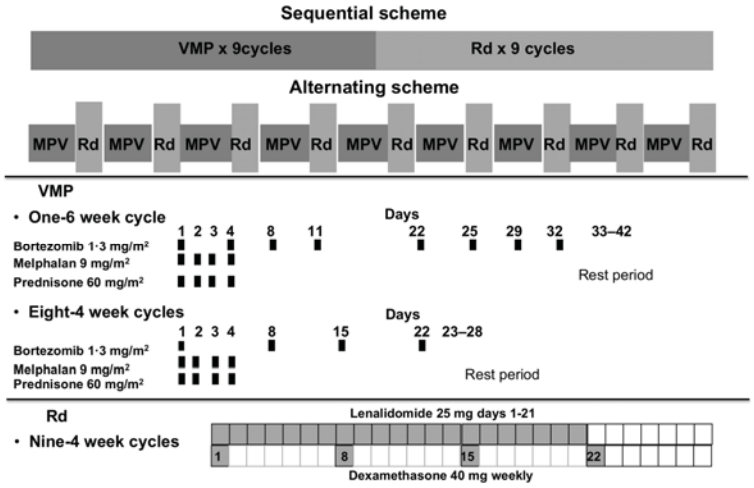
Palumbo et al, JCO 2010

RD (continuous or 18 ms) vs. MPT



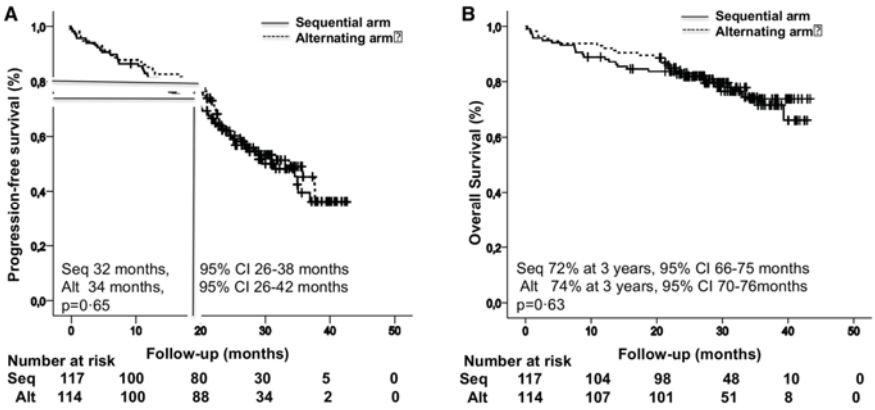
Benboubker et al, N Engl J Med 2014;371:906-17.

Alternating VMP/ Rd



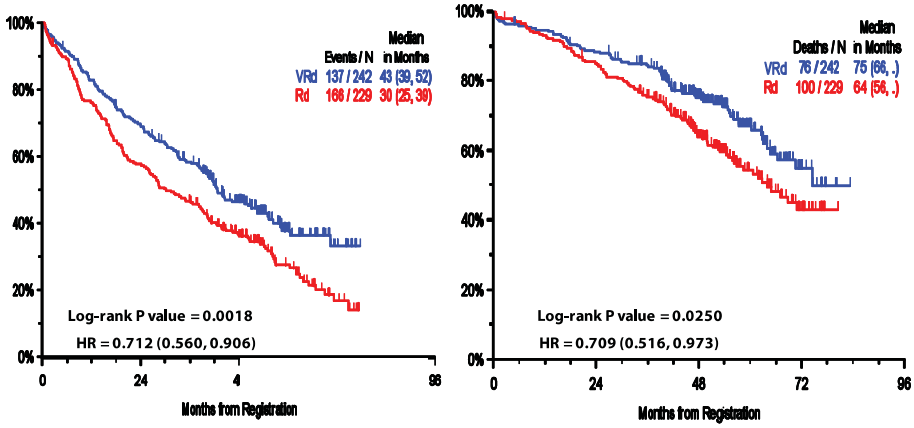
María-Victoria Mateos et al. Blood 2016;127:420-425

Alternating VMP/ Rd



María-Victoria Mateos et al. Blood 2016;127:420-425

S0777: \'Rd vs Rd



Durie et al. ASH 2015

RVD lite

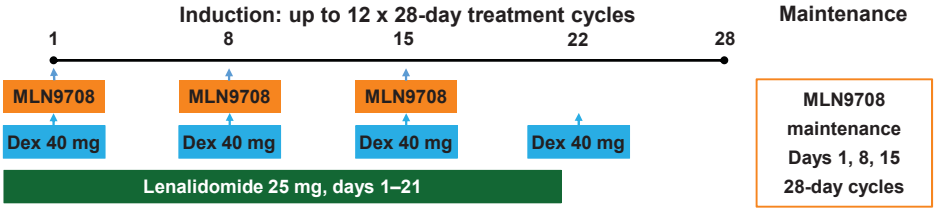
35-day cycle. Lenalidomide 15 days 1-21; bortezomib 1.3 mg/m2 once weekly subcutaneously days 1, 8, 15, and 22; and dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22 and 23 for pts ≤75 yrs and days 1, 8, 15, 22 for pts older than 75 yrs.

Response after 4 cycles (%) (n=30)	
ORR (≥PR)	**27 (90.0)**
CR	5 (16.7)
VGPR	11 (36.7)
PR	11 (36.7)
SD	3 (10.0)
VGPR or better	**16 (53.3)**

IMWG Criteria; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; VGPR, very good PR

O'Donnell et al, ASH 2014

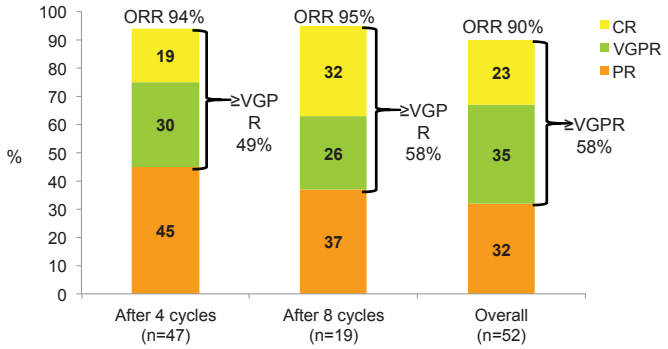
Ixazomib + Len Dex (Rd)



- Phase I: oral MLN9708 dose-escalation
  - Standard 3+3 schema, 33% dose increments, based on cycle 1 dose-limiting toxicities (DLTs)
- Phase II: oral MLN9708 at the RP2D from phase I
- Stem cell collection allowed after 3 cycles, with autologous stem cell transplantation (ASCT) deferred until after 6 cycles
- MLN9708 maintenance continued until progression or unacceptable toxicity

Kumar SK, et al. *Lancet Oncol.* 2014;15(13):1503–1512

Ixazomib-Rd: Responses



- Of 3 response-evaluable patients who completed 12 cycles, 2 achieved CR and 1 VGPR

Kumar, S. Lancet Oncology 2014

Carfilzomib weekly plus MP in elderly newly diagnosed MM patients: Ph ½ trial

Newly diagnosed MM with symptomatic, measureable disease and ineligible for transplant

Induction

Carfilzomib: 36, 45, 56 o 70 mg/m2 D 1, 8, 15, 22
Melphalan: 0,25 mg/Kg D1-4
Prednisone: 60 mg/m2 D1-4
(n = 24)

Up to nine 5-week cycles

Maintenance

Carfilzomib: 36 mg/m2
Every two weeks for 1 year

- **Phase 1: Maximum toleraled dose was not reached at the dose of 70 mg/m²**
- **Efficacy results of Phase 1 showed ORR of 87.5% and CR rate of 33%.**
- **KMP appears feasible and manageable, the primary cause of AEs coming from dose adaptation of Melphalan in very elderly NDMM**
- **The study continues with a second cohort at 70 mg/m2 of K then will move on with the phase 2.**

Leleu X et al. Abstract 3028

Carfilzomib weekly plus Cyclo-dex in elderly newly diagnosed MM patients: Ph ½ trial

The phase 1 of the study identified 70 mg/m^2 as MTD

Newly diagnosed MM with symptomatic, measureable disease and ineligible for transplant

Induction

Carfilzomib: 70 mg/m2 D 1, 8, 15, 22
Cyclophosphamide: 300 mg/m2 D1, 8, 15
Dexamethasone: 40mg D1, 8, 15 and 22
(n = 47)

Up to nine 4-week cycles

Maintenance

Carfilzomib: 70mg/m2
D1, 8, 15 until DP or toxicity

Efficacy	2nd cycle	6th cycle	9th cycle
Complete Response	17%	26%	33%
At least near Complete Response	29%	39%	40%
At least Very Good Partial Response	66%	82%	87%
At least Partial Response	86%	87%	87%

Safety profile: Acute pulmonar edema in 2 pts (5%) and hypertension in 6 pts (15%)

Bringhen S: Abstract 1828

Risk factors

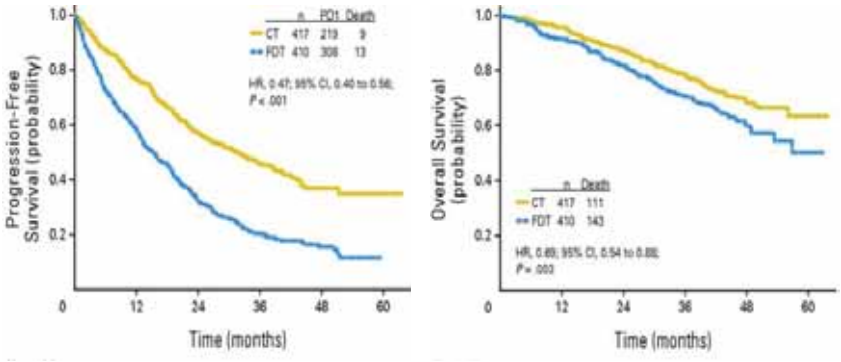
- Age over 75 years
- Mild, moderate or severe frailty:
  patients needing help for household tasks and personal care*
- Comorbidities:
  cardiac dysfunction
  pulmonary dysfunction
  hepatic dysfunction
  renal dysfunction

GO-GO	*MODERATE-GO*	*SLOW-GO*
No risk factors	At least one risk factor	At least one risk factor plus occurrence of grade 3-4 non-hematologic AE
↓ DOSE LEVEL 0	↓ DOSE LEVEL −1	↓ DOSE LEVEL −2

Agent	DOSE LEVEL 0	DOSE LEVEL −1	DOSE LEVEL −2
Dexamethasone	40 mg/d d 1,8,15,22 / 4 wks	20 mg/d d 1,8,15,22 / 4 wks	10 mg/d d 1,8,15,22 / 4 wks
Melphalan	0.25 mg/kg or 9 mg/m^2 d 1-4 / 4-6 wks	0.18 mg/kg or 7.5 mg/m^2 d 1-4 / 4-6 wks	0.13 mg/kg or 5 mg/m^2 d 1-4 / 4-6 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
Bortezomib	1.3 mg/m^2 twice weekly d 1,4,8,11 / 3 wks	1.3 mg/m^2 once weekly d 1,8,15,22 / 5 wks	1.0 mg/m^2 once weekly d 1,8,15,22 / 5 wks
Prednisone	60 mg/m^2 d 1-4 or 50 mg qod	30 mg/m^2 d 1-4 or 25 mg qod	15 mg/m^2 d 1-4 or 12.5 mg qod
Cyclophosphamide	100 mg/d d1-21/ 4 wks or 300 mg/m^2/d d 1,8,15 / 4 wks	50 mg/d d 1-21 / 4 wks or 150 mg/m^2/d D 1,8,15 / 4 wks	50 mg qod d 1-21 / 4 wks or 75 mg/m^2/d d 1,8,15 / 4 wks

Palumbo A, et al. Blood. 2011;118:4519-4529.

Continuous therapy vs. fixed duration



Antonio Palumbo et al. JCO

Duration of therapy

- Ongoing debate
- Improves PFS, effect on OS not consistent
- Increased toxicity, especially long term
- Quality of life impact
- Cost of care

Conclusions

- Ideal initial treatment is the combination of a proteasome inhibitor and an IMiD
- In older patients, frail patients, Len-Dex is a reasonable choice
- Dose modifications should be done based on patient age and frailty
- Maintenance therapy is particularly relevant in patients with high risk disease and those with residual disease

HOW DO WE USE THE FRAILTY SCORE IN THE ELDERLY?

Natalie S. Callander, MD

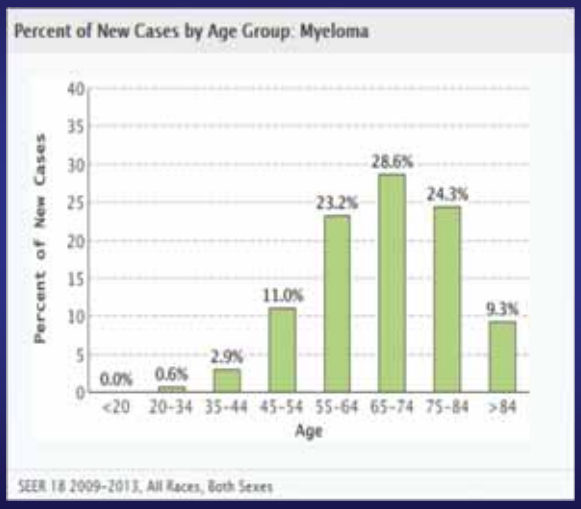
University of Wisconsin SCHOOL OF MEDICINE AND PUBLIC HEALTH

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

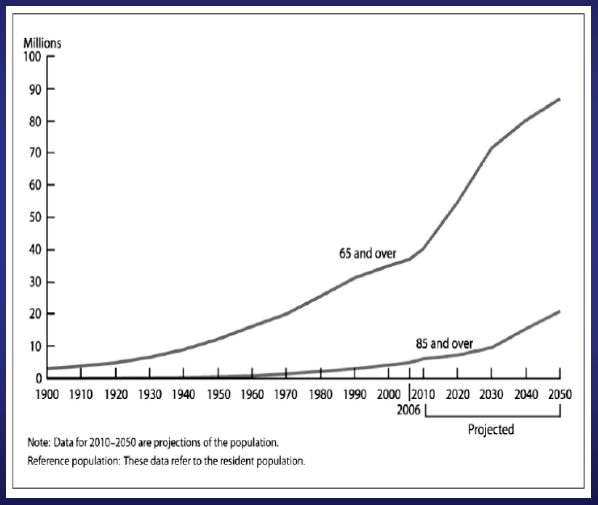
- "Because of the increase longevity of the population in the United States and the increase in the incidence of most malignant diseases with advancing age, physicians are increasingly confronted with the need to make decisions about the treatment of elderly patients with cancer"
- "Myeloma represents a disease in which the relationship of age to treatment toxicity, and ultimate outcome can be assessed and perhaps serve to some extent as a model for other malignancies

Cohen H Am J Med 1985 79:315

Majority of myeloma patients are ≥ 65



Seer Data; Blood 125:410, 2015



- Elderly pts (older than 75 y. o.) make up more than 40% of newly diagnosed patients with myeloma; more than 60% of newly diagnosed pts ≥ 65 y. o.
- Tolerance of certain therapies is lower, but frailty is likely a more important determinant of response and toxicity than chronological age
- Elderly pts may have lower rate of unfavorable cytogenetics and other high risk features
- Survival still seems to be inferior to younger patients; possibly due to less frequent use of newer and more effective agents (e.g. Schaapveld Eur J Can 2010;46;160)
- Underrepresented in clinical trials so most recommendations are extrapolated

Many known risk factors for worse outcome in Myeloma, including:

- Cytogenetic/FISH risk
- Renal impairment
- Stage III disease
- Elevated Beta-2-microglobulin
- Frailty?
- **Frailty often defined as progressive decrease in physiologic reserve that results in an increased risk of physical and cognitive disability in the face of stressors**
- **Is frailty the same as performance status? What defines a frail myeloma patient?**

• LIMITATIONS OF PHYSICIAN REPORTED ECOG PS

Oaken M et al Am J Clin Oncol 1982 5:649

- Physicians tend to overestimate PS
- Patient reported vs Physician assessed ECOG PS concordant only 50% of the time
- 92% of patients who described themselves as ECOG 2 were rated 1 by their physician
- Blagden SP Br J Canc 2003 89:1022

OTHER WIDELY USED SCALES FARE NO BETTER

Performance status

Karnofsky Scale		Zubrod Scale	
Normal, no evidence of disease Able to perform normal activity with only minor symptoms	100 90	Normal activity	0
Normal activity with effort, some symptoms Able to care for self but unable to do normal activities	80 70	Symptomatic and ambulatory Cares for self	1
Requires occasional assistance, cares for most needs Requires considerable assistance	60 50	Ambulatory >50% of time Occasional assistance	2
Disabled, requires special assistance Severely disabled	40 30	Ambulatory ≤50% of the time Nursing care needed	3
Very sick, requires active supportive treatment Moribund	20 10	Bedridden	4

Zubrod J Chron Ds 1960 11:71; Karnofsky D Cancer 1948 1:634; Schnadig I Cancer 2008; 113:2205

Analysis of 1636 pts
Enrolled on clinical trials
Through NCCTG
Pts and providers disagreed >50%; physicians overrate

"Eyeball test" likely very inaccurate

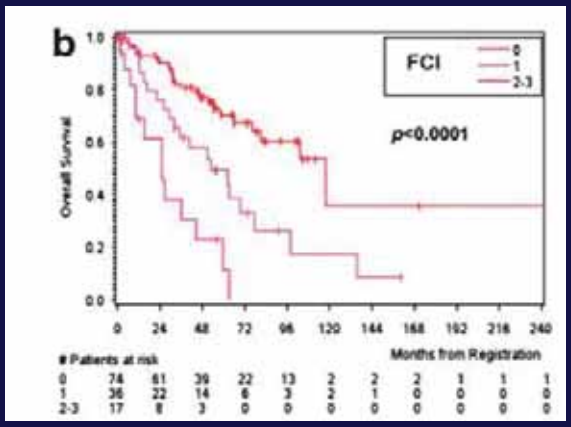
Widespread agreement to focus on function using easy to replicate measures that should have relatively easy answers:

Which is the best frailty scale(s) to use for the evaluation of myeloma patients?

- Freiburg Comorbidity Score (FCI)- evaluated age, HTN, cardiac disease, additional malignancy, hepatic, renal disease, pain, diabetes

3 factors significantly tied to OS

- eGFR ≤30ml/min
- Mod/severe impaired lung function
- KPS ≤70%



Kleber M Blood Can J 2011 1: e35

Scales that combines ADLs and medical illness may be more useful

- Activities of Daily Living
  - Locomotion and travelling
  - Dressing
  - Toileting
  - Eating
  - Climbing stairs
  - Mouth care

Katz W J Am Ger Soc 1983 31:721

- Instrumental Activities of Daily Living-includes all on left
  - Shopping
  - Cooking
  - Housekeeping
  - Laundry
  - Medication management, money management
  - Use of telephone

Lawton Gerontol 1969 3: 179

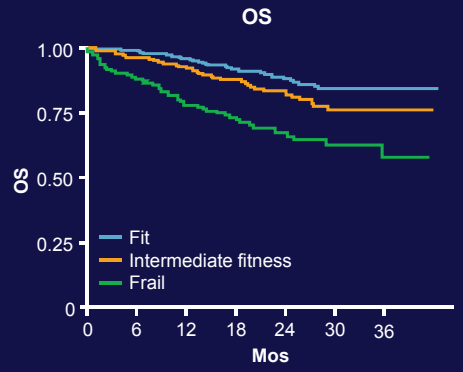
Age-adjusted Charlson Comorbidity Index (aaCCI)

- Age >50 (each decade adds 1 point
- AIDS (6 points)
- Major medical illness (2 points)
- Liver disease (3 points)
- Other medical illness- diabetes, mild COPD, CHF (1 point)
- Higher the score, more likely to experience therapy and illness related complications

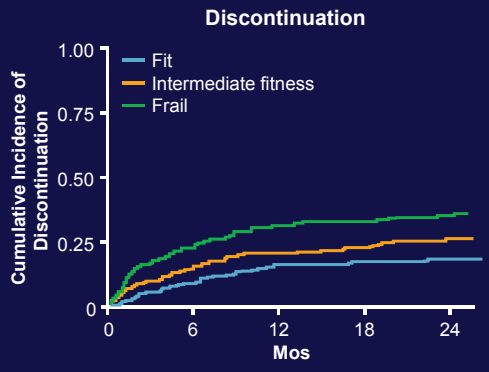
Charlson M J Clin Epidem 1994 47:1245

Effect of Pt Fitness on Myeloma Treatment Outcomes

- Pooled analysis of newly diagnosed elderly pts from 3 trials (N = 869)



3-yr OS: fit 84%, intermediate 76% (HR: 1.61; *P* = .042), frail 57% (HR: 3.57; *P* < .001)

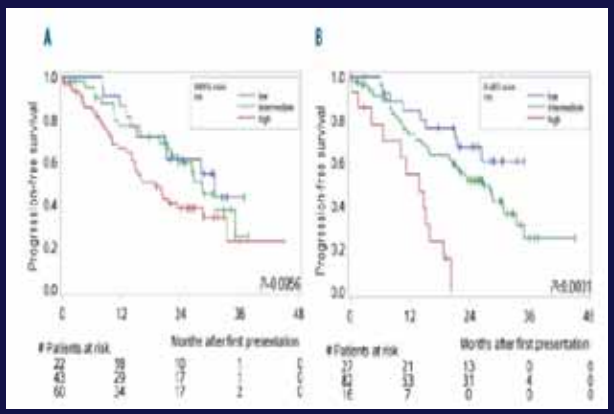


% stopping therapy at 12 mos: fit 17%, intermediate 21% (HR: 1.41; *P* = .052), frail 31% (HR: 2.21; *P* < .001)

Palumbo A, et al. Blood. 2015;125:2068-2074.

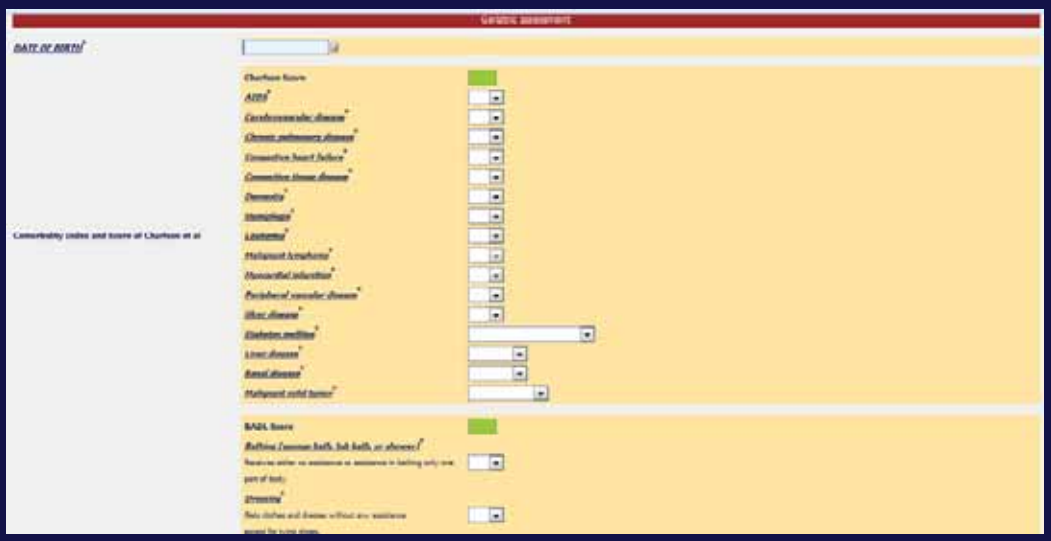
- German myeloma group validated and refined IMWG score, R-MCI sore
  - Combines IMWG score with elements of FCI, CCI,
  - Includes age, cytogenetics, frailty, hepatic, cardiac, disability, infection, pain, peripheral neuropathy and secondary malignancy
  - 13 areas; 39 total items assessed
  - Divided pts into 3 risk groups: low, intermediate, high

Englehardt M Haematol 101: 1110, 2016



- R-MCI showed better discrimination than IMWG for progression free survival
- LIMITATIONS:
  - Much more cumbersome to use than IMWG

Online version of IMWG Frailty score: www.myelomafrailtyscorecalculator.net



Suggested Age-Adjusted Dose Reduction in Patients with Multiple Myeloma.

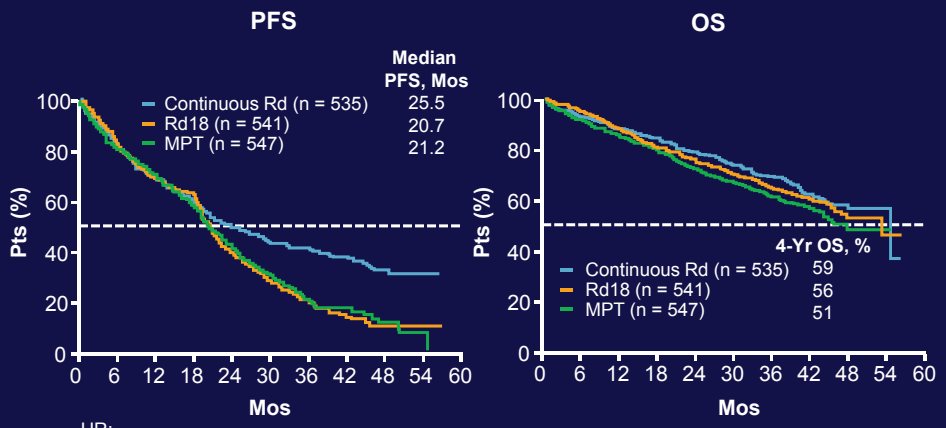
Table 3. Suggested Age-Adjusted Dose Reduction in Patients with Multiple Myeloma.

