


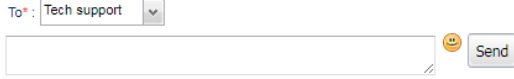
Making Sense of Myeloma Treatment Advances

January 10, 2018

Updates From the 2017 American Society of Hematology Annual Meeting



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Multiple Myeloma Research Foundation



Moderator

- **Mary DeRome**
Multiple Myeloma Research Foundation
Norwalk, Connecticut



www.themmr.org



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Speakers



- **Faith E. Davies, MBBCh, MRCP, MD, FRCPPath**
Professor of Medicine
Medical Director, Myeloma Institute
University of Arkansas for Medical Sciences
Little Rock, Arkansas



- **David S. Siegel, MD, PhD**
Division Chief of Myeloma
John Theurer Cancer Center
Hackensack University Medical Center
Hackensack, New Jersey



Topics for Discussion

- MMRF CoMMpass StudySM results
 - Genomic profiles to identify new targets for drug discovery and development
- Advances in initial therapy, minimal residual disease monitoring, and maintenance therapy
- Immunotherapy
 - CAR T-cell therapy
 - Antibody-drug conjugates
- Studies in relapsed and refractory multiple myeloma
 - Daratumumab
 - Kyprolis
- Smoldering multiple myeloma

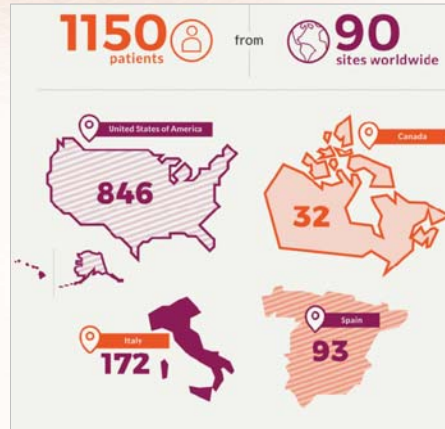


MMRF CoMMpass StudySM Results



MMRF CoMMpass StudySM: Advancing Personalized Medicine Research

- Landmark study focusing on the genomics of myeloma
- Goals
 - Learn which patients respond best to which therapies
 - Achieve better treatments targeted to each patient's biological makeup
- Newly diagnosed patients will be followed for at least 8 years



MMRF CoMMpass StudySM: Genomic Observations

Analysis of myeloma genomics from patient samples from CoMMpass



Identified 26 mutated genes (that is, genes that contain a defect or error) that have the potential to cause the development of MM (also known as oncogenes)¹

903 different fusion transcripts identified. Some that activate genes involved in myeloma cell growth and survival and some that inactivate genes that suppress myeloma cell growth²

A 7-gene signature successfully predicted which patients would benefit from Velcade and Revlimid therapy with respect to response and survival³

High RNA-editing activity (an important function for regulating normal protein production in cells) is associated with resistance to proteasome inhibitors such as Velcade⁴

Mutations most often occur in the gene that encodes for a key modulator of the anti-tumor effects of IMiDs. These mutations occur more frequently in patients after treatment⁵

CoMMpass data is revealing new insights into MM biology. These insights will help drive improvements in treatment selection and may identify new therapeutic targets

1. Walker BA et al. *Blood*. 2017;130: Abstract 60.
 2. Nasser S et al. *Blood*. 2017;130: Abstract 61.
 3. Chapman M et al. *Blood*. 2017;130: Abstract 267.
 4. Lagana A et al. *Blood*. 2017;130: Abstract 268.
 5. Garcia SB et al. *Blood*. 2017;130: Abstract 270.



The MMRF Molecular Profiling Protocol

Opened in 2016 across the entire
Multiple Myeloma Research Consortium (MMRC)

- **Goals**

- Enroll and follow 500 relapsed patients to have their genome molecularly profiled
- Identify actionable genetic alterations (that is, genetic mutations that can be a site of action for a drug or treatment)

- 76% of patient samples were found to harbor at least one actionable alteration
- In 10% of cases, the treating physician acted on the information with an applicable targeted agent

These results have spurred the launch of MyDRUG, a master protocol aimed at developing new myeloma regimens based on individual patient's genomics.

Auclair D et al. *Blood*. 2017;130: Abstract 395.