Drug	Age <65 Yr	Age 65–75 Yr	Age >75 Yr
Dexamethasone	Dose of 40 mg/day given orally on days 1–4, 15–18 every 4 wk; or 40 mg/day given orally on days 1, 8, 15, 22 every 4 wk[54]	Dose of 40 mg/day given orally on days 1, 8, 15, 22 every 4 wk[81]	Dose of 20 mg/day given orally on days 1, 8, 15, 22 every 4 wk[80]
Melphalan	Dose of 0.25 mg/kg given orally on days 1–4 every 6 wk[67]	Dose of 0.25 mg/kg given orally on days 1–4 every 6 wk[67]; or 0.18 mg/kg given orally on days 1–4 every 4 wk[67]	Dose of 0.18 mg/kg given orally on days 1–4 every 6 wk, or 0.13 mg/kg given orally on days 1–4 every 4 wk
Cyclophosphamide	Dose of 300 mg/m² given orally on days 1, 8, 15, 22 every 4 wk[50]	Dose of 300 mg/m² given orally on days 1, 8, 15, every 4 wk[41]; or 50 mg/day given orally on days 1–21 every 4 wk	Dose of 50 mg/day given orally on days 1–21 every 4 wk; or 50 mg every other day given orally on days 1–21 every 4 wk
Thalidomide	Dose of 200 mg/day given orally continuously[67,69]	Dose of 100 mg/day[66] or 200 mg/day[67,69] given orally continuously	Dose of 50 mg/day[43] to 100 mg/day[66,70] given orally continuously
Lenalidomide	Dose of 25 mg/day given orally on days 1–21 every 4 wk[54,81,82]	Dose of 15–25 mg/day given orally on days 1–21 every 4 wk[54,81,82]	Dose of 10–25 mg/day given orally on days 1–21 every 4 wk[54,81,82]
Bortezomib	Dose of 1.3 mg/m² given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 wk[73,79]	Dose of 1.3 mg/m² given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 wk[73,79]; or 1.3 mg/m² given as bolus intravenous infusion on days 1, 8, 15, 22 every 5 wk[76]	Dose of 1.0–1.3 mg/m² given as bolus intravenous infusion on days 1, 8, 15, 22 every 5 wk[76]

Palumbo A, Anderson K. N Engl J Med 2011;364:1046-1060.

The NEW ENGLAND JOURNAL of MEDICINE

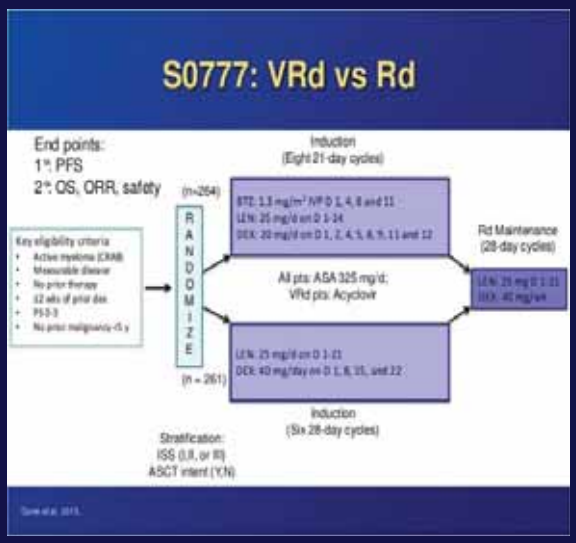
FIRST Trial: Rd (Continuous or Every 18 Mos) vs MPT

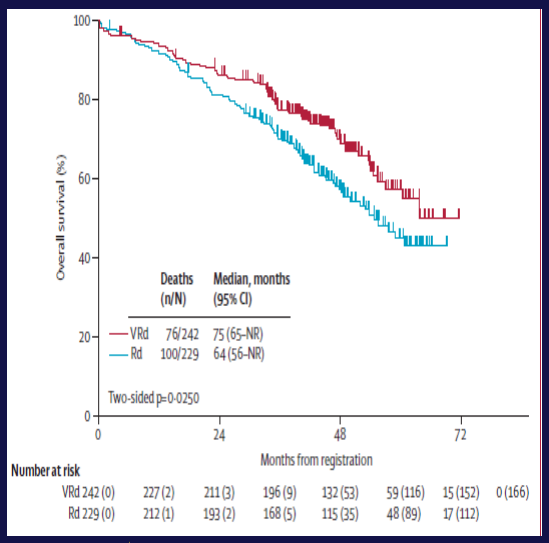


HR:
Continuous Rd vs MPT: 0.72; *P* < .001
Continuous Rd vs Rd18: 0.70; *P* < .001

35% of subjects ≥75 y.o
All subgroups benefitted from Rd

Benboubker L, et al. N Engl J Med. 2014;371:906-917.





Durie et al. Lancet 2017; 389: 519–27

43% of pts ≥65 years old

Modified Lenalidomide/Bortezomib/ Dexamethasone in ASCT-Ineligible Pts

- Phase II trial exploring utility of modified VRd (VRd lite); N = 53
  - Lenalidomide: single daily PO dose of 15 mg on Days 1-21
  - Bortezomib: 1.3 mg/m^2 SC once weekly on Days 1, 8, 15, 22
  - Dexamethasone: 20 mg 2x weekly if ≤ 75 yrs or 1x weekly if > 75 yrs
- VRd lite resulted in 90% ORR (≥ PR), ≥ VGPR: 60%
  - 5 pts d/c after < 4 cycles: worsening adrenal insufficiency (n = 1), len-based rash (n = 1), investigator discretion (n = 1), travel distance (n = 2)
- AEs manageable and well tolerated in an older population
  - Grade ≥ 3 AEs: hypophosphatemia (31%), rash (10%)

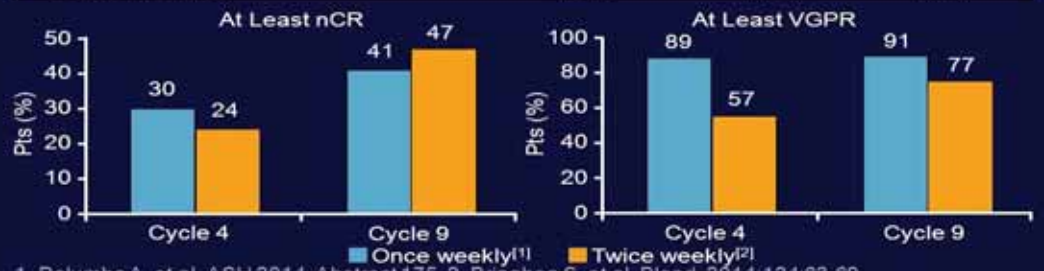
O'Donnell EK, et al. ASH 2015. Abstract 4217.

Weekly Carfilzomib in Combination With Cyclophosphamide/Dex in NDMM

- Phase I/II trial to assess feasibility of reduction of carfilzomib dosing from twice weekly to once weekly when used in combination with cyclophosphamide/dexamethasone in elderly pts with NDMM
  - Carfilzomib given weekly using standard 3+3 phase I dose-escalation (starting at 45 mg/m^2, increasing to 56 or 70 mg/m^2)
- Phase I data (n = 12) identified MTD as 70 mg/m^2
  - 3 of 12 pts in phase I portion received MTD
- Phase II cohort currently enrolling
  - 18 pts included in current analysis
- Similar baseline characteristics across all pts in phase I and II cohorts, with 30% of pts aged ≥ 75 yrs and 33% with unfavorable cytogenetics

Weekly Carfilzomib + Cyclophosphamide/ Dex: Preliminary Efficacy

Outcome	Phase I (n = 12)	MTD (n = 19)	Total (N = 28)
Median cycles received, n (range)	9 (1-9)	4 (1-9)	8 (1-9)
ORR (≥ PR), n (%)	11 (92)	15 (79)	24 (86)
• ≥ VGPR	9 (75)	11 (58)	18 (64)
• sCR + CR + nCR	4 (33)	4 (21)	7(25)



1. Palumbo A, et al. ASH 2014. Abstract 175. 2. Bringhen S, et al. Blood. 2014;124:63-69.
Reproduced with permission.

Phase II Trial of All-Oral Ixazomib/ Cyclophosphamide/Dexamethasone in R/R MM

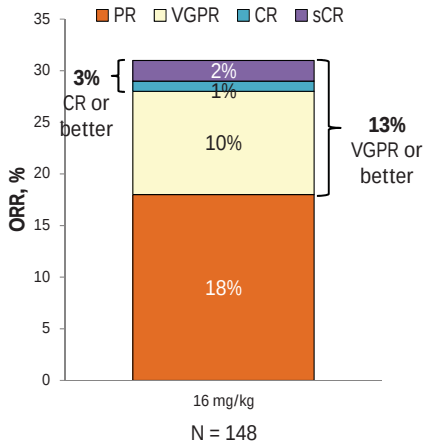
Confirmed Best Response, n (%)	All Pts (N = 73)*	Pts < 65 Yrs (n = 37)	Pts ≥ 65 Yrs (n =36)
ORR (CR + VGPR + PR)	35 (48)	12 (32)	23 (64)
CR + VGPR	12 (16)	3 (8)	9 (25)
CR	2 (3)	1 (3)	1 (3)
VGPR	10 (14)	2 (5)	8 (22)
PR	23 (32)	9 (25)	14 (39)
SD	28 (38)	19 (51)	9 (25)
PD	7 (10)	5 (14)	2 (6)

- Higher ORR (64% vs 32%) and higher CR + VGPR rate (25% vs 16%) in pts aged ≥ 65 vs < 65 yrs
- Median TTR : 1.9 mos
  - In pts aged < 65 vs ≥ 65 yrs: 1.9 vs 2.3 mos
- Median DoR: NR, with DoR up to 17 mos

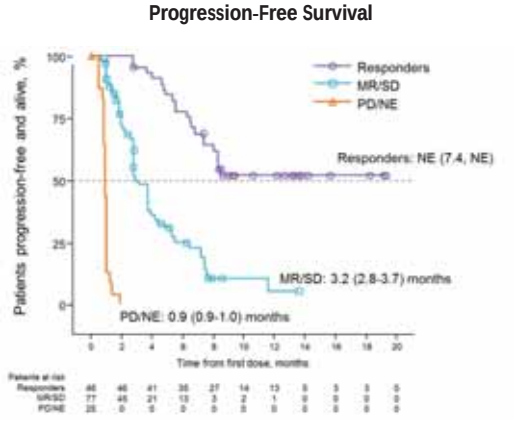
Kumar S, et al. ASH 2016. Abstract 3327.

Slide credit: clinicaloptions.com

Daratumumab as Monotherapy for Relapsed/Refractory Multiple Myeloma



N = 148



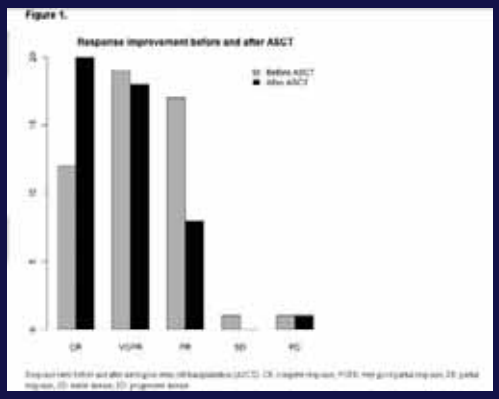
- Median OS: 19.9 months

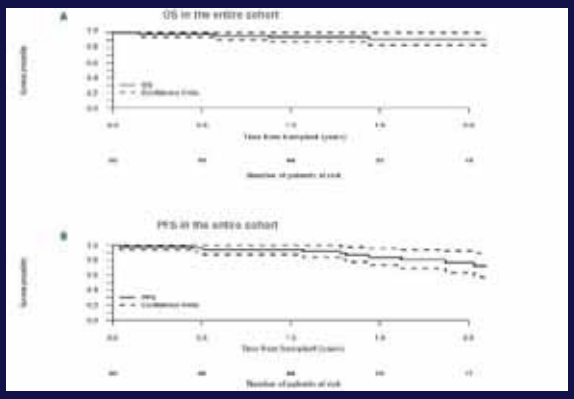
Usmani S, et al. *Blood.* 2016;128:37-44.

Aggressive prophylaxis (H2 blockade, monteleukast, reduced dosing) Increases tolerability in elderly; add IMID or PI later if response suboptimal

- Age should not be the sole determinant of frailty
- Fit older patients should be referred for clinical trials and considered for more intensive therapy, i.e. auto transplantation

Auto PBSCT also improves survival and response rate in elderly patients





Garderet L Haematologica 2016 101:1390

Comparable PFS and OS post auto PBSCT in pts > 70

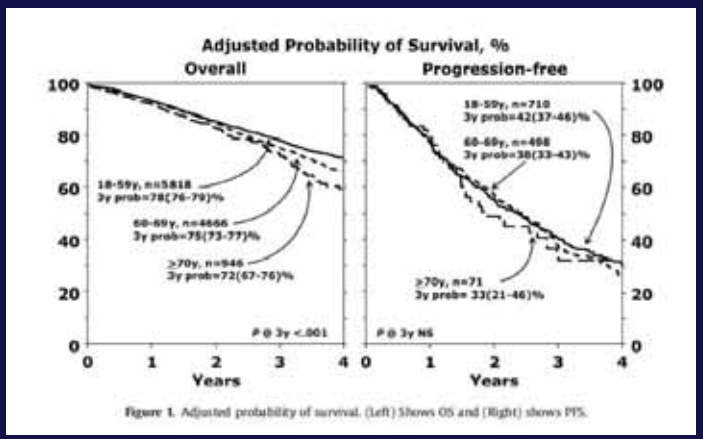


Figure 1. Adjusted probability of survival. (Left) Shows OS and (Right) shows PFS.

CIBMTR data 2008-2011, n=11,480; >70 y.o. n=946 pts

Sharma M BBMT 2014 11:1796

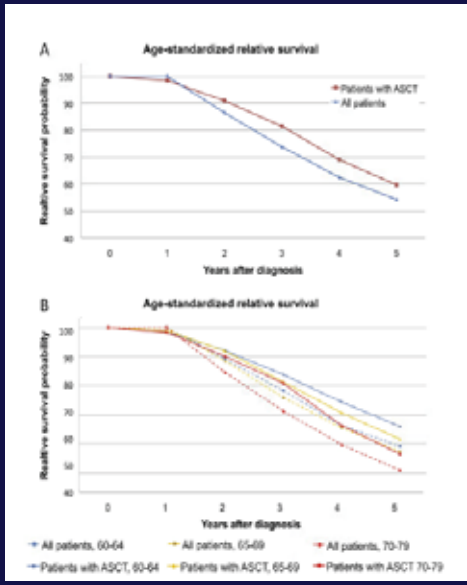
Auto PBSCT for elderly MM pts

Merz et al analyzed survival of 3591 pts aged 60-79 yrs who received auto BMT between 1998-2011 within 12 mo of dix

Compared to 13903 pts newly diagnosed with MM during the same period

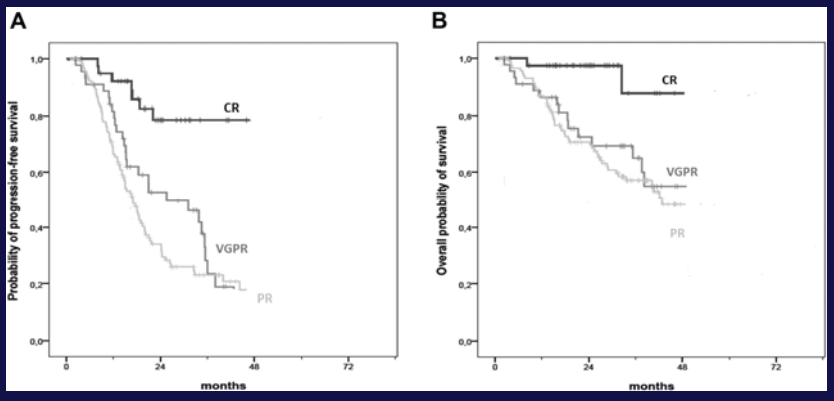
All patients benefitted from auto transplant regardless of age with superior OS

Single institution retrospective studies also support this conclusion, i.e. auto transplantation offers same benefit to elderly pts as to younger pts (Wildes TM Bone Marrow Transplantation (2015) 50, 1075–1082)



Merz M et al Euro J Canc 2016 52:1-8.

REGARDLESS OF REGIMEN, OBTAINING CR MAY BE IMPORTANT, Particularly in fit elderly patients



Survival curves according to response in patients older than 75 years
Pooled data from GISMM-2001 MP vs MPT, HOVON MP vs MPT, GIMEMA MM0305 VMP vs VMPT-VT

Francesca Gay et al. Blood 2011;117:3025-3031

blood

Case 1.

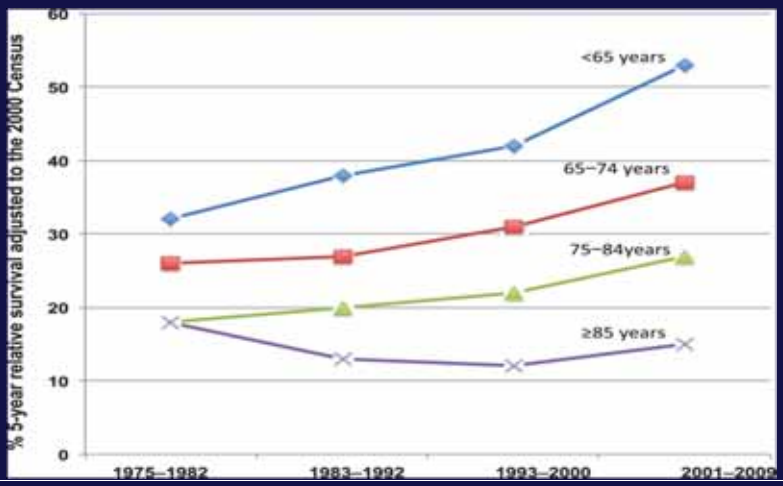
- 80 year old female referred with anemia, worsening renal insufficiency. Notes 3 month history of right hip pain
- Hgb 9.7g/dl, serum creatinine 2. 58mg/dl, IgA 20 mg/dl, IgG 340 mg/dl. IgM 10 mg/dl ↓↓
- Kappa light chains 904 mg/dl, ratio 617
- Bone survey-multiple lytic lesions skull, ribs, large lesion in right femoral head
- Bone marrow biopsy-63% plasma cells, Cytogenetics 46 x,x FISH 1q amplification
- PMH-aortic aneurysm repair 2015 (no complications), hypertension
- Current medications: amlodipine, furosemide
- Social History- lives in senior apartment complex; group activities but fixes own meals; does laundry

Case 2.

- 75 year old male presented with anemia in 7/2015
- PMH: no cardiac, renal, pulmonary disease
- Workup: bone survey without lytic lesions; low dose whole body CT showed diffuse osteopenia; Hgb 8.2g/dl; lambda 44.8mg/dl, IgA 1574 mg/dl, M spike 1.2g/dl; nl WBC, plts
- BM BX: 30% plasma cells; Cytogenetics/FISH: 1q amplification; -13; 46 x,y
- Treated with lenalidomide 15 mg d 1-21, dexamethasone 40 mg weekly
- After 6 months, Hgb 9 g/dl, lambda light chains 27 mg/dl; IgA 1108mg/dl
- Referred for second opinion
- Observed PS is 0

- Frailty score case #1:
- Charlson comorbidity: points for Age, renal disease, Cardiovascular (5)
- Also not independent in transportation, housekeeping
- IMWG Frailty score: 3
- **Recommended therapy: modified VRD**

- Frailty score case #2:
- Charlson comorbidity: 1 (point for age)
- Independent in all ADLS and IADLs
- IMWG Frailty Score: 0
- **Recommended therapy: triplet followed by auto PBSCT**



From: Multiple Myeloma in the Very Old: An IASIA Conference Report
J Natl Cancer Inst. 2014;106(5). doi:10.1093/jnci/dju067

Conclusions:

- Average age of myeloma patients will continue to climb as population ages
- Therapy for myeloma patients should be determined largely by fitness; scoring systems exist and are relatively easy to use
- Even older frail patients can benefit from newer therapies
- Consider dose modifications, rather than omission of drugs to capitalize on synergy
- Use steroids sparingly to avoid hyperglycemia, myopathy, infection
- Autologous transplantation is underutilized in older MM pts and should be offered to fit pts
- Always consider clinical trials

Management of Waldenström's Macroglobulinemia


HARVARD MEDICAL SCHOOL

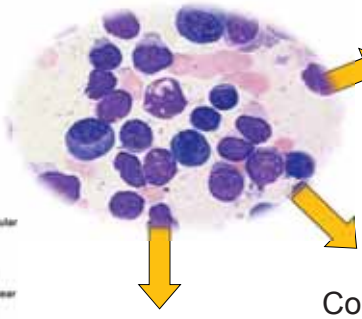
Steven P. Treon, MD, MA, MS, PhD, FRCP
Professor of Medicine, Harvard Medical School
Director, Bing Center for WM
Chair, WM Clinical Trials Group

Manifestations of WM Disease

Bing Neel Syndrome

Bone Marrow

↓Hb>>> ↓PLT> ↓WBC



Hyperviscosity Syndrome:
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP

≤20% at diagnosis;
50-60% at relapse.

Hepcidin
↓Fe Anemia

Cold Agglutinemia (5%)
Cryoglobulinemia (10%)
IgM Neuropathy (22%)
Amyloidosis (10-15%)

Treon S., Hematol Oncol. 2013; 31:76-80.

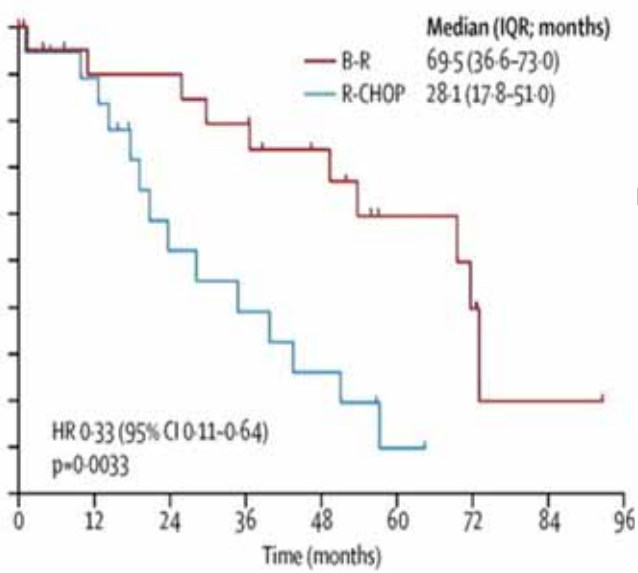
ta3

Primary Therapy of WM with Rituximab

Regimen	ORR	VGPR/CR	TTP (mo)
Rituximab x 4	25-30%	0-5%	13
Rituximab x 8	40-45%	5-10%	16-22
Rituximab/thalidomide	70%	10%	30
Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, CDR	70-80%	20-25%	30-36
Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R	70-90%	20-30%	36-62
Rituximab/Proteasome Inhibitor i.e. BDR, VR, CaRD	70-90%	20-40%	42-66
Rituximab/bendamustine	90%	30-40%	69

Reviewed in Dimopoulos et al, Blood 2014; 124(9):1404-11; Treon et al, Blood 2015; How I Treat WM

Bendamustine-R vs. CHOP-R: WM Subset Analysis



N=41

Rummel et al, Lancet. 2013 Apr 6;381(9873):1203-10.

Slide 3

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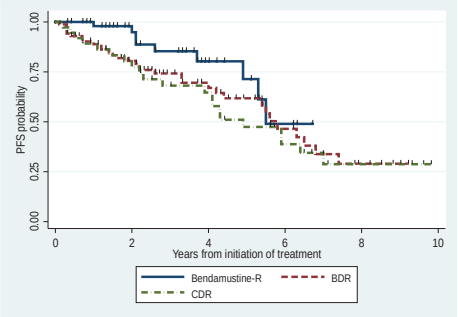
ta3 I don't know what the references for this are.
tristin.abair, 6/6/2011

Dana Farber Study of Benda-R vs. BDR vs. CDR as Primary Therapy in WM

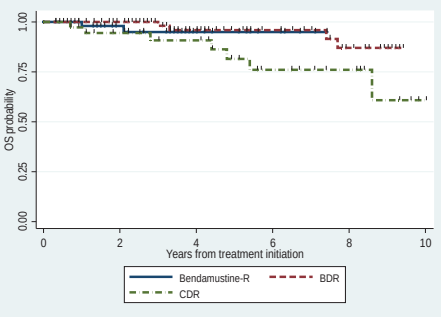
N=182

Progression Free Survival



Log rank p=0.1

Overall Survival



Log rank p=0.06

AML/MDS	**Median f/u**
2/57 Benda-R (4%)	3 yrs
0/37 CDR (0%)	4 yrs
0/88 BDR (0%)	5 yrs

Castillo et al, ASH 2017 (Accepted)

Bendamustine therapy in previously treated WM

Overall/Major RR: 83%

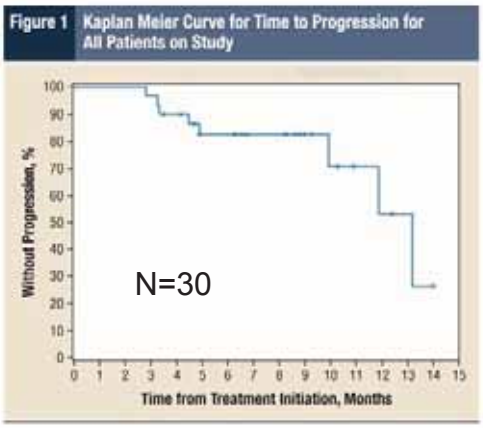
Only 46% of patients tolerated 6 cycles

RR lower in refractory patients

Prolonged cytopenias common (15%)

Gr ¾ infections (15%)

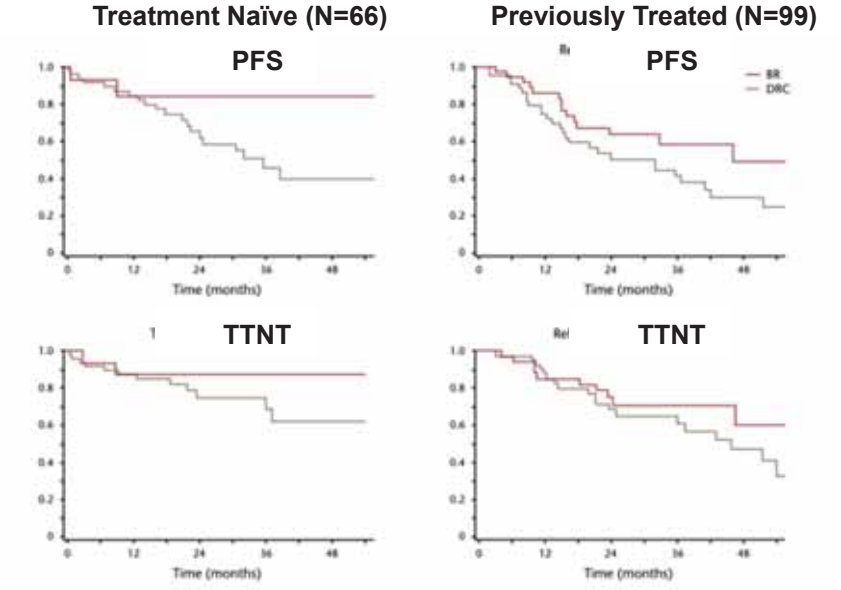
MDS/Transformation: 2 (7%)



Median PFS: 13.2 months

Treon et al, Clin. Lymph. Myeloma 2011

Mayo Study of Benda-R vs. DRC in WM



Paludo et al, ASH 2016

Mayo Study of Benda-R vs. DRC in WM
Adverse Events

	Benda-R		DRC	
% with AE	All	Gr ≥3	All	Gr ≥3
Neutropenia	39	11	39	20
Thrombocytopenia	26	2	20	7
Nausea/Vomitting	9	2	7	0
Fever/Chills	5	0	3	0
Headache	2	0	4	0
Hypotension	2	0	3	1
Infections	19	5	15	3

5% of patients developed treatment related MDS or transformation to aggressive lymphoma.

Paludo et al, ASH 2016

Italian Study: FCR vs. Benda-R in previously treated WM

	FCR	Benda-R
N=	37	50
ORR/Major RR	81%	80%
Median PFS	69 months	35 months
Discontinuation due to toxicity	40%	38%
Secondary Malignancies	32%	8%

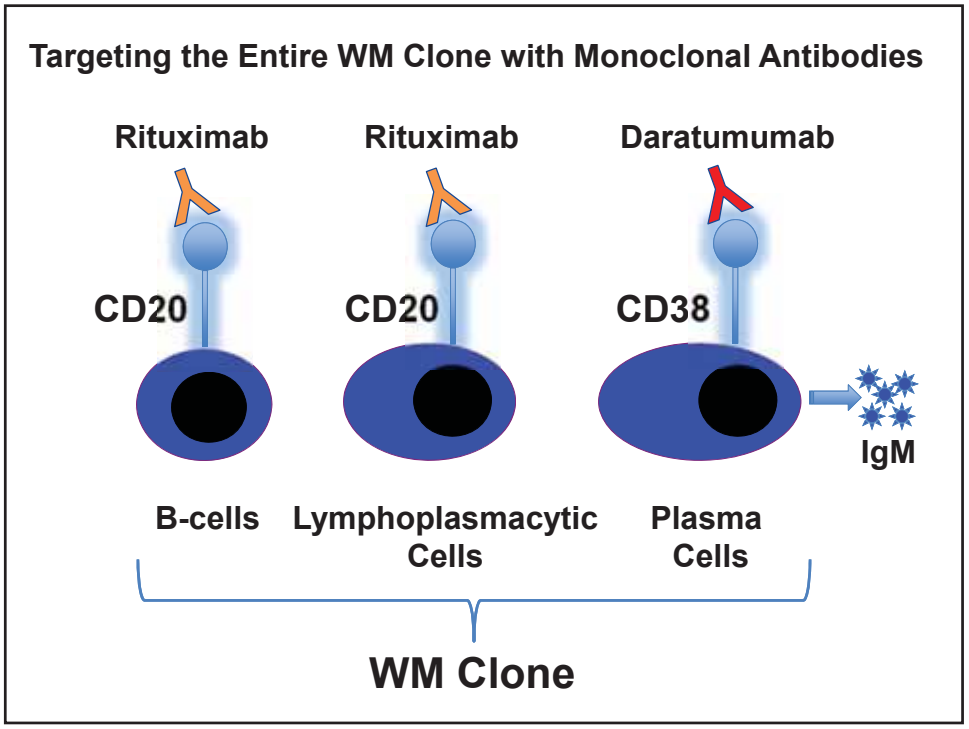
Intended therapy: 6 cycles

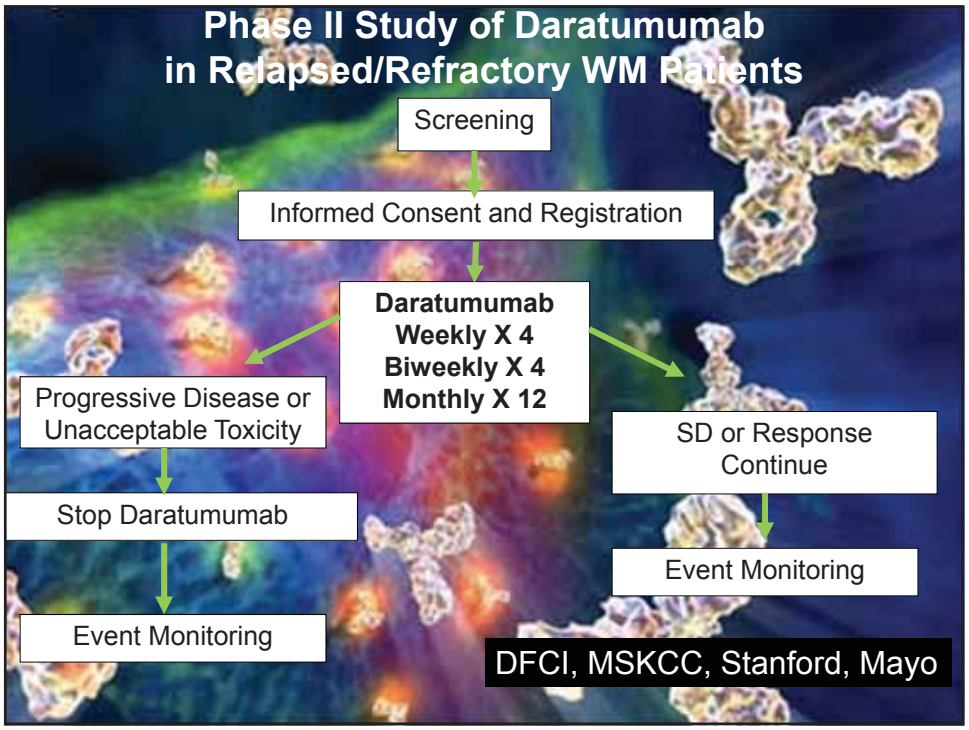
Tedeschi et al, ASH 2015

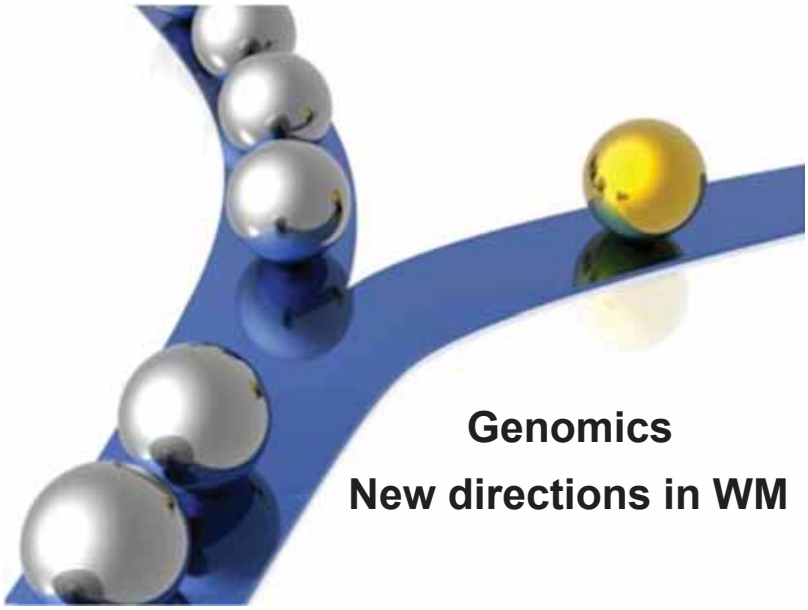
Clinical Sequelae of Rituximab Therapy in WM

- **IgM flare (50% of patients)**
  -Symptomatic hyperviscosity in patients with high serum IgM (>4,000 mg/dL).
  -Potentiate IgM Neuropathy, Cryoglobulinemia, Cold Agglutinemia
- **Hypogammablobulinemia (most patients)**
  -Recurring sinobronchial infections and nosocomial infections with IgA, IgG depletion
  -Chronic IVIG replacement
- **Intolerance with prolonged use (10% of patients)**

Anderson et al, JNCCN 2012; 10(10):1211-9.


Targeting the Entire WM Clone with Monoclonal Antibodies
Rituximab
Rituximab
Daratumumab
CD20
CD20
CD38
IgM
B-cells
Lymphoplasmacytic Cells
Plasma Cells
WM Clone


Phase II Study of Daratumumab in Relapsed/Refractory WM Patients
Screening
Informed Consent and Registration
Daratumumab
Weekly X 4
Biweekly X 4
Monthly X 12
Progressive Disease or Unacceptable Toxicity
Stop Daratumumab
Event Monitoring
SD or Response Continue
Event Monitoring
DFCI, MSKCC, Stanford, Mayo

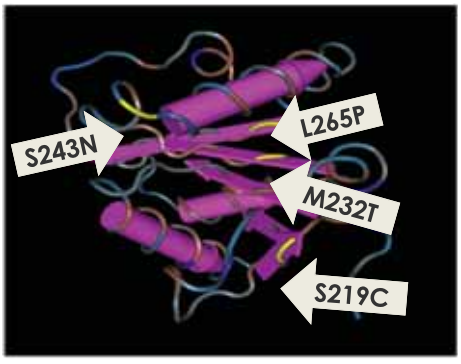


Genomics

New directions in WM

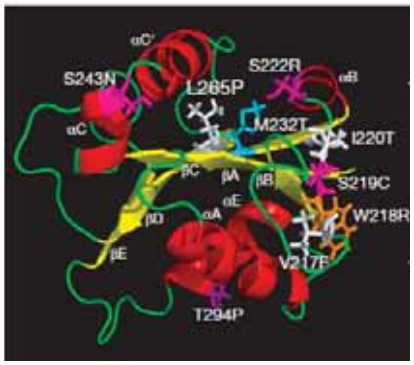
MYD88 Mutations in B-cell LPD

WM



93-95% MYD88 L265P
2% Non-L265P MYD88

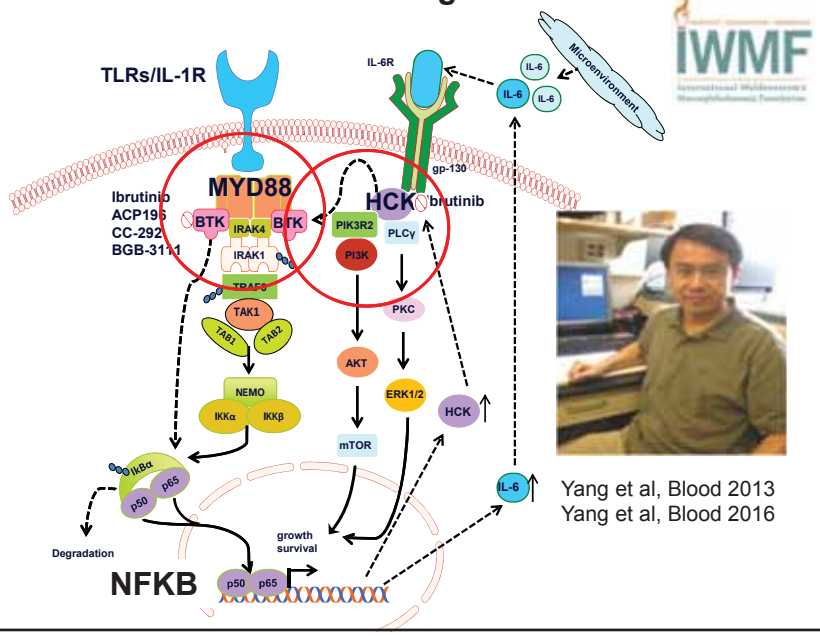
ABC DLBCL



29% MYD88 L265P
10% Non-L265P MYD88

Treon et al, NEJM 2012; Treon et al, NEJM 2015; Jiménez et al, 2013; Varettoni et al 2013; Poulain et al, 2013, Xu et al, 2013.

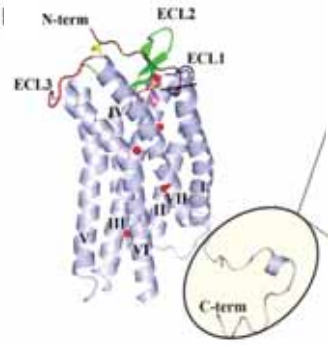
Signaling Pathways Driven by Mutated MYD88 in Waldenström's Macroglobulinemia



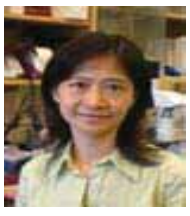
Yang et al, Blood 2013
Yang et al, Blood 2016

CXCR4 C-tail mutations in WM

- 30-40% of WM patients; v. rare in other LPD
- >30 Nonsense, Frameshift Mutations
- Segues with MYD88 mutations
- High serum IgM levels/Hyperviscosity
- Promote **ibrutinib resistance** through enhanced AKT/ERK signaling.

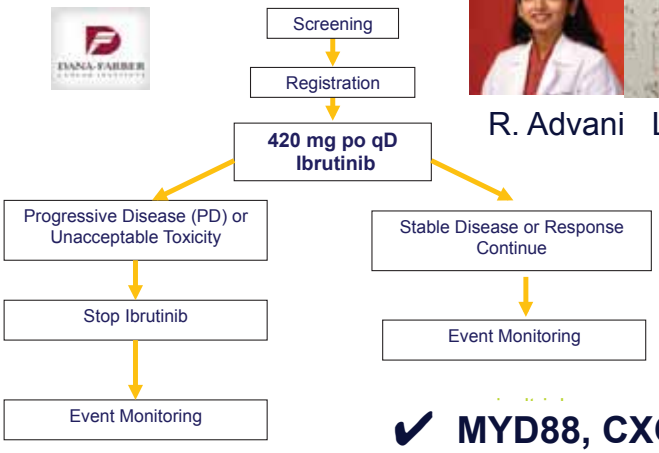


Hunter et al, Blood 2013;
Rocarro et al, Blood 2014:
Poulain et al, Blood 2016;
Cao et al, Leukemia 2014;
Cao et al, BJH 2015



Multicenter study of Ibrutinib in Relapsed/Refractory WM (≥1 prior therapy)

R. Advani L. Palomba



✔ **MYD88, CXCR4 Mutation Status**

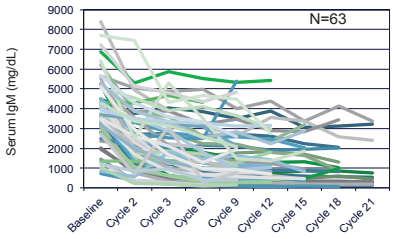
Baseline Characteristics for Study Participants (n=63)

	Median	Range
Age (yrs)	63	44-86
Prior therapies	2	1-9
Hemoglobin (mg/dL)	10.5	8.2-13.8
Serum IgM (mg/dL)	3,520	724-8,390
B_2M (mg/dL)	3.9	1.3-14.2
BM Involvement (%)	60	3-95
Adenopathy >1.5 cm	37 (59%)	N/A
Splenomegaly >15 cm	7 (11%)	N/A

Treon et al, NEJM 2015; 372:1430

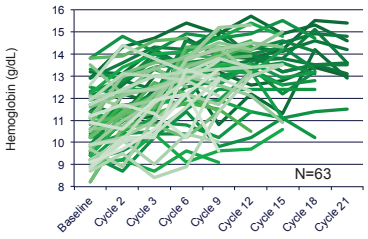
Serum IgM and Hb Levels Following Ibrutinib

Serum IgM



Best IgM Response:
3,520 to 880 mg/dL; p<0.001

Hb



Best Hemoglobin Response:
10.5 to 13.8; p<0.001

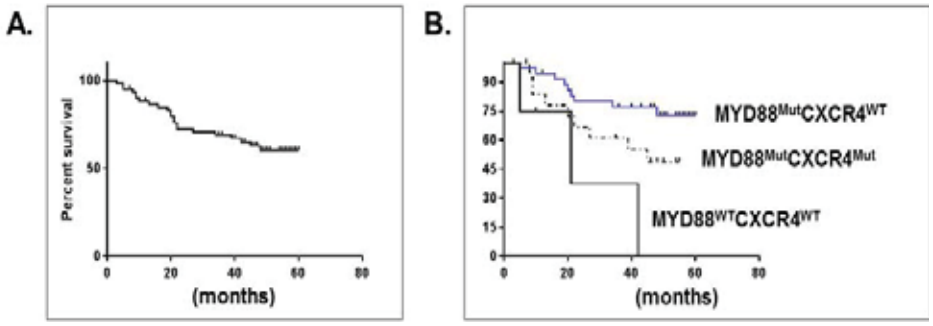
Treon et al, N Engl J Med. 2015; 372(15):1430-40.

Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations.

	ALL	MYD88^{Mut} CXCR4^{WT}	MYD88^{Mut} CXCR4^{Mut}	MYD88^{WT} CXCR4^{WT}	P-value
N=	**63**	36	21	5	
ORR	**90.4%**	100%	85.7%	60%	0.005
Major (>PR)	**77.7%**	97.2%	66.6%	0%	<0.001
VGPR	**27.0%**	**44.4%**	9.5%	0%	0.007
Time to Minor Response (mos.)	**1.0**	1.0	1.0	1.0	0.10
Time to Major response (mos.)	**2.0**	2.0	**6.0**	N/A	0.05

Treon et al, ASH 2017 (abstract accepted)

Ibrutinib in Previously Treated WM: PFS

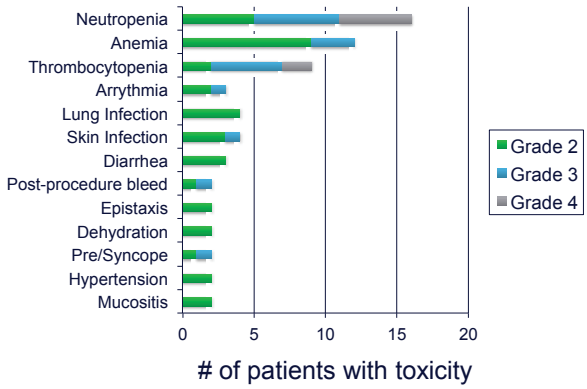


Median PFS for all patients not reached @ 5 years

Treon et al, ASH 2017 (abstract accepted)

Ibrutinib Related Adverse Events in previously treated WM patients

Toxicities >1 patient; N=63



★**No infection signal; No impact on IGA and IGG immunoglobulins**

★10% incidence with larger WM Experience; earlier presentation for those patients with prior Afib history. Most patients resumed ibrutinib with arrhythmia management.

Treon et al, NEJM 2015; Gustine et al, AJH 2016

Ibrutinib in Rituximab-Refractory WM Patients: Multicenter, Open-Label Phase 3 Substudy (iNNOVATE™)

Median Prior Therapies: 4 (range 1-7)
Median follow-up: 18.1 (range 6.3-21.1 months)

ORR: 90% Major RR (≥ PR): 71%

	(N=)	(%)
VGPR	4	13
PR	18	58
MR	6	19

Median time to ≥ MR: 4 weeks
Median time to best response: 8 weeks

18 mo PFS: 86%
18 mo OS: 97%

Dimopoulos et al, IWWM9 2016; Lancet Oncol 2017.

iNNOVATE ARM C: Frequent Adverse Events

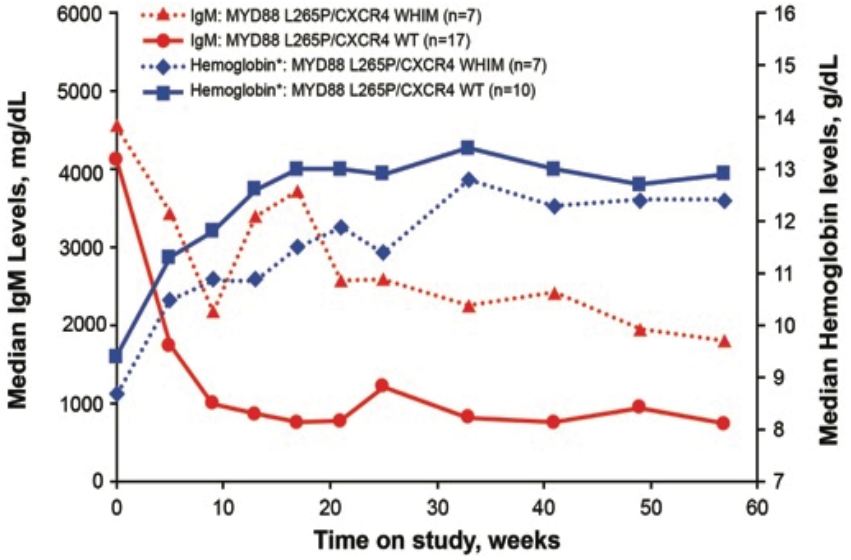
≥5% G3

	Grade 1-2	Grade 3
Neutropenia	3 (10%)	3 (10%)
Anemia	3 (10%)	2 (6%)
Thrombocytopenia	4 (13%)	1 (3%)
Diarhea	11 (36%)	2 (6%)
Hypertension	4 (13%)	3 (10%)

- No Afib events
- Dose reductions for AEs: 4 (13%)

Dimopoulos et al, Lancet Oncol. 2017

Impact of CXCR4 Mutation Status on IgM and HgB Response



Dimopoulos et al, IWWM9; Lancet Oncology, 2017

Primary Therapy of WM with Ibrutinib

N=30

420 mg a day x 4 years

All patients are undergoing whole genome sequencing at 6, 12, 24, 36, 48 months

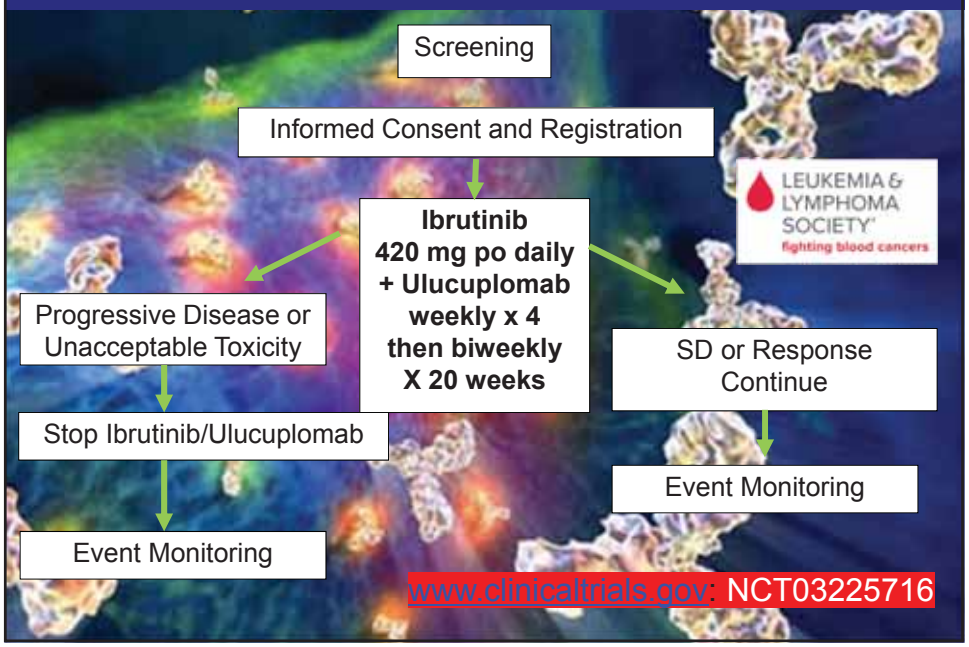
Clonal sequencing to determine how individual cells respond to ibrutinib.