Key Points: MMRF CoMMpass StudySM Findings

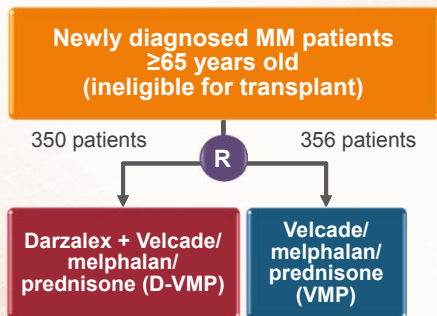
- Study of a large number of patients in a systematic fashion is important
- Allows the identification of new genetic mechanisms that
 - Drive MM cell growth and survival
 - Contribute to drug resistance
 - May predict which patients respond to which therapy
- This ultimately will result in a personalized approach to MM therapy



Advances in Initial Therapy, Minimal Residual Disease Monitoring, and Maintenance Therapy



Phase 3 Trial Integrating Darzalex Into a Frontline Treatment Regimen



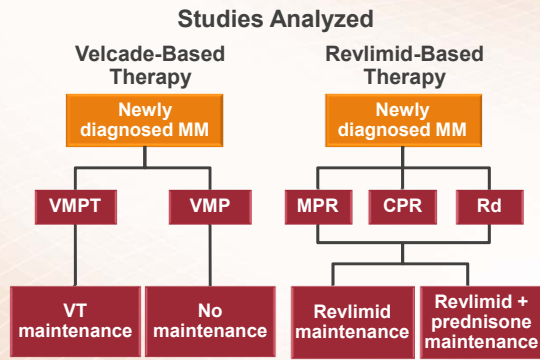
- Treatment with the Darzalex-based regimen (D-VMP) reduced the risk of disease progression by half compared to treatment with VMP
- More patients receiving Darzalex achieved a complete response or better and three times as many patients achieved minimal residual disease negativity than patients who did not receive Darzalex

Darzalex should be used as part of the VMP regimen for newly diagnosed patients who are ineligible for ASCT.

Mateos MV et al. *Blood*. 2017;130: Abstract LBA-4.
Mateos MV et al. *N Engl J Med*. 2017; Dec 12 [Epub ahead of print].



Impact of Velcade- or Revlimid-Based Therapy in Transplant-Ineligible Patients With High-Risk Disease



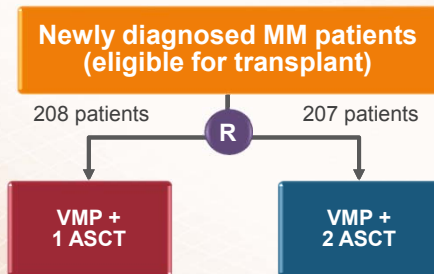
- Velcade-based, compared to Revlimid-based, treatment in patients with high-risk cytogenetics resulted in a reduced risk of death or progression

VMP induction should be considered standard treatment for newly diagnosed patients ineligible for stem cell transplant with high-risk cytogenetics.

Larocca A et al. *Blood*. 2017;130: Abstract 744.



The Role of Single or Double Autologous Stem Cell Transplant in Newly Diagnosed Patients



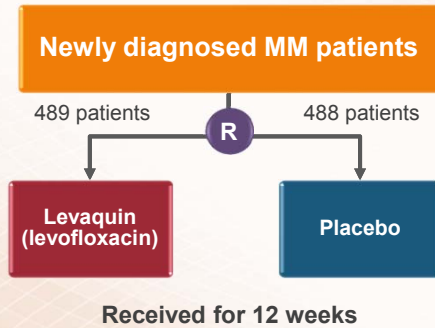
- Two transplants were better than one in terms of lengthening time before disease progression and overall survival
- The survival benefits were the same regardless of whether patients had characteristics that are associated with a worse prognosis, such as:
 - High-risk cytogenetics t(4;14), t(14;16) , or del(17p)
 - Older than 55 years of age
 - Revised-International Staging System stages II or III

This trial supports the use of 2 ASCTs especially for patients with high-risk disease features.

Cavo M et al. *Blood*. 2017;130: Abstract 401.



Tackling Early Morbidity and Mortality in Myeloma (TEAMM) With Antibiotic Prophylaxis



- Prophylactic Levaquin reduced the number of fevers and deaths in patients undergoing treatment for myeloma
- No significant increase in side effects related to the Levaquin were seen (for example, *C. difficile* diarrhea)

This trial supports the use of routine antibiotic prophylaxis in newly diagnosed patients receiving therapy.

Drayson MT et al. *Blood*. 2017;130: Abstract 903.



Phase 3 Trial to Determine the Value of Measuring Minimal Residual Disease (MRD) After Receiving Induction Therapy With Revlimid, Velcade, and Dexamethasone (RVD)

MRD

W
H
A
T

The presence of small amounts of myeloma cells left in the bone marrow following the achievement of a CR after treatment

H
O
W

MRD tests can detect at least 1 cell in 100,000. Ideally, we want to use more sensitive assays that can find 1 cell in a million—next-generation sequencing test (Adaptive Biotech)

W
H
Y

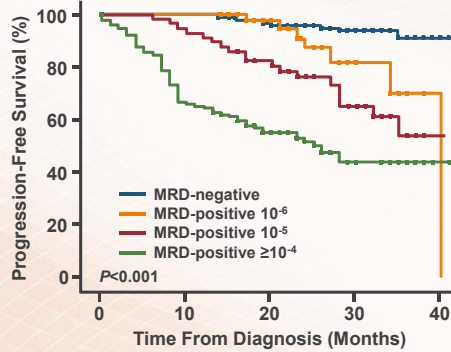
Patients who achieve MRD negativity following treatment experience longer time without disease recurrence than those who are still MRD positive after treatment

MRD negativity should be used in future clinical trials as an end point.

Avet-Loiseau H et al. *Blood*. 2017;130: Abstract 435.



Next-Generation Flow (NGF)-Based MRD Assessment Is Feasible and Highly Sensitive

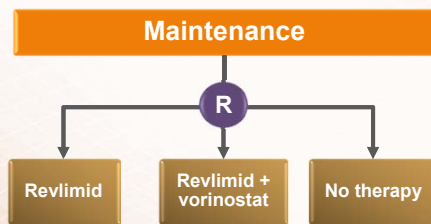


- The largest study of MRD monitoring in MM (1,134 patients)
- This study defines MRD-negativity as the most relevant clinical end point for both standard- and high-risk transplant-eligible MM patients

Paiva B et al. *Blood*. 2017;130: Abstract 905.



The Impact of MRD in the Maintenance Setting



- To date, most studies have measured MRD post transplant or at the end of therapy, not during maintenance
- Conversions to MRD negativity were observed in 32% of patients on maintenance compared to patients on no further therapy (4%)
- Patients who achieved MRD negativity earlier in treatment had a better outcome

De Tute RM et al. *Blood*. 2017;130: Abstract 904.



Maintenance Therapy: Revlimid

Response-Adapted Revlimid¹

Phase 3 study in newly diagnosed MM patients following ASCT

- Group 1: received Revlimid maintenance for 2 years
- Group 2: received Revlimid maintenance only until a complete response achieved
- Compared to Group 2, patients in Group 1 showed:
 - Improved overall survival
 - No different in the time until disease progression
 - Was associated with more toxicity

Maintenance therapy with Revlimid should be administered continuously even after achieving a complete response.

1. Goldschmidt H et al. *Blood*. 2017;130: Abstract 400.
2. Jackson G et al. *Blood*. 2017;130: Abstract 436.

Revlimid in High-Risk MM²

Phase 3 study in newly diagnosed MM patients (both ASCT eligible and ineligible)

- Patients continue to benefit from Revlimid maintenance in terms of longer time without disease recurrence
- The benefit of Revlimid maintenance is the same regardless of the risk status of the patient
- Overall survival was prolonged in ASCT-eligible patients



Maintenance Therapy: Ninlaro

Ninlaro + Revlimid¹

Phase 2 study in newly diagnosed MM patients following ASCT

- The all-oral combination of adding Ninlaro to Revlimid did not significantly increase side effects
- The combination is safe and a feasible regimen to use
- Additional trials to support its use are warranted

Ninlaro Alone²

Integrated analysis of four phase 1/2 studies in transplant-ineligible newly diagnosed MM patients

- Single-agent Ninlaro maintenance therapy following Ninlaro-based induction was associated with deepening of responses
- Feasible for long-term administration

1. Patel KK et al. *Blood*. 2017;130: Abstract 437.
2. Dimopoulos MA et al. *Blood*. 2017;130: Abstract 902.



Maintenance Therapy: Empliciti

Empliciti + Revlimid

Phase 2 study in newly diagnosed MM patients following ASCT

- The combination is well tolerated
- 36% of patients improved their initial disease response while on therapy (with some converting to complete responses and some with MRD negativity)

Thomas SK et al. *Blood*. 2017;130: Abstract 840.