Study to be reported at ASH 2017

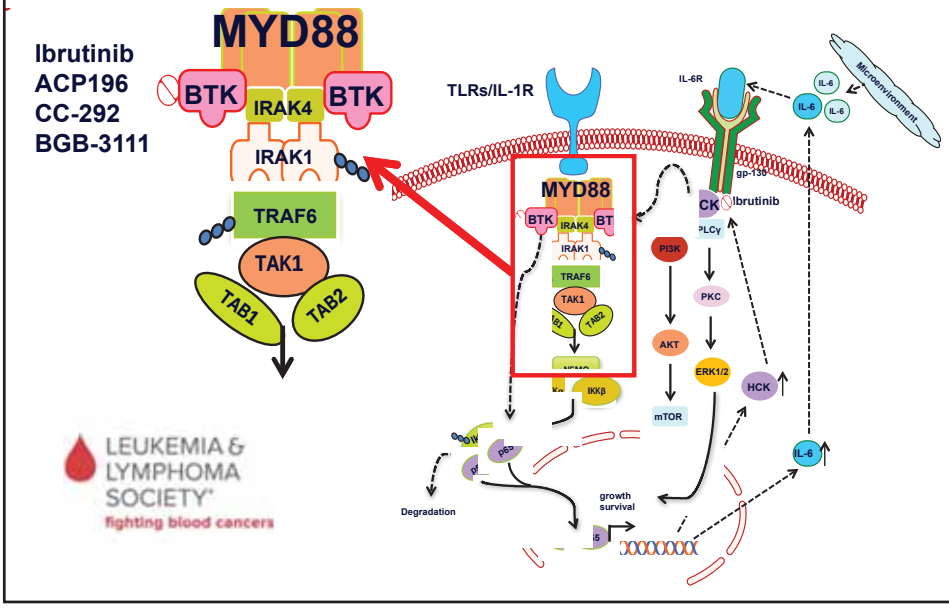
CXCR4 mutation status impacts response and time to response

Strategies to overcome Intrinsic Resistance to Ibrutinib in WM

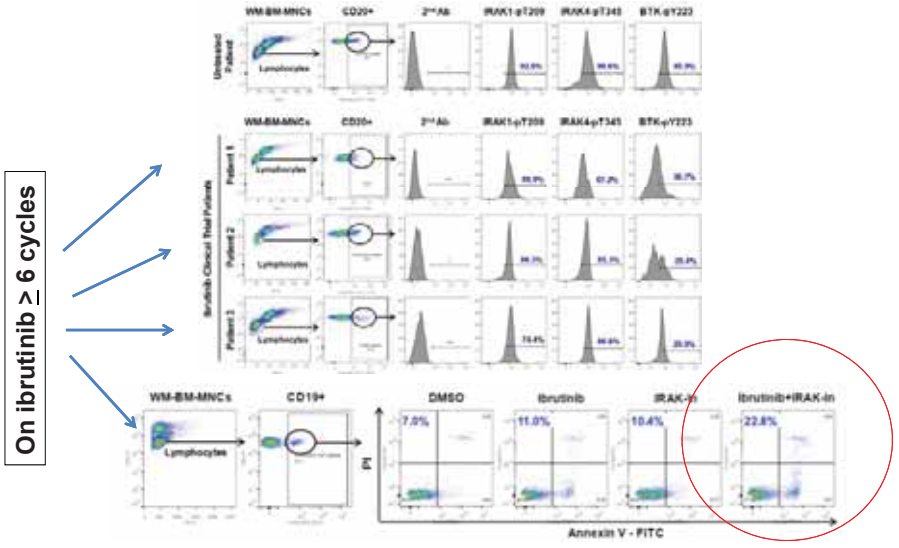
Phase II Study of Ibrutinib plus Ulucuplomab in CXCR4^{WHIM} WM Patients



Signaling Pathways Driven by Mutated MYD88 in Waldenström's Macroglobulinemia



IRAK1/4 kinase survival signaling remains intact in WM cells from ibrutinib treated patients.



Combining of Novel IRAK1 inhibitor JH-X-119 with Ibrutinb Shows Synergism in MYD88 Mutated Cells

Sara Buhrlage Nathanael Gray

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

IWMF
International Waldenström's Macroglobulinemia Foundation

BCWM.1

Ibrutinib

Combination Index

JH-X-119-01

μM	4.000	1.265	0.400	0.126	0.040
20.000	0.761	0.663	0.752	0.958	1.043
6.325	0.488	0.424	0.454	0.556	0.577
2.000	0.605	0.572	0.734	1.051	1.105
0.632	0.573	0.557	0.622	0.743	0.982
0.200	0.561	0.375	0.397	0.428	0.32

0 1 10

TMD-8

Ibrutinib

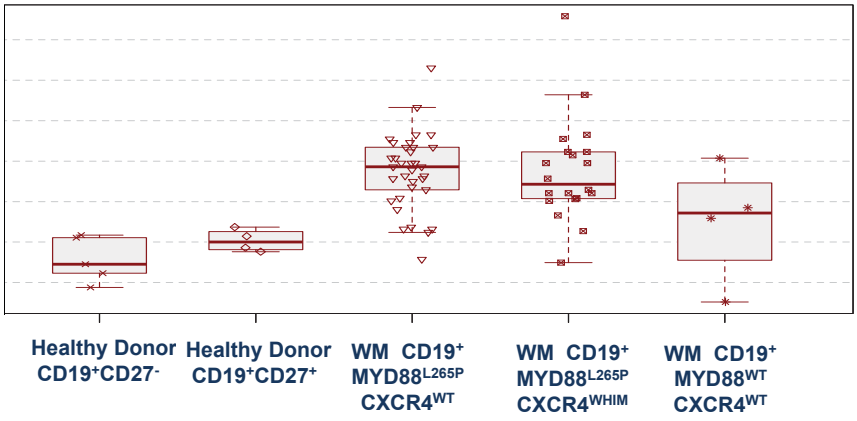
Combination Index

JH-X-119-01

μM	0.040	0.013	0.004	0.001	0.000
20.000	0.193	0.035	0.025	0.066	0.502
6.325	0.126	0.022	0.014	0.08	0.379
2.000	0.375	0.115	0.082	0.343	0.879
0.632	0.914	0.321	0.179	0.485	0.941
0.200	1.112	0.387	0.232	0.649	0.696

0 1 10

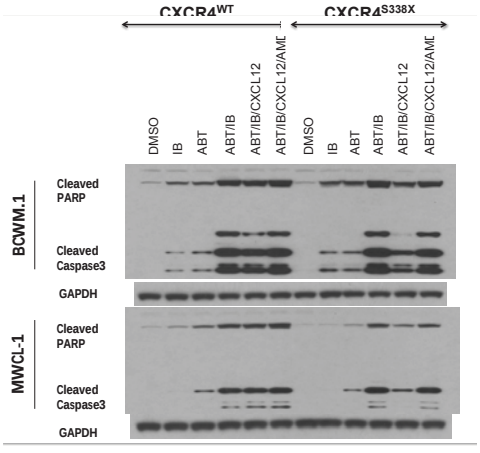
BCL-2 is overexpressed in primary WM patient cells by transciptome analysis in MYD88 mutated patients regardless of CXCR4 mutation status.



p<0.001 for healthy donor samples versus any MYD88^{L265P}CXCR4$^{WT\ or\ WHIM}$

Castillo et al, ICML 2015; Hunter et al, BLOOD 2016

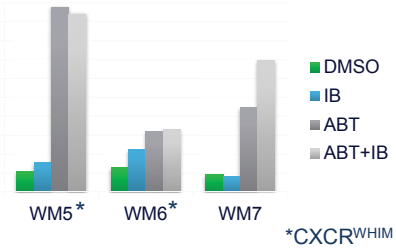
Venetoclax (ABT-199) enhances Ibrutinib killing in CXCR4^{WT} and CXCR4^{WHIM} WM Cells.



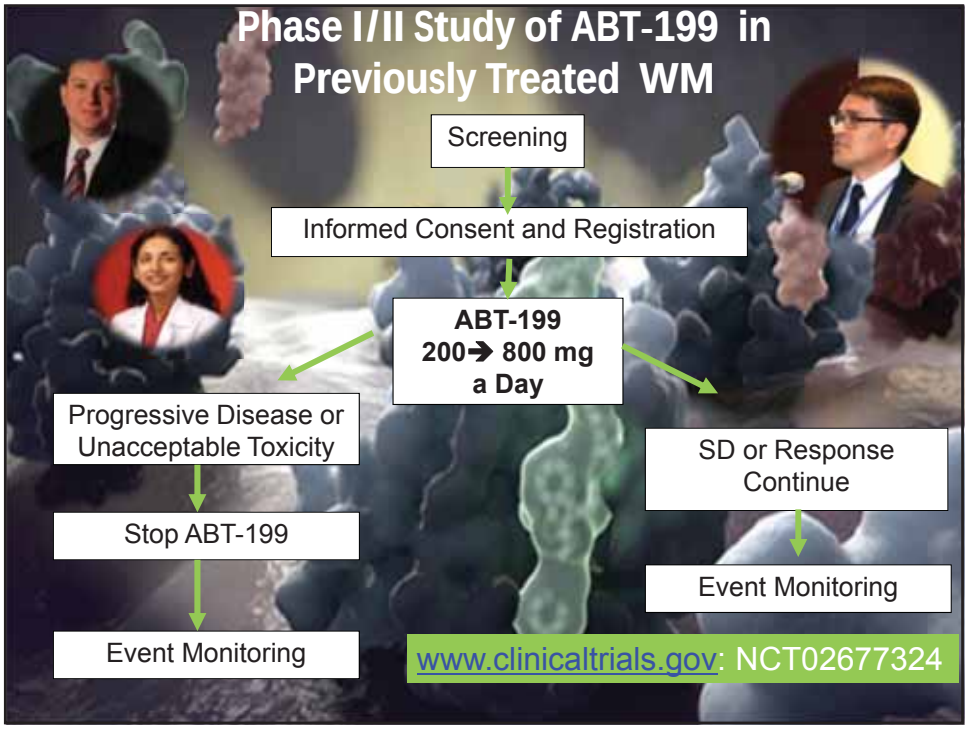
Cao et al, BJH 2015

Untreated

Ibrutinib >6 mo.



*CXCR^{WHIM}



Approach to Frontline Therapy of Symptomatic WM

Hyperviscosity, Severe Cryos, CAGG, PN➔ Plasmapheresis

MYD88 Mutated/No CXCR4 mutation
No bulky disease, no contraindications➔ Ibrutinib (if available)
Bulky disease ➔ Benda-R
Amyloidosis ➔ Bortezomib/Dex/Rituximab (BDR)
IgM Peripheral Neuropathy ➔ Rituximab ± Alkylator

MYD88 Mutated/CXCR4 mutation
Same caveats as above
If immediate response needed, either BDR or Benda-R

MYD88 Wild-Type
✓ non-L265P MYD88 mutations
BDR or Benda-R

- **Hold Rituximab until IgM <4000 mg/dL or empiric pheresis is performed.**
- **Consider Maintenance Rituximab**
- **Consider Ofatumumab if R intolerant.**

Hunter et al, JCO 2017

Salvage Therapy of Symptomatic WM

Consider repeat primary therapy if response >2 years

MYD88 Mutated/No CXCR4 mutation
Same caveats as primary therapy

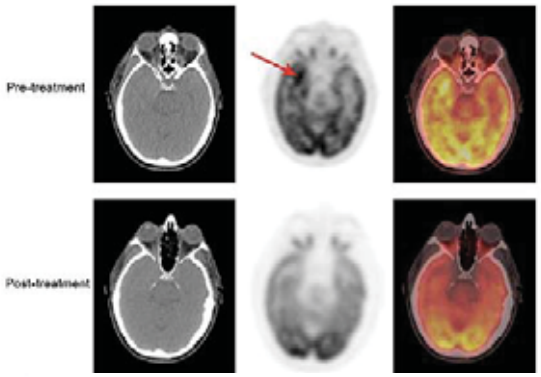
MYD88 Mutated/CXCR4 mutation
Same caveats as primary therapy
If immediate response needed, either BDR or Benda-R

MYD88 Wild-Type
Same caveats as primary therapy
✓ non-L265P MYD88 mutations

- **Everolimus >2 prior therapies**
- **Nucleoside analogues (non-ASCT candidates)**
- **ASCT in multiple relapses, chemosensitive disease**

Hunter et al, JCO 2017

Ibrutinib (560 mg/day) induced response in a WM patient with Bing Neel Syndrome



		Ibrutinib (nM)		
Study Day	Time post-dose (h)	CSF	Plasma	%CSF/Plasma
Day 1	0	BLQ	BLQ	NA
	2	34	1133	3·0
1 Month	3	16	463	3·5
4 Months	2·5	7	318	2·2

Mason et al, BJH 2016

Acknowledgements

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10th International Workshop on Waldenstrom's Macroglobulinemia

New York City, NY
October 10-13, 2018

Patient Symposium
October 14, 2018

www.wmworkshop.org

Co-Organizers
Rick Furman
Ari Melnick
Lia Palomba

BU School of Medicine
Amyloidosis Center

AL Amyloidosis: An Under-diagnosed Disorder

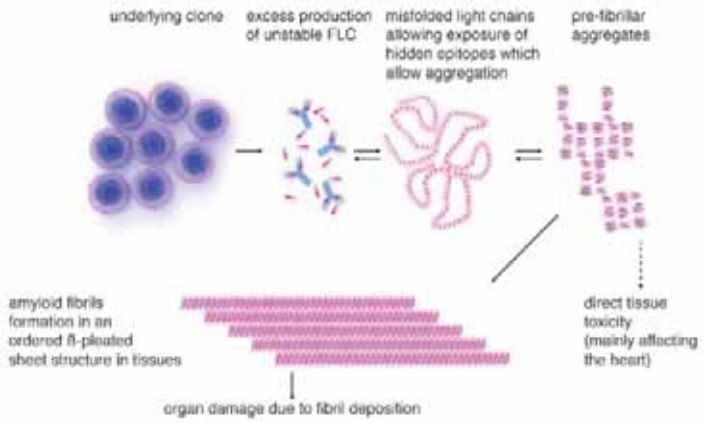
Shayna Sarosiek
Boston University Amyloidosis Center

Objectives

- What is amyloidosis?
- Types of amyloidosis
- Diagnosis of AL amyloidosis
- Presenting signs & symptoms
- Approach to treatment and supportive care

What is amyloidosis?

- **Misfolding of a precursor protein**
  - Light chain, transthyretin, etc
- **Misfolded proteins aggregate and form amyloid fibrils**
  - Anti-parallel β strands that form sheets
- **Deposit in organs and cause dysfunction**



Mahmood, et al Haematologica 2014

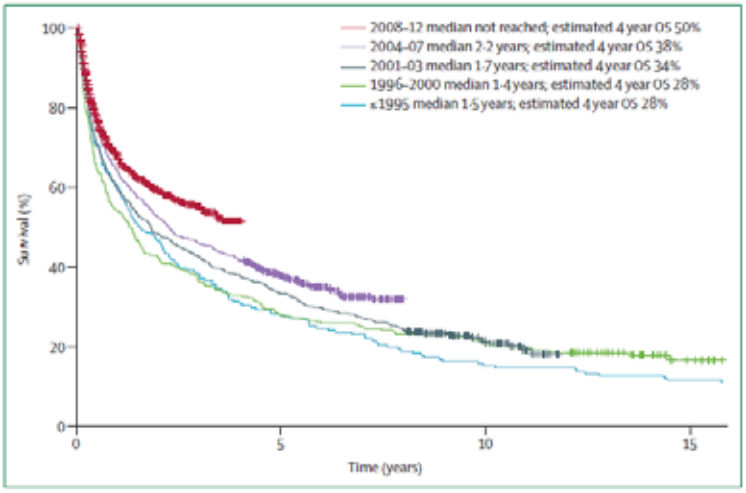
Types of Amyloidosis

- **AL amyloidosis**
  - Most common in USA
- **Transthyretin** (ATTR)
  - Wild-type TTR
  - Mutant TTR (hereditary)
- **Secondary**
- **Other hereditary types**
  - Fibrinogen, Apolipoprotein A1 and A2, lysozyme, gelsolin

**Consider ATTR amyloidosis in older patients with MGUS and cardiac amyloidosis

AL Amyloidosis

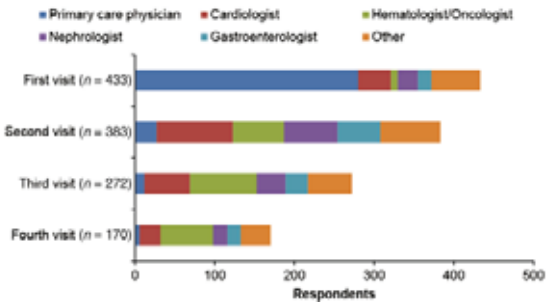
- **Rare disorder**
- **~10 patients/million per year**
  - Similar to Hodgkin's lymphoma or CML
- **Poor prognosis**
  - Overall survival is increasing
  - No recent change in early mortality



Wechalekar, et al Haematologica 2015

Making the Diagnosis

- **Diverse presentation**
  - Fibrils can affect most organs
  - Tissue specificity is poorly understood
  - Varied initial clinical presentation



Lousada, et al Adv Ther 2015

Making the Diagnosis in MGUS and SMM patients

- ****A patient with MGUS or smoldering multiple myeloma and…**
  - Nephrotic syndrome
  - Bilateral carpal tunnel syndrome
  - Heart failure
  - Peripheral neuropathy, especially in non-diabetic
  - Autonomic neuropathy
  - Hepatomegaly
  - Macroglossia or periorbital bruising
  - Severe fatigue and weight loss

****Evaluate for signs/symptoms of organ dysfunction (including NT-proBNP, albuminuria) during routine MGUS evaluations**

Four steps for diagnosis of AL Amyloidosis

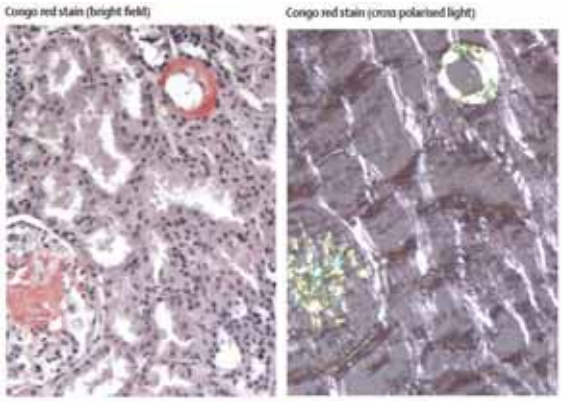
1. Demonstrate amyloid deposition
2. Type amyloid deposits
3. Assess for monoclonal disease
4. Determine the extent of organ involvement

Four steps for diagnosis of AL Amyloidosis

1. **Demonstrate amyloid deposition**
2. Type amyloid deposits
3. Assess for monoclonal disease
4. Determine the extent of organ involvement

Demonstrate amyloid deposition by biopsy

- **Congo red stain, Apple-green birefringence**
- **Fat pad**
  - aspirate (bedside, beneficial in coagulopathy)
  - biopsy (surgical)
- **Involved organ**
  - kidney, heart, GI tract, tongue
- **Salivary gland**



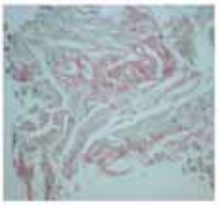
Wechalekar, et al Lancet 2015

Four steps for diagnosis of AL Amyloidosis

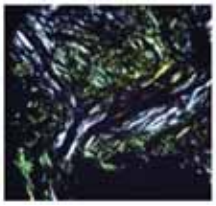
1. Demonstrate amyloid deposition
2. **Type amyloid deposits**
3. Assess for monoclonal disease
4. Determine the extent of organ involvement

Characterize the type of amyloid

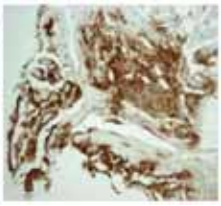
- **Immunohistochemistry**
  - Widely available
  - Low sensitivity in AL amyloidosis



Congo Red Stain



Apple-green birefringence

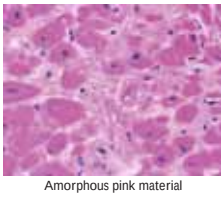


Immunohistochemistry

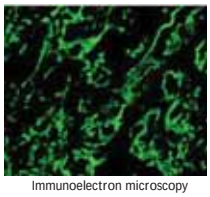
Patel, et al J of Int Med 2015

- **Immunogold electron microscopy**
  - Gold-labeled anti-fibril protein antibodies

- **Laser microdissection and mass spectrometry**
  - Gold standard



Amorphous pink material



Immunoelectron microscopy

Falk Circulation 2011

Four steps for diagnosis of AL Amyloidosis

1. Demonstrate amyloid deposition
2. Type amyloid deposits
3. **Assess for monoclonal disease**
4. Determine the extent of organ involvement

Assess for monoclonal disease

- **SIFE and UIFE**
- **SPEP and UPEP**
- **Serum Free Light Chains**
- **Bone marrow biopsy** (with cytogenetics and FISH)
- **Evaluate for MM, lymphoma, or other diseases**

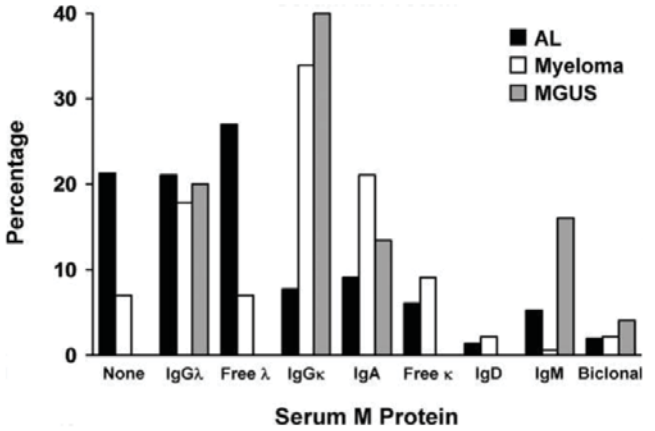
**Typically modest plasma cell infiltrate on bone marrow (median 5-10%), >10% is poor prognostic marker

**t(11;14) may predict poor response to bortezomib

Bochtler, et al J Clin Oncol 2015
Kourelis, et al J Clin Oncol 2013

Findings in AL amyloidosis compared to multiple myeloma

- >20% have no measurable M-spike
- ~50% produce light chain only
- Lambda clone is *more* common than kappa (4:1)



Gertz Am J Hematol 2013

Four steps for diagnosis of AL Amyloidosis

1. Demonstrate amyloid deposition
2. Type amyloid deposits
3. Assess for monoclonal disease
4. **Determine the extent of organ involvement**

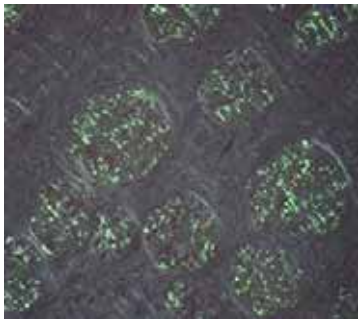
Organ involvement

- Kidney (common organ involved)
- Heart (most common cause of morbidity and mortality)
- Autonomic nervous system
- Peripheral nervous system
- GI tract
- Soft tissue
- Liver
- Coagulopathy (Factor X deficiency)
- Other organs

****Localized: bronchial/lung, bladder, skin/subcutaneous, GI**
-resection, radiation, or observation
-typically not treated with systemic therapy

Renal involvement

- Nephrotic syndrome (edema, weight gain, foamy urine)
  - Majority have glomerular involvement
  - Creatinine often preserved until late stage
- ~10% have vascular or tubulointerstitial involvement without significant proteinuria
  - Often with rapidly worsening renal function
- 24 hour urine protein (BJ v. albuminuria)



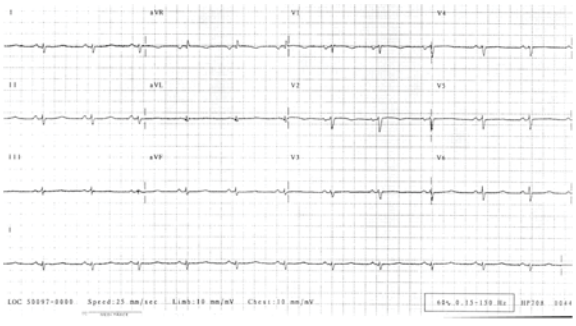
24 hour urine >500mg (predominantly albumin)

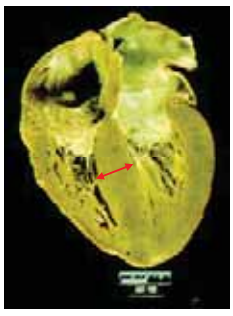
Cardiac involvement

- Restrictive cardiomyopathy
  - dyspnea on exertion, peripheral edema, elevated JVP, ascites, syncope, congestive hepatomegaly
- Typically preserved ejection fraction
  - Low cardiac output seen in advanced disease or light chain toxicity
- Cardiac imaging
  - MRI (late gadolinium enhancement)
  - Technetium pyrophosphate scan – for ATTR cardiomyopathy

Cardiac involvement

- **Serum biomarkers**
  - Troponin
  - NT-proBNP
- **EKG**
  - low voltage, arrhythmia
- **Echocardiography**
  - Wall thickening (IVSd)
  - Global longitudinal strain



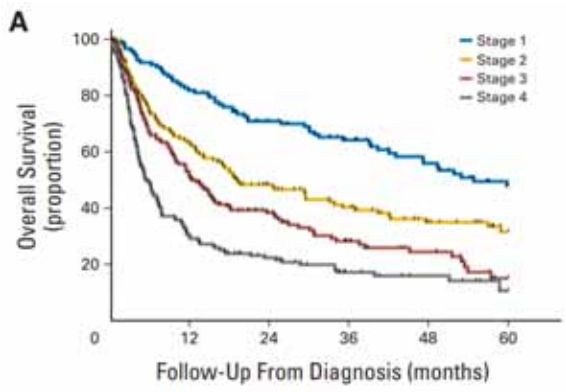


Falk Circulation 2005

Echo: IVSd >12mm (no other cause)
or
NTproBNP >332 (with no renal failure)

Cardiac involvement

- Leading cause of morbidity and mortality
- Revised staging system:
  - NT-proBNP >1800 pg/mL
  - Troponin-T >0.025 ng/mL
  - dFLC >180 mg/L
- Median OS for Stages 1-4: 94.1, 40.3, 14, and 5.8 months
- Very poor risk subgroup (NT-proBNP >8500 ng/L)



NT-pro BNP or BNP can be affected by renal function

Kumar, et al J Clin Oncol 2012

Peripheral Nervous System Involvement

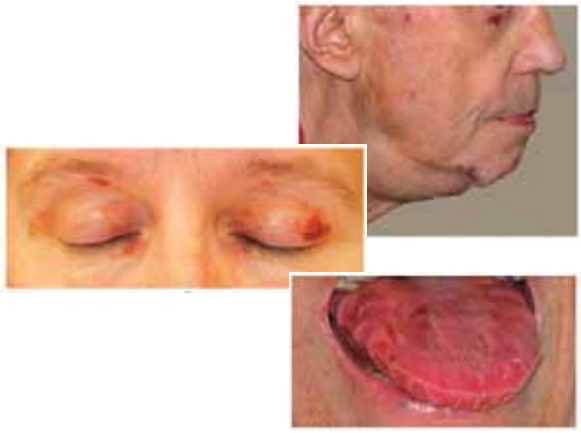
- Rare to have only PNS involvement
- Neuropathy
  - Loss of small fiber mediated sensation (heat v. cold) initially and progresses to motor involvement
  - Begins in feet, then progresses to hands
- Symptoms: paresthesias, pain, burning, numbness, motor deficits

Autonomic Nervous System Involvement

- Check orthostatic BP measurements
- Lightheadedness/Syncope
  - Postural hypotension
- Erectile Dysfunction
- GI symptoms: diarrhea, constipation, early satiety

Soft tissue involvement

- **Macroglossia**
- **Peri-orbital bruising**
- Submandibular/Salivary gland enlargement
- Carpal tunnel syndrome
- Nail dystrophy
- Skin nodules
- Claudication (jaw)
- Bone/joint



Merlini, et al Blood 2013

Gastrointestinal Involvement

- Nausea/Vomiting
- Abdominal pain
- Gastroparesis/early satiety
- Difficulty swallowing
- GERD
- Malabsorption
- Melena or bright red blood per rectum

Biopsy verification with symptoms

Other organ involvement

- Liver (hepatomegaly, elevated alk phos or GGT)
- Coagulopathy (Factor X deficiency)
- Spleen
- Lungs
- Other

Liver span >15cm (in the absence of heart failure)
or
Alk Phos >1.5 times upper limit of normal

Treatment of systemic AL Amyloidosis

Treatment of systemic AL Amyloidosis

- Goal: suppress production of free light chains and remove amyloid deposits
- Treatment differs from multiple myeloma
  - Shorter therapy courses may be sufficient, treat 1-2 cycles beyond best hematologic response
  - Limited data on maintenance therapy
  - May not require induction therapy prior to ASCT

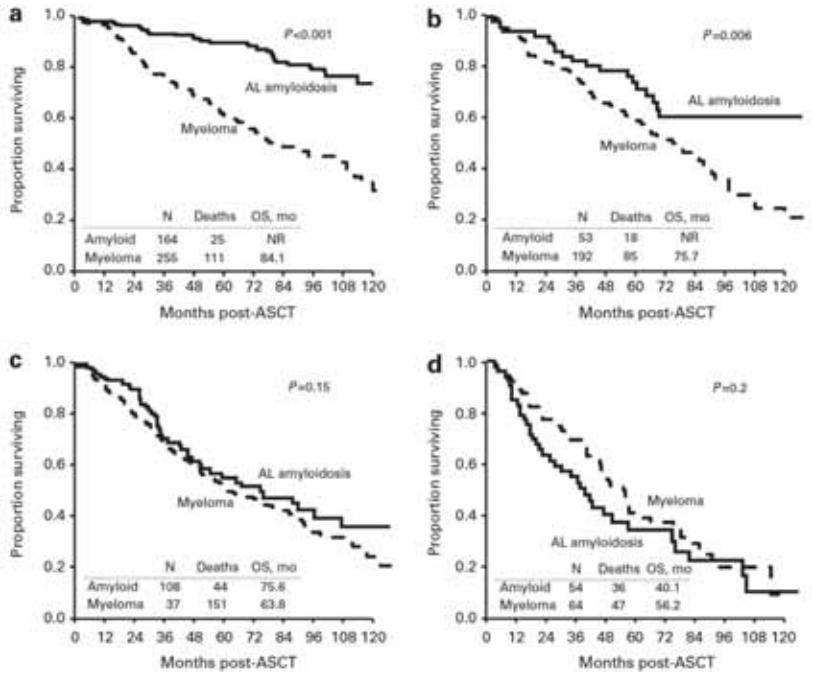
Upfront treatment of systemic AL Amyloidosis

- High-dose melphalan and autologous stem cell transplantation
- Cytoxan-bortezomib-dexamethasone (CyBorD)
- Melphalan-dexamethasone +/- bortezomib (Mdex or BMDex)

**Adjust doses of dexamethasone based on organ involvement

ASCT outcomes in Myeloma v. Amyloid

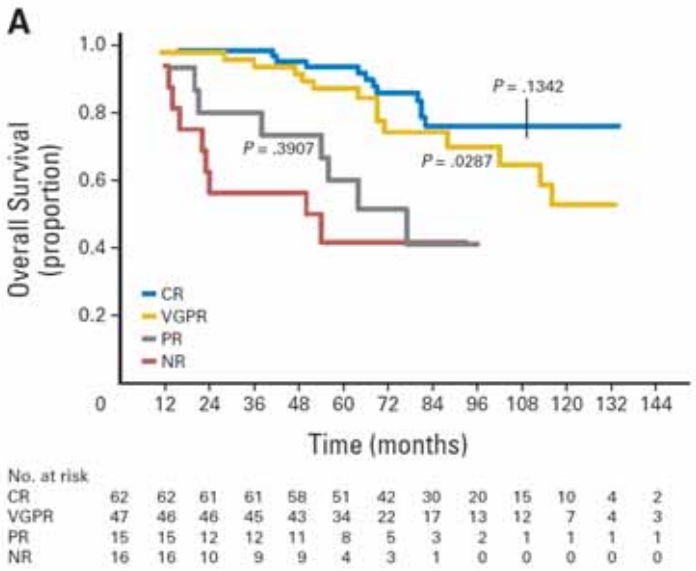
- A. Complete response
- B. Very Good Partial Response
- C. Partial response
- D. No Response



Dispenzieri Bone Marrow Transplant 2013

Survival after HDM/ASCT

- 140 patients
- Superior OS in those with CR or VGPR
  - No significant difference
  - Median OS not reached
- Worse OS in PR and NR
  - 77 months and 50 months
  - No significant difference



Girnius J Clin Oncol 2013

HDM with Autologous Stem Cell Transplantation

Table IV. Data regarding outcomes of high dose melphalan with autologous stem cell transplantation in patients with AL amyloidosis performed in tertiary centres.

Institution/ Study period/ Reference	*N*	HR/CR	Organ responses	TRM	PFS/OS
Boston University/ 1994–2013/ Sanchorawala (2014)	607	34%	NR	9%	Median OS: 6·7 years Median OS for those in CR: >12 years
Mayo Clinic/ 1996–2010/ Gertz *et al* (2010)	434	39%	47%	10%	CR: >10 years PR: 8·9 years NR: 2·7 years
MD Anderson Cancer Center/ 1998–2011/ Parmar *et al* (2014)	80	51%	39%	12·5%	OS: >10 years (56% at 10 years)
Heidelberg University Hospital/ 1998–2014/ Hegenbart *et al* (2014)	174	58%	40%	2%	Median OS: 11·3 years

HR, haematological response; CR, complete response; NR, no response; TRM, treatment-related mortality; PFS, progression-free survival; OS, overall survival.

Kastritis and Dimopoulos BJH 2015

HDM with Autologous Stem Cell Transplantation

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Kastritis and Dimopoulos BJH 2015

HDM with Autologous Stem Cell Transplantation

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Consider consolidation after transplant

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Landau, et al Leukemia 2017

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HR, haematological response; CR, complete response; NR, no response; TRM, treatment-related mortality; PFS, progression-free survival; OS, overall survival.

Mortality lower in recent years

Kastritis and Dimopoulos BJH 2015

Selecting patients for transplant

- **Recommended transplant criteria**
  - NTproBNP <5000 pg/mL
  - Troponin-T <0.06 ug/mL
  - EF >40-45%
  - Systolic blood pressure >90 mmHg
  - DLCO >50%

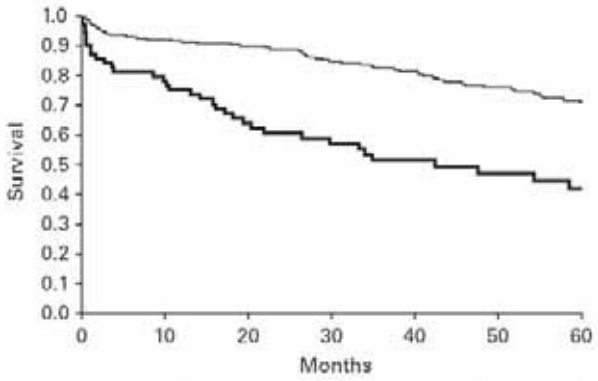


Figure 3. Survival of Mayo stage III ($N = 72$, bold) transplant recipients compared with stage I and II ($N = 294$, narrow). $P < 0.0001$.

Gertz Bone Marrow Transplant 2013

**Treatment for relapsed/refractory disease

- **Bortezomib/dex-** SC, weekly, can worsen autonomic dysfunction and peripheral neuropathy
- **Carfilzomib-** concern for cardiac toxicity, not typically used
- **Ixazomib/dex-** in Phase III trials, seems to be well-tolerated
- ****Lenalidomide/dex-** not typically used upfront, high risk of renal dysfunction, 15mg recommended
- **Pomalidomide/dex-** monitor for renal dysfunction
- **Daratumumab-** recent case series, ongoing Phase II trial, monitor fluid status
- **Rituximab-** consider in WM/LPL associated

Supportive therapy

Supportive therapy

Cardiac:

- Diuretics (+/- albumin)
- Avoid digoxin, calcium channel blockers, and beta blockers
- Limited data on the use of ICDs or VADs

**Consider heart transplant prior to treatment if needed

Supportive therapy

Orthostasis from ANS involvement

- Midodrine for postural hypotension, avoid florinef due to fluid overload
- Compression stockings

Gastrointestinal

- Assess for and treat bacterial overgrowth
- Prokinetic agents or anti-diarrhea medications

Assessment of response

- Evaluation of **hematologic response**
  - Rapid response
- Evaluation of **organ response**
  - May occur over many months to years
  - **Organ function may worsen even in hematologic remission

Comenzo, et al Leukemia 2012

Prevention/Removal of amyloid deposits to improve organ dysfunction

- Doxycycline
- Anti-SAP antibodies
- NEOD001
  - PRONTO study, previously treated, stable plasma cell disease
  - VITAL study, upfront with CyBorD

Richards, et al NEJM 2015
Liedtke, et al ASH 2016
Gertz, et al J Clin Oncol 2016

Summary

- Accurate and early diagnosis is imperative, although difficult
- Very high early mortality
- Long-term outcomes are improving
- Effective treatments available, many more in development
  - Monitor for adverse side effects not typically seen in multiple myeloma

Acknowledgements

BU School of Medicine
Amyloidosis Center

- Patients and their families
- Vaishali Sanchorawala, MD- Director
- Mark Sloan, MD
- Martha Skinner, MD
- John Berk, MD
- Many more colleagues, collaborators, and researchers
- In memory of David Seldin, MD

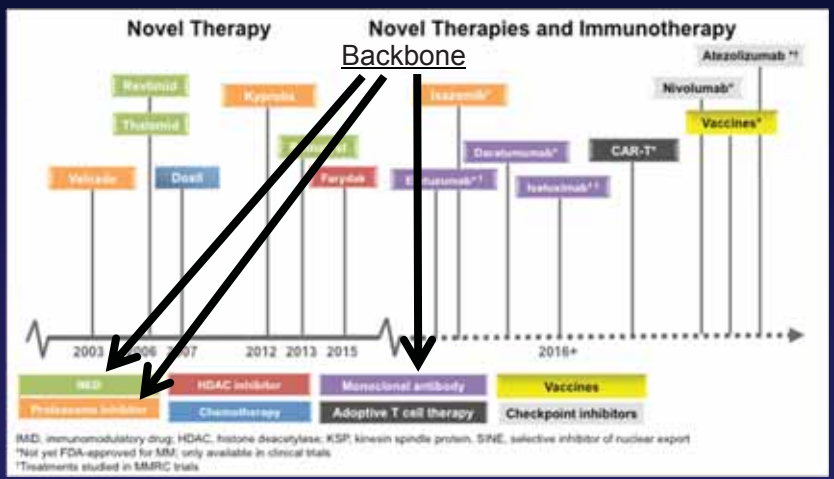
EMORY WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

EMORY UNIVERSITY SCHOOL OF MEDICINE

Management of Early Relapse

Sagar Lonial, MD
Professor and Chair
Department of Hematology and Medical Oncology
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine

Myeloma Drug Development and Relapse Management



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Who are the Players

- Still have 'older' novel agents
  - Bortezomib, Lenalidomide
  - Carfilzomib, Dose/Schedule
  - Pomalidomide
- 'New' Novel agents
  - Ixazomib, Panobinostat
  - Elotuzumab, Daratumumab

} earlier lines or induction, partner for newer agents

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Factors to Consider to for Treatment Selection : Disease related Factors

- Nature of relapse
  - indolent vs aggressive
- Risk stratification
  - Genetics of initial and relapsed marrow
- Disease burden
  - High vs low
- R-ISS staging
  - 1 vs 2-3

1. Nooka AK, et al. Blood. 2015;125:3085-3099.
2. Palumbo A, et al. N Engl J Med. 2011;364:1046-1060.
3. Palumbo A, et al. Blood. 2011;118:4519-4529.
4. Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Factors to Consider to for Treatment Selection : Treatment related Factors

- Previous therapy
  - Pts with PD receiving IMiDs, PIs, or cytotoxic doublet/triplet therapies can benefit from next-generation regimens
  - Avoid agents of previous regimen-related toxicity
  - Maintenance therapy
- Regimen-related toxicity
  - Toxicity profile should be considered in light of pt comorbidities
  - Neuropathy: consider neuropathy sparing durgs (avoid bortezomib, thalidomide)
  - Cardiac issues (uncontrolled HTN, CHF): careful consideration of carfilzomib
  - COPD: monoclonal antibodies with caution (daratumumab)
  - DVT/PE: use anticoagulation with IMiDs
- Depth and duration of previous response, tumor burden at relapse
- Retreatment with previous therapies an option if pt had previous response to the treatment, acceptable tolerance, and relapse occurred at least 6 mos after previous exposure

1. Nooka AK, et al. Blood. 2015;125:3085-3099.
2. Palumbo A, et al. N Engl J Med. 2011;364:1046-1060.
3. Palumbo A, et al. Blood. 2011;118:4519-4529.

Factors to Consider to for Treatment Selection : Patient related Factors

- Renal insufficiency: disease related or due to comorbidities (hypertension, vascular disease, diabetes, nephrotoxicity)[1]
- Hepatic impairment common in pts with RRMM[1]
- Comorbidities and frailty[1]
  - Treatment decisions complicated in elderly
    - ↑ toxicity due to ↓ organ function, physiologic reserve
    - European Myeloma Network vulnerability assessment algorithm anticipates regimen-related toxicities and assists individualizing therapy with least potential for interruption[2,3]
- Patient preferences
  - Convenience, ease of travel, insurance and other social factors

1. Nooka AK, et al. Blood. 2015;125:3085-3099.
2. Palumbo A, et al. N Engl J Med. 2011;364:1046-1060.
3. Palumbo A, et al. Blood. 2011;118:4519-4529.

Lenalidomide and Bortezomib-Based Early Relapse Regimens: PFS and OS

Trial	Regimen	PFS (mon)	ORR (%)	VGPR (%)	PFS (HR, 95% CI)	OS (HR, 95% CI)
ASPIRE[1] N=792	Rd + Carfilzomib	26.3	87.1	69.9	.69 (.57-.83) *P*=.0001	.79 (.63-.99) *P*=.04
	Rd	17.6	66.7	40.4		
TOURMALINE-MM-1[2] N=722	Rd + Ixazomib	20.6	78.3	48.1	.74 (.59-.74) *P*=.01	NR
	Rd	14.7	71.5	39		
ELOQUENT-2[3] N=646	Rd + Elotuzumab	19.4	79	33	.70 (.57-.85) *P*<.01	.78 (.63-.96)
	Rd	14.9	66	28		
POLLUX[4] N=569	Rd + Daratumumab	NR	93	75.8	.37 (.28-.50) *P*<.0001	.63 (.42-.95)
	Rd	18.4	76	44.2		
PANORAMA[5] N=768	Vd + Panobinostat	11.99	60.7	28	.63 (.52-.76) *P*<.0001	.87 (.69-1.10) *P*=.26
	Vd	8.08	54.6	16		
CASTOR[6] N=498	Vd + Daratumumab	NR	83	59	.39 (.28-.53) *P*<.0001	.63 (.42-.96)
	Vd	7.2	63	29		
ENDEAVOR[7] N=929	Carfilzomib + Dex	18.7	76.7	54	.53 (.44-.65) *P*<.0001	.79 (.58-1.08) *P*=.06
	Vd	9.4	62.3	29		

1. Stewart K, et al. *N Engl J Med* 2015;372:142-52. 2. Moreau P, et al. *N Engl J Med* 2016; 374:1621-1634.
3. Lonial S, et al. *N Engl J Med* 2015; 373:621-631. 4. Dimopoulus M, *et al. N Engl J Med* 2016; 375:1319-1331.
5. San Miguel J, *Lancet Oncol* 2014; 15: 1195–206. 6. Palumbo A, et al. *N Engl J Med* 2016; 375:754-766.
7. Dimopoulos M, et al. *Lancet Oncol.* 2016;17:27-38.

Ixazomib (MLN9708)

- Ixazomib citrate (MLN9708) is a, reversible 20S proteasome inhibitor.
- First oral proteasome inhibitor in trials
- In plasma, ixazomib citrate rapidly hydrolyzes to the biologically active form (MLN2238).
- Preclinical studies have demonstrated antitumor activity in MM cell lines and xenograft models.

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TOURMALINE-MM1: Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone

Global, double-blind, randomized, placebo-controlled study design

N=722

Randomization

1:1

Ixazomib + Lenalidomide + Dexamethasone
Ixazomib: 4 mg on days 1, 8, and 15
Lenalidomide: 25 mg* on days 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22

Repeat every 28 days until progression, or unacceptable toxicity

Placebo + Lenalidomide + Dexamethasone
Placebo: on days 1, 8, and 15
Lenalidomide: 25 mg* on days 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22

Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

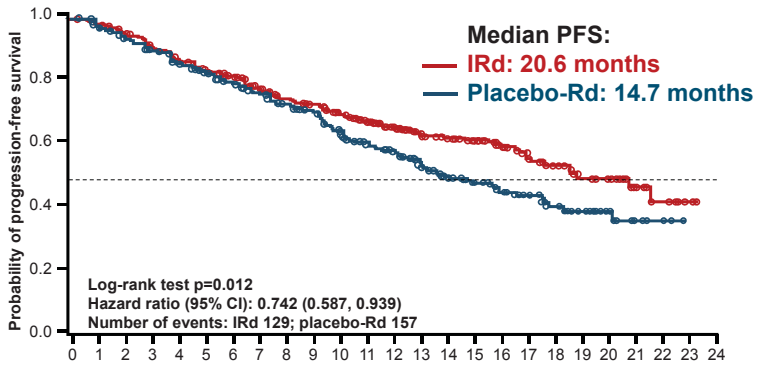
Key secondary endpoints:
- OS
- OS in patients with del(17p)

Response and progression (IMWG 2011 criteria[1]) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

*10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

1. Rajkumar S, et al. Blood 2011;117:4691–5.

Final PFS analysis: A significant, 35% improvement in PFS with IRd vs placebo-Rd



Number of patients at risk:																									
IRd	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo-Rd	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Median follow-up: ~15 months

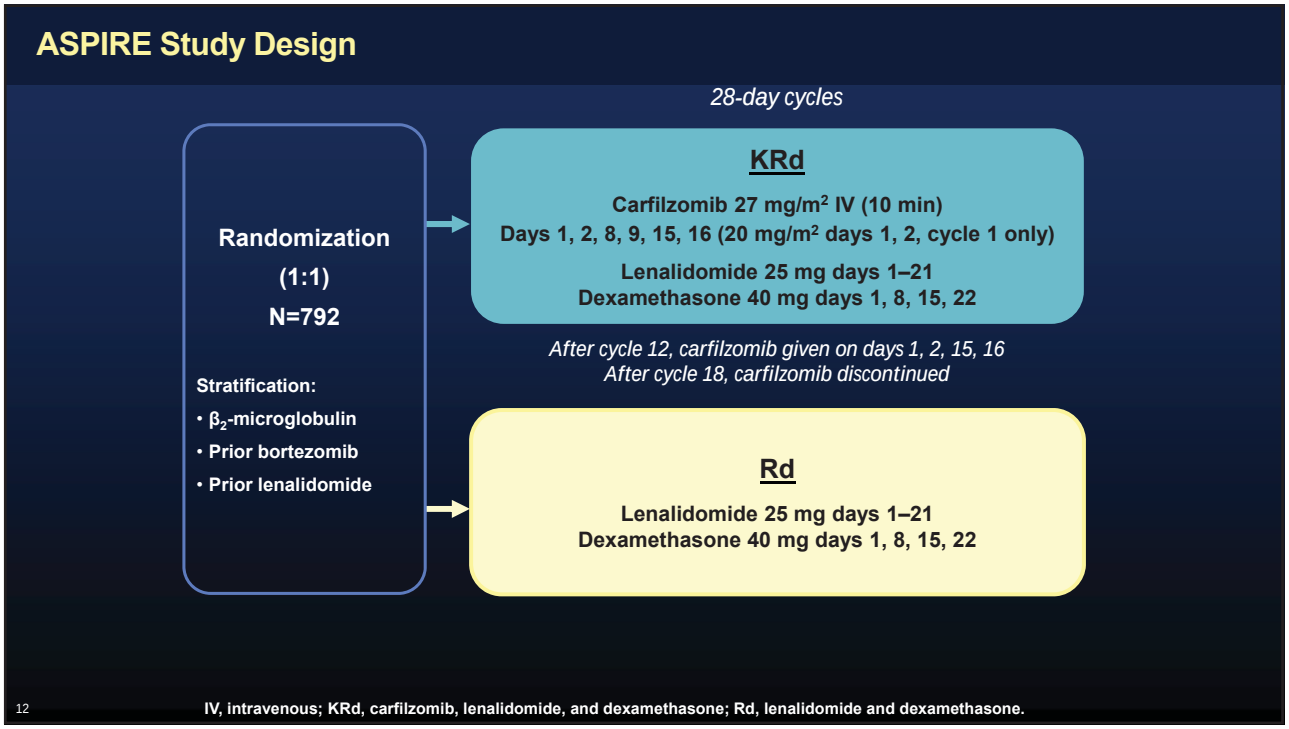
Outcomes by cytogenetic risk group

	ORR, %		≥VGPR, %		≥CR, %		Median PFS, months		
	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	HR
All patients	78.3*	71.5	48.1*	39	11.7*	6.6	20.6	14.7	0.742*
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*
All high-risk patients	79*	60	45*	21	12*	2	21.4	9.7	0.543
Patients with del(17p)†	72	48	39	15	11*	0	21.4	9.7	0.596
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12.0	0.645

*p<0.05 for comparison between regimens. †Alone or in combination with t(4;14 or t(14;16).
Data not included on patients with t(14:16) alone due to small numbers (n=7).

- Median OS could not be estimated
- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics

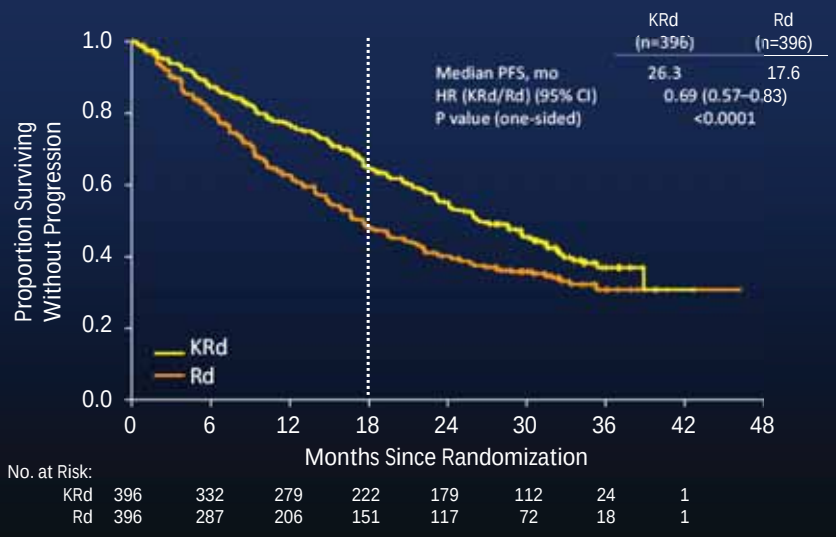
ASPIRE Study Design



12

IV, intravenous; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.

Primary Endpoint: Progression-Free Survival
ITT Population (N=792)



13

ENDEAVOR Study Design

Randomization 1:1

N=929

Stratification:

- **Prior proteasome inhibitor therapy**
- **Prior lines of treatment**
- **ISS stage**
- **Route of V administration**

Kd

Carfilzomib 56 mg/m² IV
Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)
Infusion duration: 30 minutes for all doses

Dexamethasone 20 mg
Days 1, 2, 8, 9, 15, 16, 22, 23
28-day cycles until PD or unacceptable toxicity

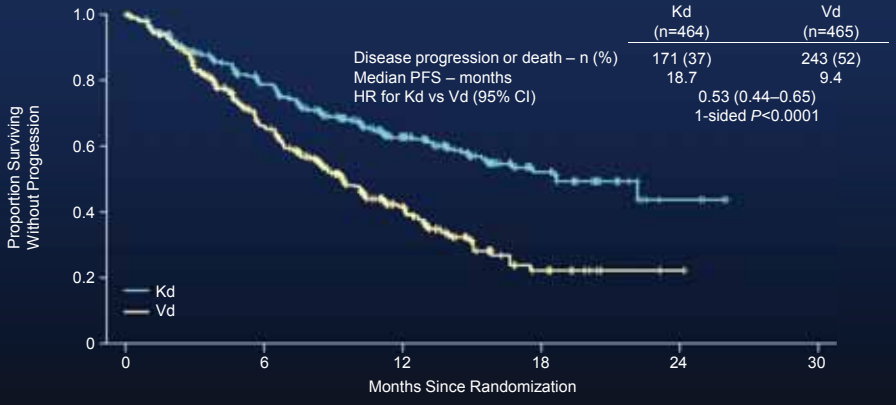
Vd

Bortezomib 1.3 mg/m² (3–5 second IV bolus or subcutaneous injection)
Days 1, 4, 8, 11
Dexamethasone 20 mg
Days 1, 2, 4, 5, 8, 9, 11, 12
21-day cycles until PD or unacceptable toxicity

ISS, International Staging System; IV, intravenous; Kd, carfilzomib and dexamethasone; PD, progressive disease; Vd, bortezomib and dexamethasone; V, bortezomib.

14

Primary End Point: Progression-Free Survival
Intent-to-Treat Population (N=929)



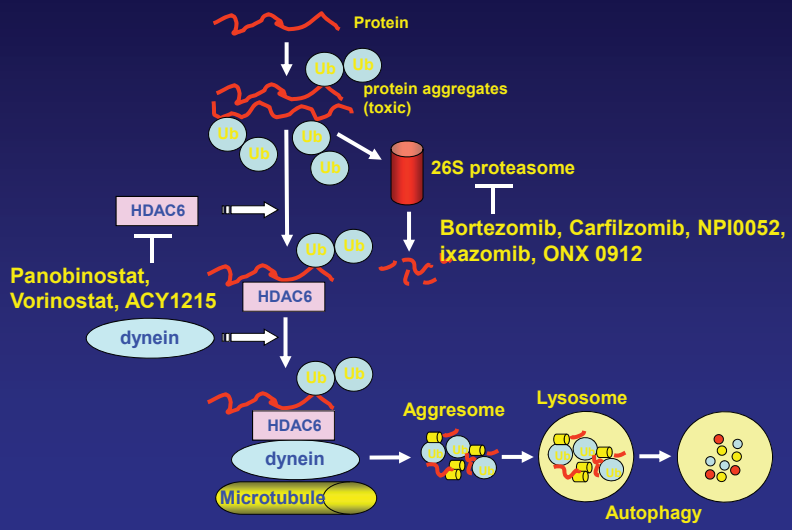
	Kd (n=464)	Vd (n=465)
Disease progression or death – n (%)	171 (37)	243 (52)
Median PFS – months	18.7	9.4
HR for Kd vs Vd (95% CI)	0.53 (0.44–0.65)	
	1-sided *P*<0.0001	

- **Median follow-up: 11.2 months**

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Kd, carfilzomib and dexamethasone; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

15

HDAC MOA in MM not only Related to Epigenetic Effects



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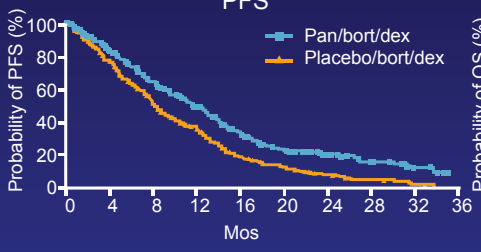
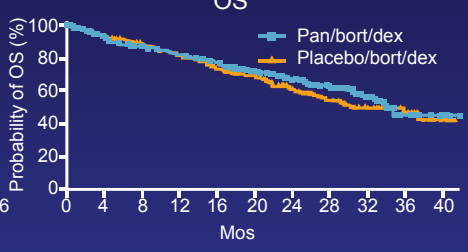
Hideshima et al. *Clin Cancer Res*. 2005;11:8530.Catley et al. *Blood*. 2006;108:3441-9.

Panorama Trial Validates Preclinical Data

- Primary endpoint reached: median PFS ↑ by 3.9 mos
- Interim OS analysis; final analysis **Abstract 3026**





Events, n/N	Median PFS, Mos (95% CI)	HR (95% CI)	*P* Value
207/387	12.0 (10.3-12.9)	0.63 (0.52-0.76)	< .0001
260/381	8.1 (7.6-9.2)		

Events, n/N	Median OS, Mos (95% CI)	HR (95% CI)	*P* Value
134/387	33.6 (31.34-NE)	0.87 (0.69-1.10)	.26
152/381	30.4 (26.87-NE)		

San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206

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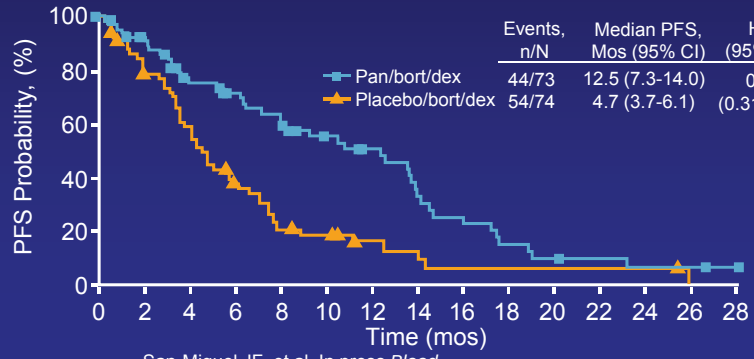
In Absence of Biomarker, Other Predictors of Benefit

Subgroup analysis of pts who received ≥ 2 previous treatments, including bortezomib and an IMiD

FDA approved indication based on subgroup analysis



Events, n/N	Median PFS, Mos (95% CI)	HR (95% CI)
44/73	12.5 (7.3-14.0)	0.47 (0.31-0.72)
54/74	4.7 (3.7-6.1)	

San-Miguel JF, et al. In press *Blood*

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Toxicity Across studies

Table 3. Drug-related adverse events (≥20% grade 3/4): panobinostat monotherapy vs combinatorial therapy.

Adverse event	Phase II (N = 38)		Phase Ib Dose Expansion (n = 15)		PANORAMA 2 (N = 55)		PANORAMA 1 (n = 381)	
	All grades, %	Grade 3/4, %	All grades, %	Grade 3/4, %	All grades, %	Grade 3/4, %	All grades, %	Grade 3/4, %
Hematologic								
Thrombocytopenia	40	26	73	67	66	64	98	67
Neutropenia	34	32	60	47	18	15	75	35
Anemia	34	18	33	7	47	15	62	20
Nonhematologic								
Diarrhea	42	3	87	20	71	20	68	25
Fatigue	47	5	73	20	69	20	61[a]	24[a]

Note: [a] In PANORAMA 1, fatigue/asthenia were combined.

Richardson et al, *Expert Review of Pharmacology*, 2015

Are There Better Partners?

- Data with other PIs now available
- Carfilzomib appears to have a better pattern of potential synergy with less overlapping GI tox (Kaufman, Berdeja, Shah each have Car/Pan data)
- SQ Bz and ixazomib being explored
- IMID combinations being explored

- Pan based combinations likely better suited for overcoming drug resistance in later lines.

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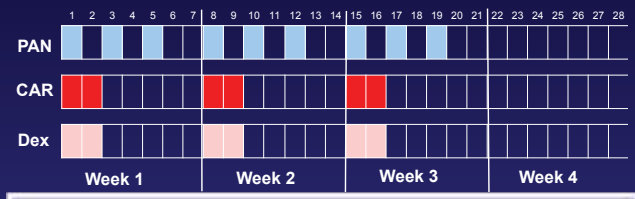
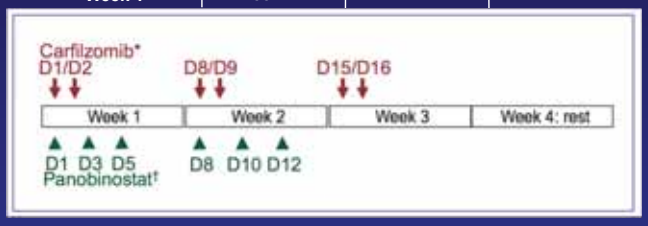
Different Car/Pan Schedules

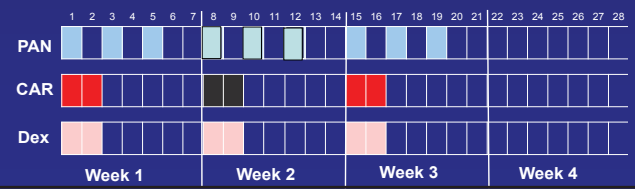
Kaufman Schedule



Shah Schedule



Berdeja Schedule



Kaufman Car/Pan Schedule

Best confirmed response	N = 26 (%)	BTZ Refractory N = 16 (%)
Overall response (CR + VGPR + PR)	45#79,	:#77,
Complete response	1 (4)	1 (6)
VGPR	5 (19)	1 (6)
Partial response	6 (23)	5 (31)
MR	3 (12)	1 (6)
SD	3 (12)	3 (19)
PD	6 (23)	4 (25)

- All responses occurred in the first 2 cycles
- Two patients maintained response for 18 months
- Median DOR is 7.5 months and 8 patients remain on treatment
- 1 patient was not evaluable for response

Kaufman et al, ASH 2014

Berdeja Car/Pan Schedule

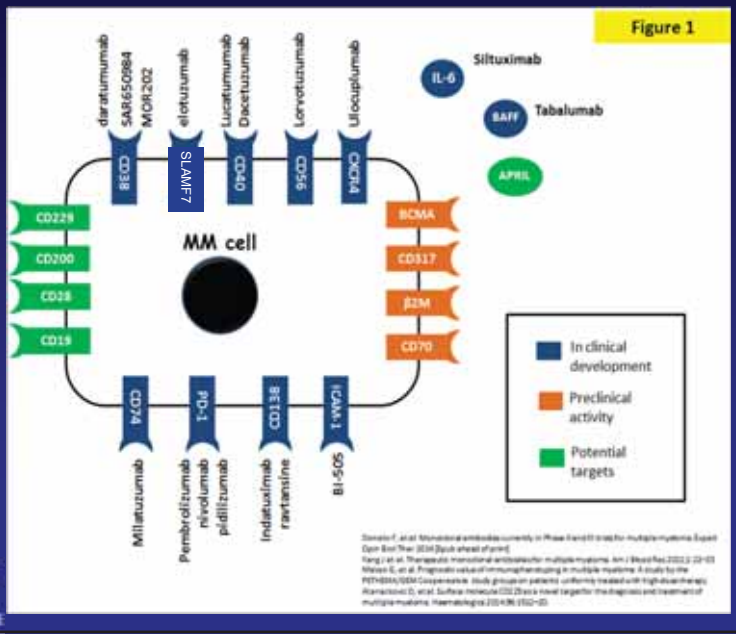
Table 3. Response to treatment.

Response assessment	All patients n=42	Dose level 4 n=32	Prior bortezomib n=37	Refractory to bortezomib n=15	Refractory to IMiD n=12	Dual refractory n=5	High risk* n=11	Standard risk** n=21
ORR, n. (%)	28 (67%)	23 (72%)	26 (70%)	10 (67%)	9 (75%)	4 (80%)	8 (73%)	15 (71%)
CBR, n. (%)	33 (79%)	28 (88%)	31 (84%)	13 (87%)	11 (92%)	5 (100%)	9 (82%)	16 (76%)
≥VGPR, n. (%)	14 (33%)	12 (38%)	13 (35%)	3 (20%)	5 (42%)	1 (20%)	5 (46%)	8 (38%)
PR, n. (%)	14 (33%)	11 (34%)	13 (35%)	7 (47%)	4 (33%)	3 (60%)	3 (27%)	7 (33%)
MR, n. (%)	5 (12%)	5 (16%)	5 (14%)	3 (20%)	2 (17%)	1 (20%)	1 (9%)	1 (5%)
SD, n. (%)	7 (17%)	2 (6%)	5 (14%)	2 (13%)	1 (8%)	0	1 (9%)	4 (19%)
PD, n. (%)	2 (5%)	2 (6%)	1 (3%)	0	0	0	1 (9%)	1 (5%)

*High risk is defined as fluorescence in situ hybridization showing (FISH) 1q amp, or 1p del, or t(4;14), or t(14;16), or 17p del, or cytogenetics 13 q del. **Excludes patients without FISH data.IMiD: immune modulating drug.

Berdeja et al, Haematologica 2015

Targets for MoABs in MM



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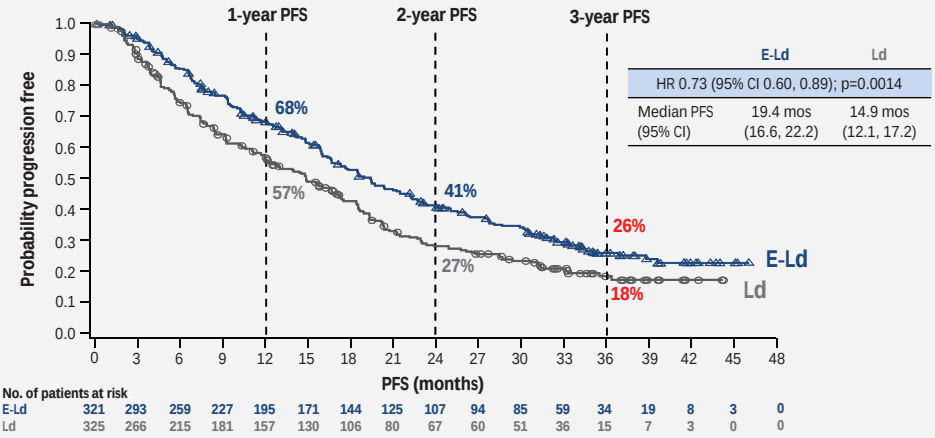
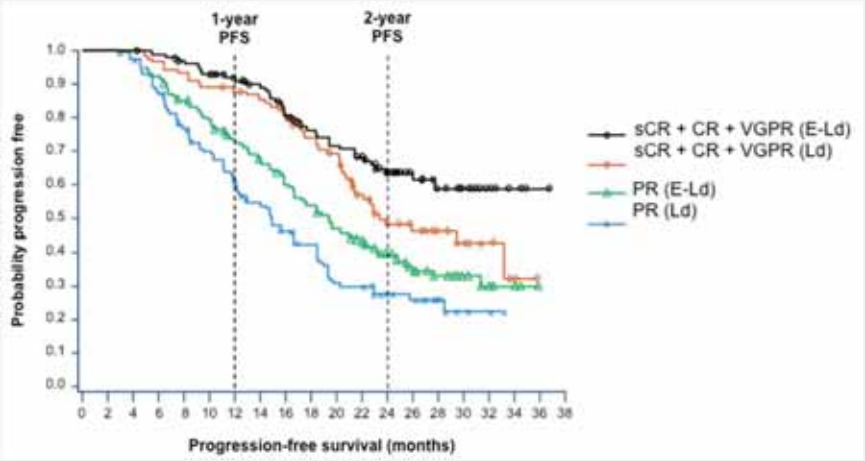
ELOQUENT-2
Extended Progression-Free Survival



	E-Ld	Ld
HR 0.73 (95% CI 0.60, 0.89); p=0.0014		
Median PFS (95% CI)	19.4 mos (16.6, 22.2)	14.9 mos (12.1, 17.2)

PFS benefit with E-Ld was maintained over time (vs Ld):
- **Overall 27% reduction in the risk of disease progression or death**
- **Relative improvement in PFS of 44% at 3 years**

Progression-Free Survival by Tumor Response



Patients achieving ≥PR showed improved PFS with E-Ld vs Ld alone

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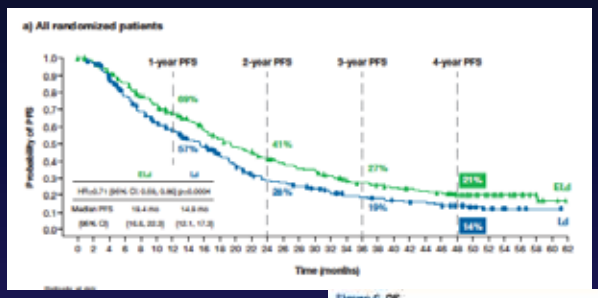
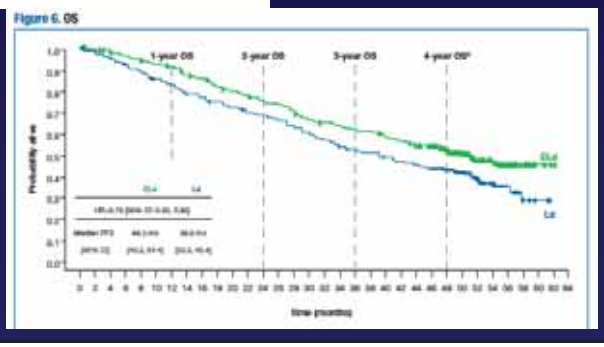
Lonial, S et al. *N Engl J Med 2015*
Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Eloquent 2 Update





Lonial et al, ASCO 2017

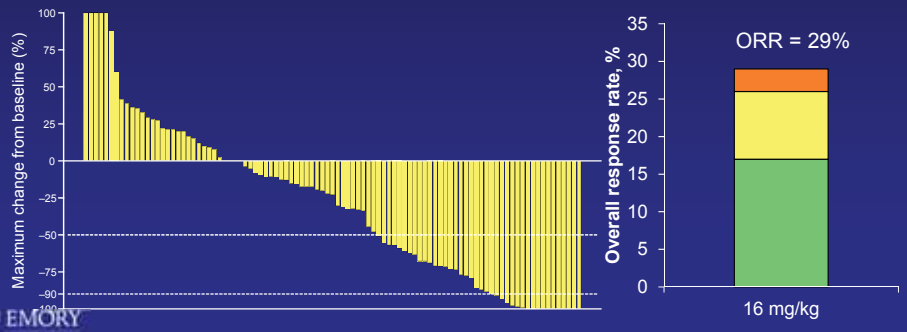
Daratumumab: Mechanism of Action

- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]

1. Lammerts van Bueren J, et al. *Blood*. 2014;124:Abstract 3474.
2. Jansen JMH, et al. *Blood*. 2012;120:Abstract 2974.
3. de Weers M, et al. *J Immunol*. 2011;186:1840-8.
4. Overdijk MB, et al. *MAbs*. 2015;7:311-21.
5. Krejcik J, et al. *Blood*. 2016. Epub ahead of print.

Phase 2 Study of Daratumumab (DARA) in Patients with ≥3 Lines of Prior Therapy or Double Refractory Multiple Myeloma: 54767414MMY2002 (Sirius)*

Sagar Lonial,[1] Brendan Weiss,[2] Saad Usmani,[3] Seema Singhal,[4] Ajai Chari,[5] Nizar Bahlis,[6] Andrew Belch,[7] Amrita Krishnan,[8] Robert Vescio,[9] Maria Victoria Mateos,[10] Amitabha Mazumder,[11] Robert Z. Orlowski,[12] Heather Sutherland,[13] Joan Blade,[14] Emma C. Scott,[15] Huaibao Feng,[16] Clarissa Uhlar,[17] Imran Khan,[16] Tahamtan Ahmadi,[17] Peter Voorhees,[18].



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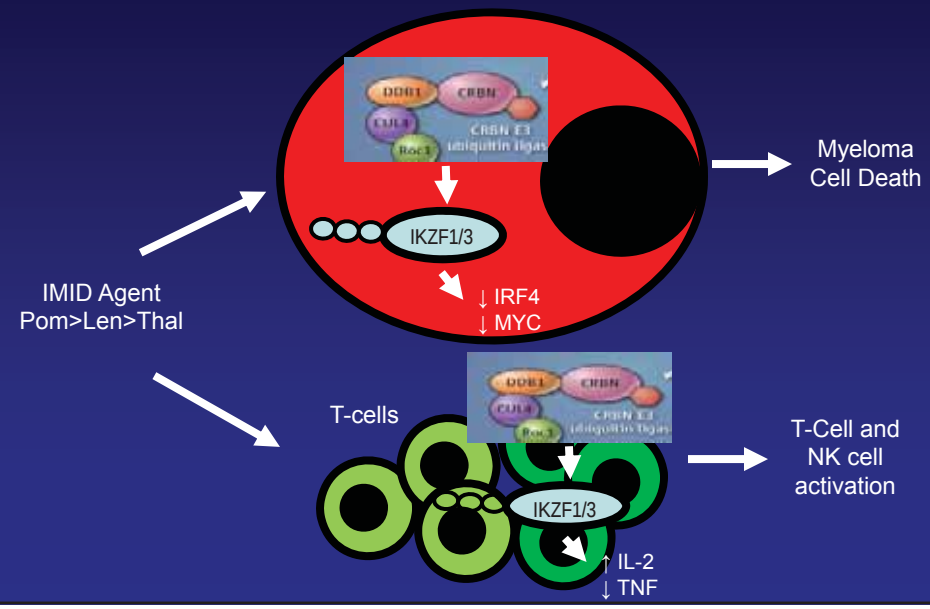
Lonial et al, Lancet 2016

Differential Effects the Same Target



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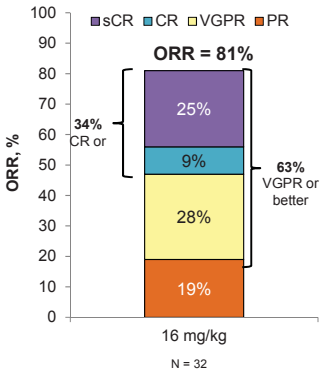
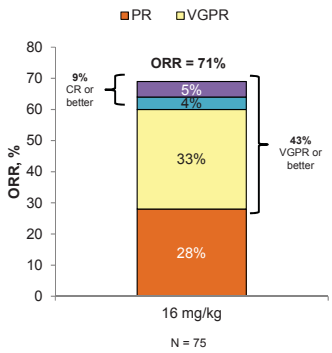
Overall Response Rate

DARA + LEN/DEX



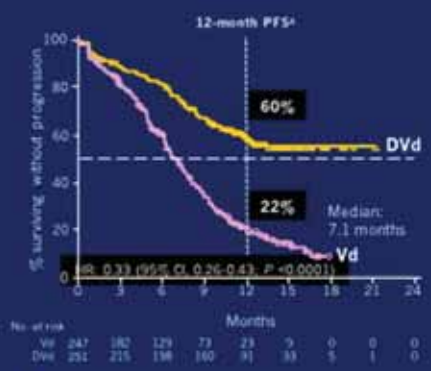
- ORR = 81%
- Clinical benefit rate (ORR + minimal response) = 88%

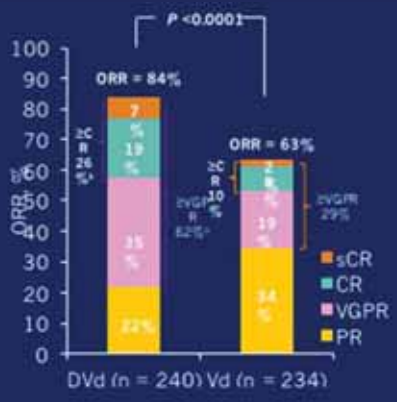
DARA + POM/DEX



- ORR = 71%
- ORR in double-refractory patients = 67%
- Clinical benefit rate (ORR + minimal response) = 74%

Castor Updated Efficacy





- Median (range) follow-up: 13.0 (0-21.3) months
- An additional 7% of patients receiving DVd achieved ≥CR with longer follow-up

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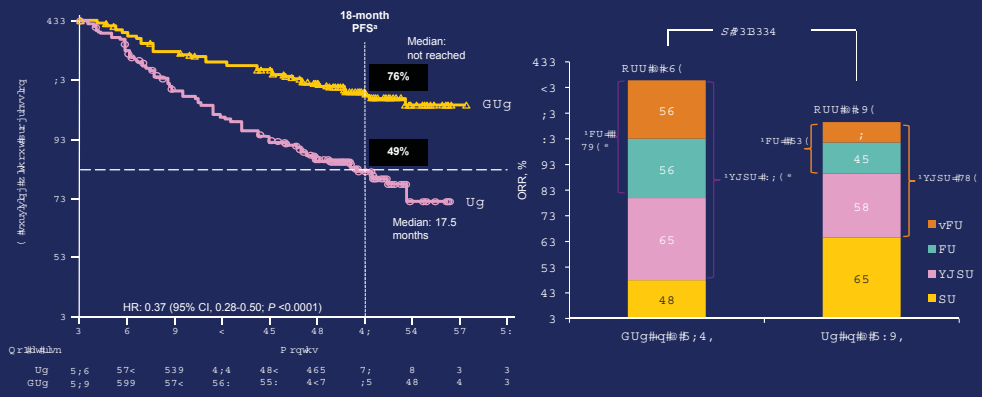
Pollux Updated Efficacy



- Median (range) follow-up: 17.3 (0-24.5) months

HR, hazard ratio; CI, confidence interval; sCR, stringent complete response; PR, partial response; ITT, intent-to-treat.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate.
[b]P <0.0001 for DRd vs Rd.

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Treatment Approach before November 2015

Symptomatic relapse

Consider clinical trial

Factors to consider
- Treatment related factors
- Disease related factors
- Patient related factors

Prior SCT

Yes

Relapse within first 12 months
-Newer combination strategies CRD, CPD, RVD or clinical trial
-Allogeneic transplant clinical protocol

Relapse beyond the first 12 months
*Bortezomib ± Dexamethasone
*Lenalidomide + Dexamethasone
*Bortezomib ± PLD
RVD, VTD, CFZ, CRD, VCD, RCD, DCEP±V, DT-PACE±V, Cytoxan, Pd, Td

Relapse with maintenance therapy after SCT

Relapse without maintenance therapy after SCT

Relapse within 36 months

Relapse beyond 36 months

Relapse beyond 18-24 months

Relapse within 18-24 months

Subsequent relapse

Subsequent relapse

Subsequent relapse

SCT2

No

Transplant eligible; has good PS
- Primary refractory- SCT
- Relapsed/refractory- SCT

Transplant ineligible
-If patient has previously responded to the therapy, tolerated and relapsed at least 6 months after prior drug exposure
- repeat prior therapy

- Otherwise, consider
- *Bortezomib ± Dexamethasone
- *Bortezomib + PLD
- *Lenalidomide + Dexamethasone
- RVD, VTD, CFZ, CRD, VCD, RCD, DCEP, DT-PACE±V, Cytoxan, Pd, T

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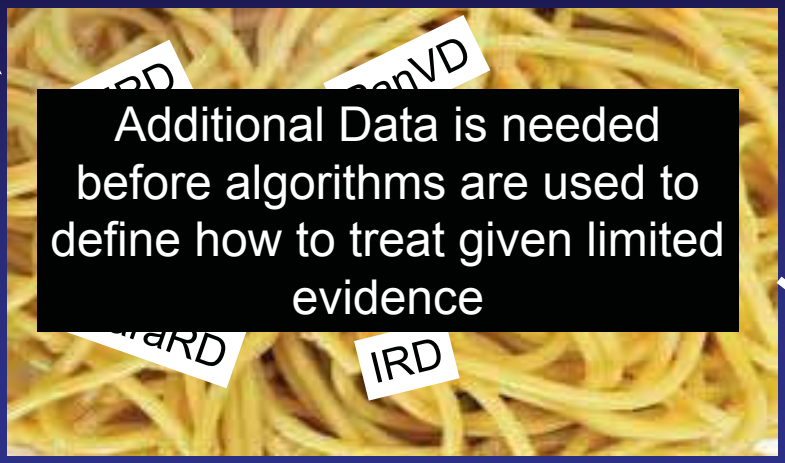
*NCCN category 1 recommendations; RVD: lenalidomide, bortezomib and dexamethasone; VTD: bortezomib, thalidomide and dexamethasone, CFZ: carfilzomib; CRD: carfilzomib, lenalidomide and dexamethasone; CPD: carfilzomib, pomalidomide and dexamethasone VCD: bortezomib, cyclophosphamide and dexamethasone; RCD: lenalidomide, cyclophosphamide and dexamethasone; DCEP±V: dexamethasone, cyclophosphamide, etoposide, and cisplatin ± bortezomib; DT-PACE±V: dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide ± bortezomib; Pd: pomolidomide and dexamethasone; Td: thalidomide and dexamethasone; PLD: liposomal doxorubicin, PS: performance ststus; SCT: autologous stem cell transplant; PFS: progression free survival; SCT2: second SCT

Nooka AK, Kastritis E, Dimopoulos MA, Lonial S. Blood. 2015 May 14;125(20):3085-99

Treatment Approach After November 2015

Relapse



Remission

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Emory Approach to Early Relapse

Clinical Trial
Check if pt is t(11;14)

Slow indolent relapse		Aggressive relapse	
+ Len maintenance	- Len maintenance	+ Len maintenance	- Len maintenance
Consider adding Ixazomib/Dex*	Consider Dara/Len/Dex	Consider Dara/Pom/Dex	Consider Dara/Len/Dex
Consider Adding Elo/Dex*	Consider Elo/Len/Dex	Consider Car/Pom/Dex	Consider Dara/Vel/Dex
* Increase len dose	Consider Car/Len/Dex		Consider Car/Pom/Dex

Car/Pan as second salvage if IMID used

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Patients and Families

Thanks to:
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Jing Chen
Mala Shanmugan
Fadlo Khuri
Vikas Gupta
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Larry Boise
Cathy Sharp
Jennifer Shipp

Lisa Allan

And the Clinical Research Team

IMS

Golfers Against Cancer
T.J. Martell Foundation

And Many Others who are part of the B-cell Team

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Approaches to Management of Refractory Myeloma

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Disclosures

- **Research Funding:** Novartis, Takeda, Celgene, Bristol Myers Squibb
- **Consulting:** Novartis, Takeda, Janssen

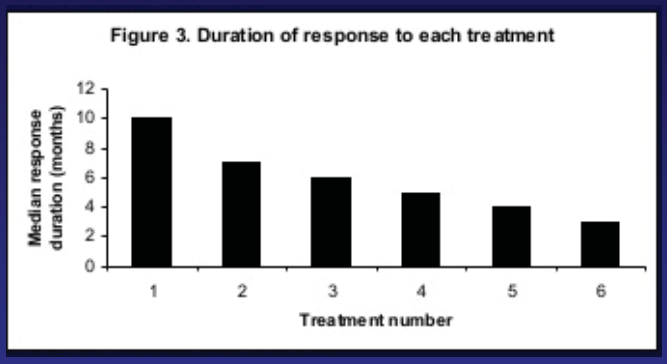
Patient Case

- 52 year old woman develops lightheadedness/dizziness
- Laboratory studies show hyponatremia, anemia, elevated total protein
- SPEP: 5.07 g/dL, IgG lambda M-protein with total IgG 5660 mg/dl
- Skeletal survey: lucencies of the calvarium and humeri
- Bone marrow biopsy:
  - Hypercellular marrow with 80% plasmacytosis
  - Deletion 13, translocation (4:14)
- Receives RVD followed by ASCT and lenalidomide maintenance, achieves complete response post-ASCT

- Progresses based on increase in M-protein two years after ASCT, transitions to ixazomib plus lenalidomide and dexamethasone
- Best response to Ixazomib plus len-dex is partial response. Progresses after 14 months on ixazomib plus len-dex.

- She then receives carfilzomib plus pomalidomide and dexamethasone. After best response of partial response, she progresses after 8 months.

Duration of Response Decreases with Successive Lines of Treatment



Kumar SK et al. Mayo Clinic Proc. 2004; 79: 867 - 879

Important Clinical Questions

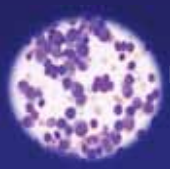
- Ideal regimen as next line of therapy
- Optimal sequence of regimens for treatment over time
- Duration of therapy with selected regimen

Combinations in Relapsed and Relapsed-Refractory MM

KRd
Carfilzomib plus lenalidomide-dex

IRd
Ixazomib plus lenalidomide-dex

Kd
Carfilzomib plus dex



Pan-Vd
Panobinostat plus bortezomib-dex

Pom-dex
Pomalidomide-dexamethasone

ERd
Elotuzumab plus lenalidomide-dex

Daratumumab-based regimens
(Dara monotherapy, DaraRd, DaraVd)

Management of Relapsed and RR Myeloma

Definitions

- Relapsed myeloma
  - 25% increase in serum or urine M-protein, percentage of bone marrow plasma cells, and/or difference between involved and uninvolved free light chains
  - Development of new bone lesions or plasmacytoma, hypercalcemia, renal impairment that cannot be attributed to another cause
- Relapsed and refractory myeloma
  - Disease that progresses on salvage therapy or within 60 days of the last treatment in patient who previously achieved at least a minimal response to therapy
- Primary refractory myeloma
  - Disease that fails to achieve at least minimal response with any treatment

Laubach J, et al. Leukemia 2016; 30: 1005 – 1017

Determinants of Therapy in RR MM

Disease Characteristics

- Biochemical progression only versus biochemical progression with significant symptoms and/or organ involvement
- Rapid versus slow, gradual increase in paraprotein
- High- versus standard risk cytogenetics
- Presence or absence of extramedullary disease

Determinants of Therapy in RR MM

Characteristics of prior or ongoing therapy

- Brief versus prolonged response
- Depth of response
- Progression on current therapy
- Toxicities associated with prior therapy, including neuropathy, decreased cell counts, GI, or cardiac toxicity

Patient characteristics

- Performance status
- Co-morbid medical conditions
- Overall goals of care, including preference for mode of chemotherapy administration

Categories of Relapsed Disease

Aggressive relapse
Fit

Aggressive relapse
Frail

Indolent relapse, any risk
Fit

Indolent, high risk
Frail

Indolent, standard risk
Frail

Recommendations for 2nd Relapse and Beyond

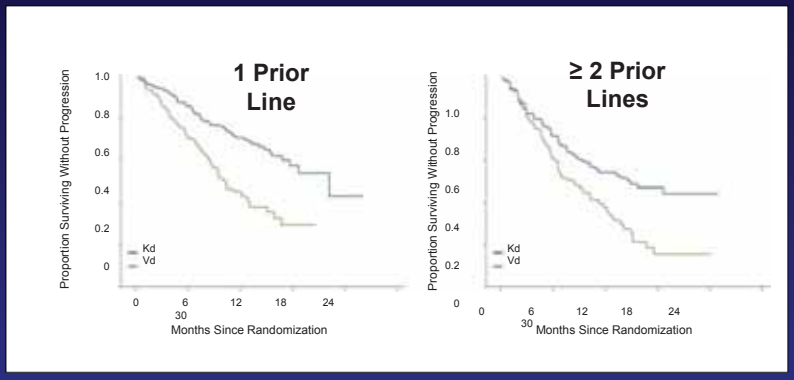
- Salvage regimen should incorporate at least one agent to which there has not been prior evidence of resistance or intolerability
- Patients with aggressive disease characteristics at time of relapse should be considered for three- or four-drug regimens while those with indolent disease can be considered for two- or three drug regimens
- Clinical trial participation should be offered if appropriate study is available.
- Patients in second relapse and beyond should receive ongoing therapy until the particular regimen is no longer tolerated or there is evidence of disease progression.

Laubach J, et al. Leukemia 2016; 30: 1005 – 1017

Availability of Clinical Trial Data Applicable to a Specific Clinical Scenario

- **Multiple previous lines of therapy**
- **High-risk cytogenetics**
- **Elderly patients**

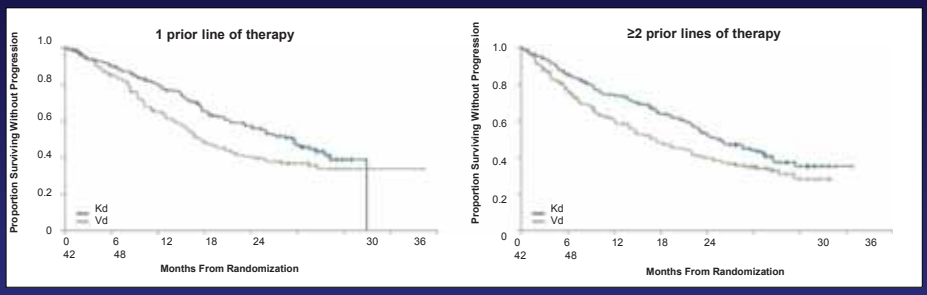
ENDEAVOR: PFS by Prior Lines of Therapy
Intent-to-Treat Population (N = 929)



	Kd n = 232	Vd n = 232		Kd n = 232	Vd n = 233
Median PFS, months	22.2	10.1	Median PFS, months	14.9	8.4
Hazard ratio (95% CI)	0.447 (0.330–0.606)		Hazard ratio (95% CI)	0.604 (0.466–0.783)	
P value (1-sided)	<.0001		P value (1-sided)	<.0001	

Moreau P, et al. Leukemia. 2017;3(1)1:115-122.

ASPIRE: PFS by Prior Lines of Therapy



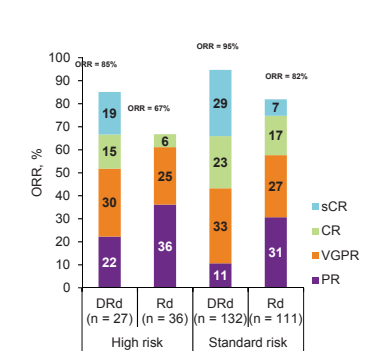
	KRd n = 184	Rd n = 157		KRd n = 212	Rd
PFS, median months	29.6	17.6	PFS, median months	25.8	16.7
Hazard ratio (95% CI)	0.69 (0.52–0.94)		Hazard ratio (95% CI)	0.69 (0.54–0.89)	
P value (one-sided)	.008		P value (one-sided)	.002	

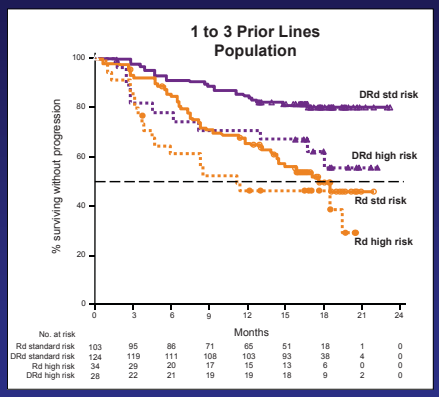
Dimopoulos MA, et al. *Blood Cancer J.* 2017;7(4):e554

Availability of Clinical Trial Data Applicable to a Specific Clinical Scenario

- Multiple previous lines of therapy
- High-risk cytogenetics
- Elderly patients

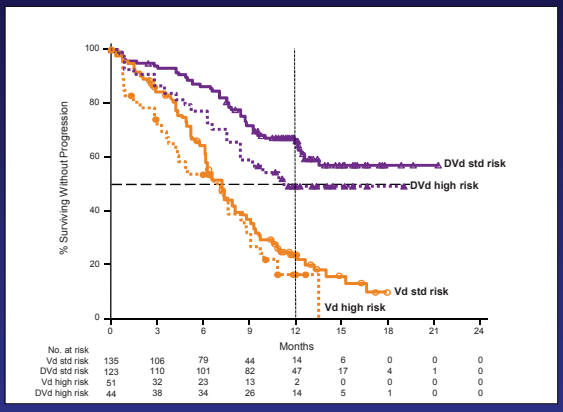
POLLUX: Responses and PFS by Cytogenetic Status





Moreau P, et al. *Blood*. 2016;128: Abstract 489

CASTOR: PFS by Cytogenetic Risk



High risk[b]	DVd n = 44	Vd n = 51
Median PFS, mo	11.2	7.2
HR (95% CI)	0.49 (0.27-0.89)	
P value	.0167	
	n = 44	n = 47
ORR, %	82	62
P value	.039	

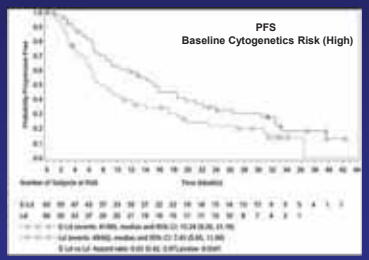
Standard risk	DVd n = 123	Vd n = 135
Median PFS, mo	NR	7.0
HR (95% CI)	0.29 (0.20-0.43)	
P value	<.0001	
	n = 118	n = 131
ORR, %	85	64
P value	.0003	

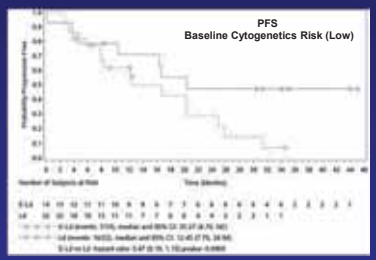
NR, not reached.
[a]ITT/Biomarker risk–evaluable analysis set.
[b]Central NGS. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

Mateos M, et al. *Blood*. 2016;128: Abstract 1150

ELOQUENT-2 (Elo-Rd vs Rd): PFS in del17p and t(4;14)

		Elo-Rd	Rd
del(17p)+	0.70 (0.49–0.99) p=0.042	21.2 (16.6–27.5)	14.9 (10.6–18.5)
del(17p)–	0.73 (0.58–0.92) p=0.007	18.5 (15.8–22.8)	14.8 (11.7–18.4)
t(4;14)+	0.52 (0.29–0.93) p=0.027	15.8 (8.4–18.5)	5.6 (3.1–10.3)
t(4;14)–	0.74 (0.60–0.91) p=0.004	20.3 (17.3–23.3)	15.7 (13.0–18.5)





EloRd improves the outcome of patients with high risk CA in comparison with Rd
High risk defined by: t(4;14) or t(14;16) or with del(17p) in ≥1% of PCs

Moreau P, et al. *Blood*. 2015;126: Abstract 727

TOURMALINE-MM1: Outcomes by Cytogenetic Risk Group

	ORR, %		≥VGPR, %		≥CR, %		Median PFS, Months		
	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	HR
All patients	78.3*	71.5	48.1*	39	11.7*	6.6	20.6	14.7	0.742*
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*
All high-risk patients	79*	60	45*	21	12*	2	21.4	9.7	0.543
Patients with del(17p)†	72	48	39	15	11*	0	21.4	9.7	0.596
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12.0	0.645

*P<.05 for comparison between regimens. †Alone or in combination with t(4;14 or t(14;16).
Data not included on patients with t(14:16) alone due to small numbers (n = 7).

- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics
- High risk was defined by t(4;14) or t(14;16) or del17p in ≥ 5% of PCs

Moreau P, et al. *Blood*. 2015; 126: Abstract 727

Availability of Clinical Trial Data Applicable to a Specific Clinical Scenario

- Multiple previous lines of therapy
- High-risk cytogenetics
- Elderly patients

ENDEAVOR: Kd vs Vd by Age

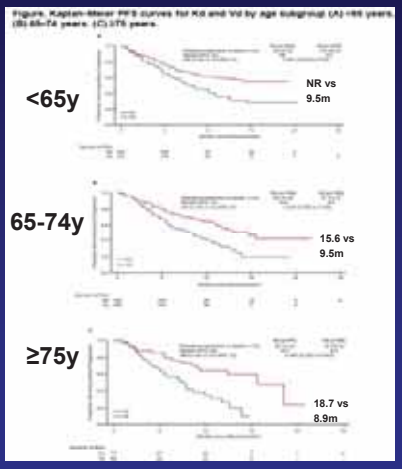
Table. Efficacy outcomes and grade ≥3 adverse events of interest

Outcome	<65 years		65–74 years		≥75 years	
	Kd (n=223)	Vd (n=218)	Kd (n=164)	Vd (n=169)	Kd (n=77)	Vd (n=66)
Median PFS, months	NE	8.8	15.6	8.8	18.7	8.9
HR for Kd vs Vd (95% CI)	0.58 (0.44–0.77)		0.53 (0.38–0.73)		0.38 (0.23–0.65)	
Best overall response, n (%)						
Complete response or better	35 (16)	16 (8)	19 (12)	11 (6)	4 (5)	2 (3)
Very good partial response or better	118 (53)	64 (30)	88 (54)	34 (20)	48 (62)	15 (23)
ORR, % (95% CI)	74 (68–80)	61 (54–68)	77 (70–84)	66 (58–72)	84 (74–92)	59 (46–71)
Median DOR, months	NE	11.1	NE	10.3	21.3	10.2
Select grade ≥3 AEs of interest, n (%)*						
Hypertension†	20 (9)	6 (3)	12 (7)	4 (2)	9 (12)	2 (3)
Dyspnea†	8 (4)	3 (1)	11 (7)	5 (3)	4 (5)	1 (2)
Cardiac failure†	2 (1)	1 (1)	5 (3)	1 (1)	3 (4)	1 (2)
Renal failure†	3 (1)	0	3 (2)	2 (1)	1 (1)	0
Treatment discontinuations due to an AE, n (%)*	37 (17)	31 (15)	35 (21)	41 (22)	20 (26)	23 (35)

*In the <65 year subgroup, 223 (Kd) and 208 (Vd) patients were evaluable for safety; in the 65–74 year subgroup, 163 (Kd) and 163 (Vd) patients were evaluable for safety; in the ≥75 year subgroup, 77 (Kd) and 65 (Vd) patients were evaluable for safety.

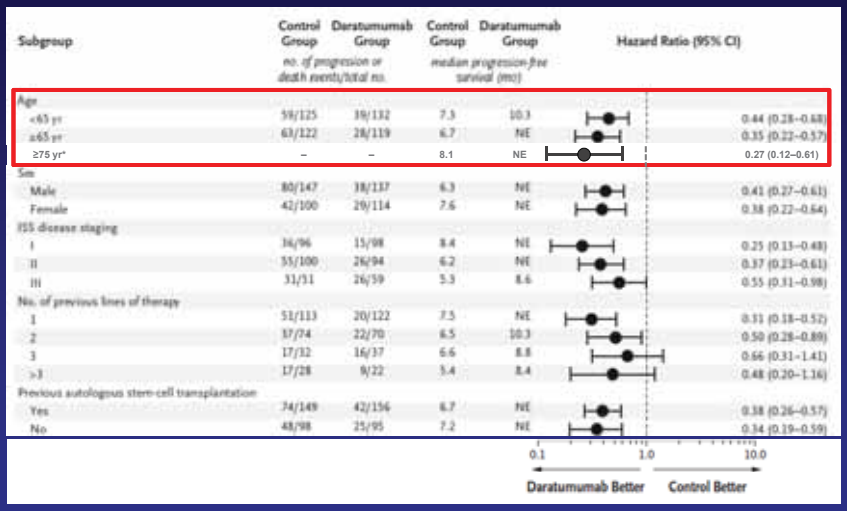
†Preferred term

AE, adverse event; CI, confidence interval; DOR, duration of response; HR, hazard ratio; Kd, carfilzomib and dexamethasone; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; Vd, bortezomib and dexamethasone.



Ludwig H, et al. *Leuk Lymphoma.* 2017

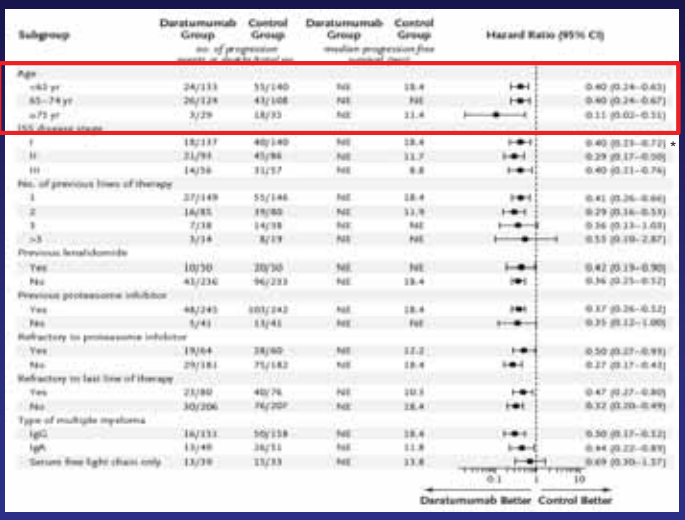
CASTOR: PFS Subgroup Analysis



*Mateos MV, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 8033.

Palumbo A, et al. *N Engl J Med.* 2016;375(8):754-766.

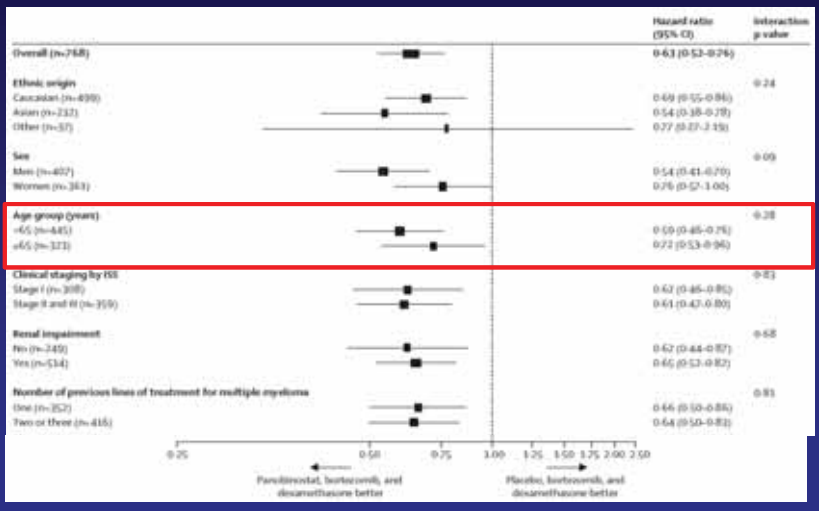
POLLUX: PFS Subgroup Analysis



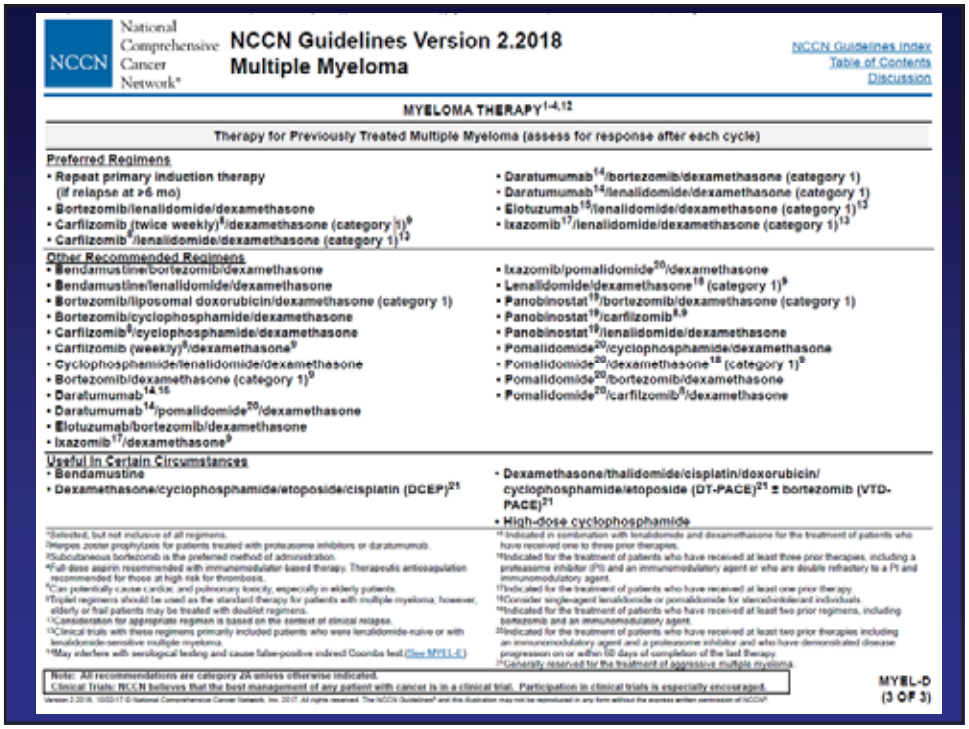
Dimopoulos MA, et al. *N Engl J Med.* 2016;375(14):1319-1331.

[a]Data updated at ASCO 2017: HR 0.19 (0.06-0.55); *P* = .00007
Mateos MV, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 8033.

PANORAMA 1: Panobinostat + Bortezomib-Dex versus Bortezomib-Dex



San-Miguel JF, et al. *Lancet Oncol.* 2014;15(11):1195-1206.



National Comprehensive Cancer Network

NCCN Guidelines Version 2.2018
Multiple Myeloma

NCCN Guidelines Index
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Discussion

MYELOMA THERAPY[1-4,12]

Therapy for Previously Treated Multiple Myeloma (assess for response after each cycle)

Preferred Regimens

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib (twice weekly)[9]/dexamethasone (category 1)[9]
- Carfilzomib[9]/lenalidomide/dexamethasone (category 1)[13]
- Daratumumab[14]/bortezomib/dexamethasone (category 1)
- Daratumumab[14]/lenalidomide/dexamethasone (category 1)
- Elotuzumab[15]/lenalidomide/dexamethasone (category 1)[12]
- Ixazomib[17]/lenalidomide/dexamethasone (category 1)[13]

Other Recommended Regimens

- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib[9]/cyclophosphamide/dexamethasone
- Carfilzomib (weekly)[9]/dexamethasone[9]
- Cyclophosphamide/lenalidomide/dexamethasone
- Bortezomib/dexamethasone (category 1)[9]
- Daratumumab[14,16]
- Daratumumab[14]/pomalidomide[20]/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Ixazomib[17]/dexamethasone[9]
- Ixazomib/pomalidomide[20]/dexamethasone
- Lenalidomide/dexamethasone[18] (category 1)[9]
- Panobinostat[19]/bortezomib/dexamethasone (category 1)
- Panobinostat[19]/carfilzomib[8,9]
- Panobinostat[19]/lenalidomide/dexamethasone
- Pomalidomide[20]/cyclophosphamide/dexamethasone
- Pomalidomide[20]/dexamethasone[18] (category 1)[9]
- Pomalidomide[20]/bortezomib/dexamethasone
- Pomalidomide[20]/carfilzomib[9]/dexamethasone

Useful In Certain Circumstances

- Bendamustine
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[21]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[21] ± bortezomib (VTD-PACE)[21]
- High-dose cyclophosphamide

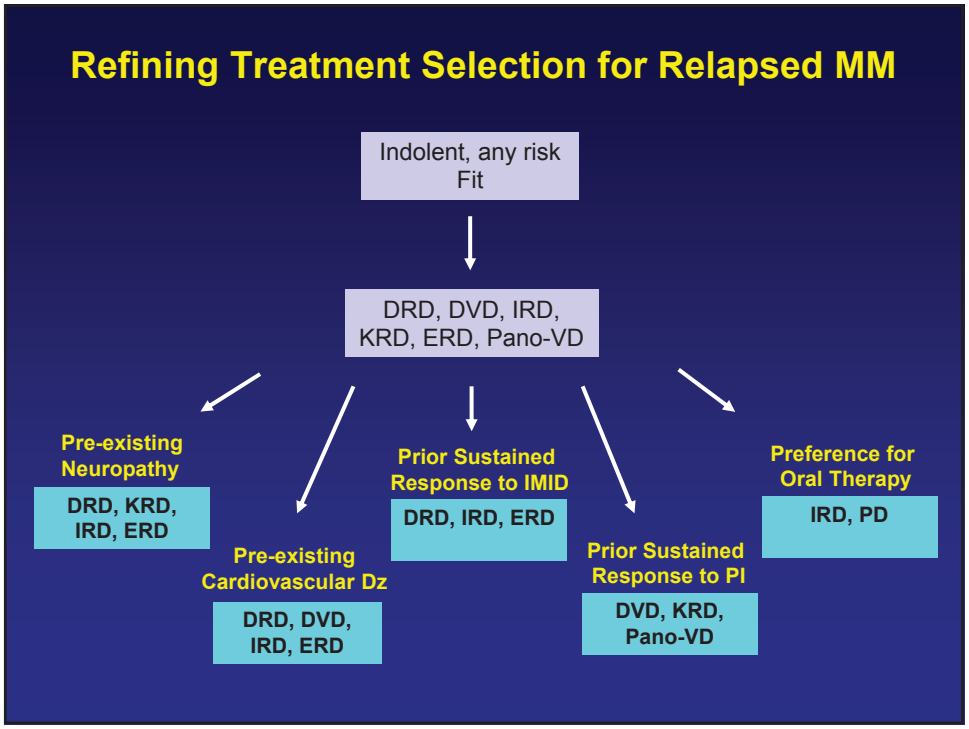
[a]Selected, but not inclusive of all regimens.
[b]Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.
[c]Subcutaneous bortezomib is the preferred method of administration.
[d]Full-dose aspirin recommended with immunomodulator based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[e]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[f]Tripled regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.
[g]Consideration for appropriate regimen is based on the context of clinical relapse.
[h]Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.
[i]May interfere with serological testing and cause false-positive indirect Coombs test (See MYEL-E)
[j] Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.
[k]Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.
[l]Indicated for the treatment of patients who have received at least one prior therapy.
[m]Consider singleagent lenalidomide or pomalidomide for steroidintolerant individuals.
[n]Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.
[o]Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.
[p]Generally reserved for the treatment of aggressive multiple myeloma.

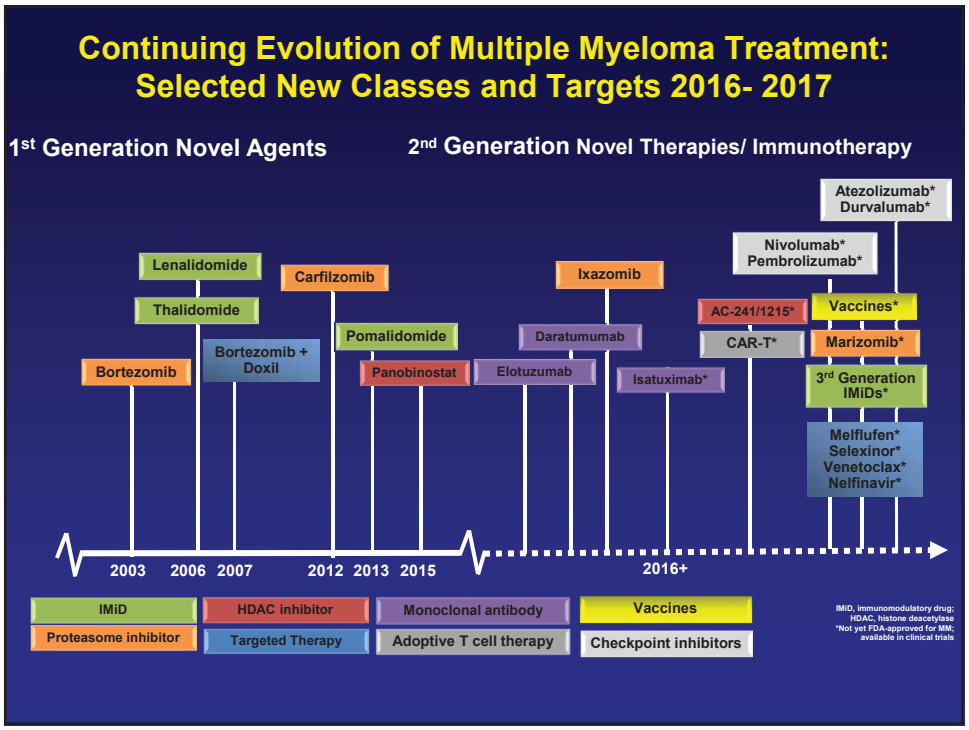
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MYEL-D
(3 OF 3)

Treatment Options for Relapsed and Refractory MM

Aggressive relapse Fit	→	KRD, KPD, DRD, DVD, Pano-VD
Aggressive relapse Frail	→	IRD, KD, PD
Indolent, any risk Fit	→	DRD, DVD, IRD, KRD, ERD, Pano-VD
Indolent, high risk Frail	→	IRD, ERD, KD, PD
Indolent, standard risk Frail	→	IRD, PD, KD


Refining Treatment Selection for Relapsed MM
Indolent, any risk
Fit
DRD, DVD, IRD,
KRD, ERD, Pano-VD
Pre-existing
Neuropathy
DRD, KRD,
IRD, ERD
Pre-existing
Cardiovascular Dz
DRD, DVD,
IRD, ERD
Prior Sustained
Response to IMID
DRD, IRD, ERD
Prior Sustained
Response to PI
DVD, KRD,
Pano-VD
Preference for
Oral Therapy
IRD, PD


Continuing Evolution of Multiple Myeloma Treatment:
Selected New Classes and Targets 2016- 2017
1st Generation Novel Agents
2nd Generation Novel Therapies/ Immunotherapy
Lenalidomide
Thalidomide
Bortezomib
Bortezomib + Doxil
Carfilzomib
Pomalidomide
Panobinostat
Ixazomib
Daratumumab
Elotuzumab
Isatuximab*
Atezolizumab*
Durvalumab*
Nivolumab*
Pembrolizumab*
AC-241/1215*
CAR-T*
Vaccines*
Marizomib*
3rd Generation IMiDs*
Melflufen*
Selexinor*
Venetoclax*
Nelfinavir*
2003
2006
2007
2012
2013
2015
2016+
IMiD
Proteasome inhibitor
HDAC inhibitor
Targeted Therapy
Monoclonal antibody
Adoptive T cell therapy
Vaccines
Checkpoint inhibitors
IMiD, immunomodulatory drug; HDAC, histone deacetylase
*Not yet FDA-approved for MM; available in clinical trials

Patient Case

- 52 year old woman develops lightheadedness/dizziness
- Laboratory studies show hyponatremia, anemia, elevated total protein
- SPEP: 5.07 g/dL, IgG lambda M-protein with total IgG 5660 mg/dl
- Skeletal survey: lucencies of the calvarium and humeri
- Bone marrow biopsy:
  - Hypercellular marrow with 80% plasmacytosis
  - Deletion 13, translocation (4:14)
- Receives RVD followed by ASCT and lenalidomide maintenance, achieves complete response post-ASCT
- Progresses based on increase in M-protein two years after ASCT, transitions to ixazomib plus lenalidomide and dexamethasone
- Best response to Ixazomib plus len-dex is partial response. Progresses after 14 months on ixazomib plus len-dex.
- She then receives carfilzomib plus pomalidomide and dexamethasone. After best response of partial response, she progresses after 8 months.

THANK YOU!

- Our Patients
- The International Myeloma Society
- The meeting sponsors
  - Janssen
  - Celgene
  - Takeda
  - Amgen

Elderly'ish' patient with multiple myeloma

Case capsule-IMS educational workshop, Washington D.C.

Saurabh Zanwar,
Research fellow, Mayo Clinic

History and presentation

A 69 year old lady presented with complaints of new onset back pain and anemia in September 2009

Relevant past history:

- Pulmonary embolism one and a half years back; treated with warfarin for 6 months; thrombophilia work-up was negative
- History of fall twice-one antecedent to the PE and again one year later resulting in a pelvic fracture
- Dyslipidemia, HTN, Hypothyroidism-well controlled on medications
- Osteopenia

Baseline Evaluation

- Hb 11.6 g/dL (dropped from 13.2 g/dL two months prior)
- Sr. Calcium 9.6 mg/dL
- Sr Creatinine: 0.9 mg/dL
- Sr. albumin: 4 g/dL; LFTs: WNL
- B2M: 3.84 ug/dL
- Bone survey: L3 and T8 compression; fracture of Left 3rd rib
- Serum M spike: 4 g/dL; Serum IgG 5460 mg/dL
- SFLC: kappa: 18.4 mg/dL; lambda: 0.186 mg/dL; kappa:lambda ratio: 98.9
- Bone marrow Bx: 70% plasma cells
- FISH: t(11;14)noted; Conventional cytogenetics: no abnormality

Diagnosis

- Multiple myeloma standard risk
  - ISS stage II
  - Salmon Durie Stage IIA
- ECOG 1 at presentation

Any additional information that you would want prior to planning therapy in this lady?

Evaluation of an elderly myeloma

- Comprehensive geriatric assessment
- Frailty index
- Any form of validated geriatric assessment

Is geriatric assessment a part of your routine practice for elderly myelomas?

What would you choose as a frontline therapy for this patient?

- She was enrolled in a clinical trial of lenalidomide and dexamethasone in September 2009
- She received **lenalidomide** without dexamethasone as part of the trial, along with bisphophonates and coumadin
- Her best response to lenalidomide was a **partial response**
- Partial response was sustained till April of 2015 when she developed biochemical progression with elevation of M spike to 2.1 g/dL from a nadir of 1.2 g/dL
- Dexamethasone was added at that time but the disease continued to progress biochemically
- Bone marrow evaluation showed 20% plasma cells with CSK1B gene duplication along with t(11;14) on FISH

What factors dictate treatment choice at relapse for an elderly fit patient?

Asymptomatic progression, ECOG PS of 0 and no end organ damage

- Options of combination chemotherapy (CyBorD), ASCT and available clinical trials were discussed with the patient
- She opted for **Venetoclax (ABT-199)-Dexamethasone** as part of a clinical trial in June 2015
- Unfortunately she progressed biochemically within three months and was taken off the trial in Aug 2015

Further therapy

- She refused ASCT and opted for Cyclophosphamide-Bortezomib-Dexamethasone (CyBorD) in Aug 2015
- She completed 12 cycles in Aug 2016 with excellent tolerance and had a **partial response** with M spike of 1.0 g/dl
- She had no peripheral neuropathy at that time

Would you opt for any maintenance therapy in this patient at this point ?
If yes, with what ?

Maintenance therapy

- She was started on a two weekly bortezomib regimen which was well tolerated
- Serum M protein remained stable on maintenance bortezomib for 8 months
- She had biochemical disease progression in April 2017
  - 30% plasma cells in bone marrow
  - 1q duplication on FISH with t(11;14)
- She was started on **Daratumumab-Pomalidomide-Dexamethasone** in April 2017
- She is tolerating the treatment well so far and has achieved a partial response

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Case Presentation: Elderly Patients with Multiple Myeloma

Surbhi Sidana,MBBS

International Myeloma Society Educational Workshop
October 28th, 2017

Case 1

Initial Presentation

- 88 year old lady diagnosed with multiple myeloma in December 2013 during evaluation of anemia
  - Hemoglobin: 9.6 g/dL
  - Calcium: 9.7 mg/dL
  - Creatinine: 1.2 mg/dL
  - Albumin: 3.4 g/dL
  - Beta-2-microglobulin: 2.3
  - M-Spike, IgG kappa: 2.3 g/dL
  - Bone marrow: 55% plasma cells
  - FISH: trisomy 7, 9, 11 and 15.
  - Skeletal survey: Few indeterminate lesions
- Other causes of anemia ruled out

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Relevant Medical History

- In relatively good health for her age
- Ambulating with cane/walker in preceding few months due to mild unsteadiness of gait, cause indeterminate
- Past Medical History
  - Hypertension, well-controlled
  - Mild diastolic dysfunction, grade 2/4
  - Grade 2 CKD, stable
  - Osteopenia
  - Hyperlipidemia

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What would you recommend for further management?

- Lenalidomide-dexamethasone
- Bortezomib-dexamethasone
- Dose reduced bortezomib-lenalidomide-dex
- Cyclophosphamide-bortezomib-dex
- Other chemotherapy regimen
- Supportive care only

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Treatment

March 2014

- M-spike gradually increased after 2-3 months of observation (2.3 → 2.8 g/dL)
- Lenalidomide 10 mg days 1-21 of 28 d cycle
  Dex 20 mg weekly

Subsequently well tolerated
Best Response: PR (in 2 cycles)

After one cycle:
M-spike 2.8 → 1.6 g/dL

Mild cytopenias and fatigue
Platelets 100,000; ANC 1.5; Hb 8

Lenalidomide decreased to 5 mg
days 1-21 of 28 day cycle

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Sept 2014:

- Developed pneumonia 6 months into treatment
- Lenalidomide held for 2 months→ gradual rise in M-spike (1 to 1.2)
- Resumed lenalidomide on "maintenance" approach 5 mg every other day in Dec 2014

April 2015 (13 months after starting)

- Gradual biochemical progression (M-spike 1.2 to 1.4)
- Anemia stable and no other symptoms

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What would you recommend for this 90 year old patient gradually progressing on first line therapy?

- Switch therapy
- Continue current therapy and monitor
- Increase dose of lenalidomide

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April 2015:

- Continued lenalidomide 5 mg every other day
- Anemia stable and no other symptoms

July 2015:

- Ongoing biochemical progression
- M-spike: 1.7 g/dL
- Remains asymptomatic and tolerating treatment well

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July 2015:

- Switched to bortezomib 1.3 mg/m^2 SQ weekly + dex 20 mg weekly
- Anemia stable and no other symptoms

- Best Response: Minor response (nadir M-spike 1.7→ 1.4)
- Gradual progression in Feb 2016 (M-spike 1.6 g/dL)
- Remains asymptomatic

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What would you recommend for second biochemical progression in this elderly patient?

- Continue current approach
- Increase bortezomib dose
- Switch therapy

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Feb 2016:

- Bortezomib dose increased → response, but fatigue
- Bortezomib scaled back to 1.3 mg/m2
- Cyclophosphamide 50 mg daily added
- Cytopenias with triplet regimen

Nov 2016:

- Cytopenias
- Treatment held
- Rise in M-spike to 1.4 g/dL

- Switched to daily cyclophosphamide + dex 20 mg weekly
- Well tolerated
- Best response: Minor response (1.7→ 1.2)
- Brief 1 month interruption: Mechanical fall with SAH→ resumed therapy

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What would you recommend for fourth line therapy in this 91 year old patient, now intolerant to low dose alkylator?

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Jan 2017

- Switched to pomalidomide 1 mg days 1-21 + Dex 12 mg weekly
- Clarithromycin added in Feb 2017
- Best response: stable disease

March-May 2017

- Cytopenias and gradual decline in performance status
- May 2017: Gradual progression
- Elected to pursue supportive care only in May 2017 at age of 92 years (3.5 years after diagnosis)

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Takeaways:

- Less intense, dose adjusted therapy
- Can receive multiple regimens, if appropriately selected
- Treatment can prolong survival meaningfully, with good quality of life

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CASE-2

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Initial Presentation

- 75 year old gentleman diagnosed with multiple myeloma in April 2013 in setting of anemia, acute kidney injury, weight loss and bone pain
  - Hemoglobin: 5.8 g/dL
  - Calcium: 9.0 mg/dL
  - Creatinine 1.5 mg/dL
  - Albumin: 2.6 g/dL
  - M-spike, IgG kappa: 6.1 g/dL
  - Beta-2-microglobulin: 9.8 mg/dL
  - Bone marrow aspirate: 90% plasma cells
  - FISH: t(11;14)
  - Skeletal survey: Diffuse lytic lesions
- Revised ISS: Stage 2

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Relevant Medical History

- Was active prior to onset of symptoms
- Now with limited mobility from pain (thoracic compression fracture)
- Past Medical History
  - Hyperlipidemia
  - Osteoarthritis
  - GERD

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What would you recommend for further management?

- Induction followed by transplant
- Lenalidomide-dexamethasone
- Bortezomib-dexamethasone
- Bortezomib-lenalidomide-dex
- Cyclophosphamide-bortezomib-dex
- Other chemotherapy regimen

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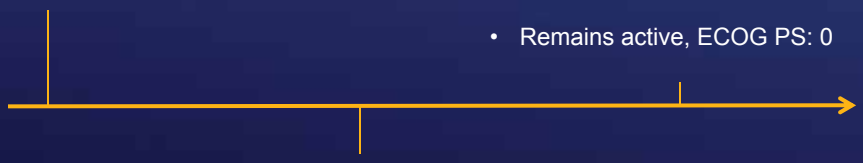
April 2013

- Cyclophosphamide-bortezomib-dex
- Best response: Partial response (6→2 g/dL)

Jan/Feb 2014

- Progression with concern for new lytic lesion in shoulder→ palliative radiation for pain
- M-spike ~ 3 g/dL
- Bone marrow: 50% plasma cells
- Remains active, ECOG PS: 0



Oct 2013

- Treatment discontinued after 6 cycles due to AEs significantly affecting quality of life
- Progressive fatigue, asthenia, nausea, GI symptoms

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What would you recommend?

March 2014

- Bortezomib (1.3 mg/m2 SQ weekly) - lenalidomide (15 mg on days 1-14) - dex 40 mg weekly
- Well tolerated, except steroids
- Response after 3 cycles: Minor response (3.8 → 2.8)
- Lenalidomide increased to 25 mg

Aug 2014

- Grade 1 neuropathy
- M-spike 2 g/dL (almost PR)
- Bortezomib decreased to 1 mg/m^2 weekly and dex to 20 mg weekly

Nov 2014

- Slight worsening of PNP
- M-spike 1.7 g/dL (PR)
- Bortezomib discontinued after 9 cycles of VRD

Nov 2014- Feb 2016

- Lenalidomide 25 mg
- Decrease in steroid dose due to poor tolerance
- Response: Ongoing partial response (nadir 1.5 g/dL)

March 2016

- Rising M-spike (1.5-1.9)

Feb 2016

- Sepsis, Atrial fibrillation with RVR
- Lenalidomide held for 1 month

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What would you recommend?

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April 2016

- Ixazomib- pomalidomide- dex (12 mg) initiated
- Well tolerated, some side effects with steroids

July 2016

- No response after 3 cycles
- Gradual rise in M-spike

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What would you recommend?

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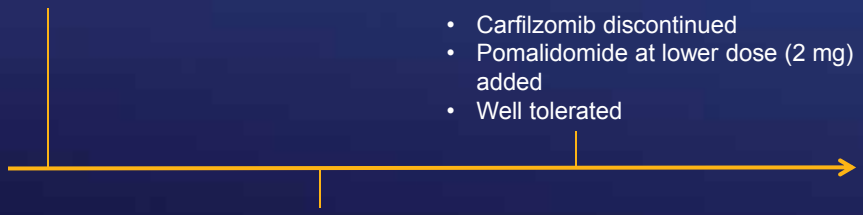
August 2016

- Daratumumab-pomalidomide-dex initiated
- Neutropenia → pomalidomide discontinued after 1 cycle
- Daratumumab well tolerated
- Partial response

March 2017

- Carfilzomib discontinued
- Pomalidomide at lower dose (2 mg) added
- Well tolerated



Feb 2017

- Carfilzomib added due to biochemical progression
- Admitted to the hospital 2 weeks after initiation with chest discomfort, leg swelling and shortness of breath
- Atrial fibrillation with RVR
- Echo: EF stable at 55%

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Sept/Oct 2017

- Progression with rapid rise in M-spike
- Bortezomib with nelfinavir initiated (off-label)

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Questions and Discussion
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