Key Points: Initial Therapy, MRD, and Maintenance

- Darzalex has shown that it is safe and effective in newly diagnosed patients
- Patients with high-risk disease should consult with their doctors about different treatment approaches
- Patients who achieve MRD negativity do better than patients who don't; however, we still don't know which test is best to detect MRD
- Maintenance therapy is effective and a number of additional drugs have been shown to be safe as maintenance

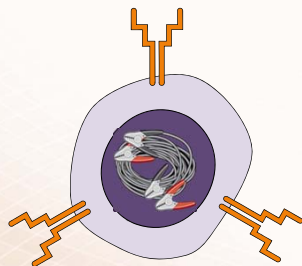


Immunotherapy



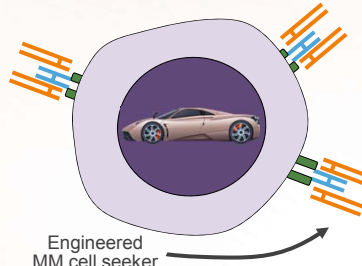
CAR T-Cell Therapy

Natural T cell with
T-cell receptor
(TCR)



- Needs a jump start to target and kill MM cells

Engineered T cell with
chimeric antigen receptor
(CAR)



- Homing beacon built in to target and kill MM cells!



B-Cell Maturation Antigen (BCMA)–Targeted CAR T-Cell Therapy in Refractory MM Patients With Limited Treatment Options

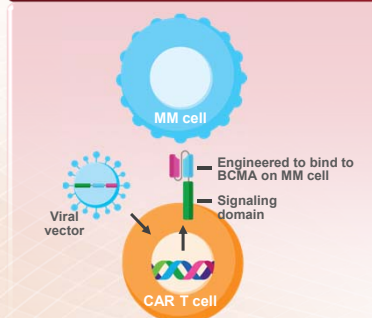
- NIH Study (21 patients)
 - CAR-T cell therapy: bb2121
 - Over 90% had a response; of those patients assessable for minimal residual disease (MRD) testing, 90% were negative
 - 1 case of serious neurotoxicity observed; CRS was reported in 71% of patients

Berdeja JG et al. *Blood*. 2017;130: Abstract 740.



B-Cell Maturation Antigen (BCMA)–Targeted CAR T-Cell Therapy in Refractory MM Patients With Limited Treatment Options

Chimeric antigen receptor (CAR) T cells



- UPenn Study (24 patients)¹
 - BCMA-CAR T–cell infusion
 - 11 patients achieved at least a partial response
 - Side effects included cytokine release syndrome (CRS) and neurotoxicity; there was one death on the study
- NIH Study (11 patients)²
 - BCMA-CAR T–cell therapy
 - 9 of 11 patients achieved a response
 - 8 of 10 patients in whom minimal residual disease (MRD) was measured had achieved MRD negativity
 - Toxicities such as CRS was significant but limited in duration and controllable

1. Cohen AD et al. *Blood*. 2017;130: Abstract 505.
2. Brudno J et al. *Blood*. 2017;130: Abstract 524.



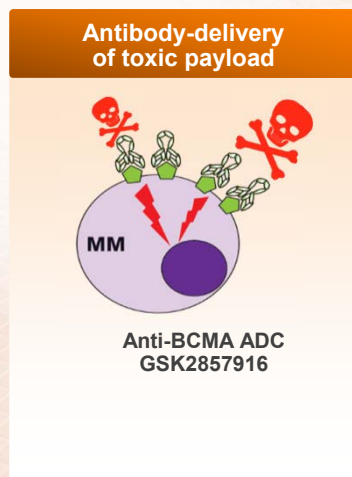
Other CAR T-Cell Therapy Approaches

- Chinese study (8 patients)¹
 - Combination of two types of engineered CAR T cells: ones that target CD19 and ones that target BCMA
 - All patients experienced acute CRS, but none experienced neurologic complications nor were there any treatment-related deaths
 - Only 6 of the patients could be evaluated for a treatment response and 4 of these patients experienced a partial response or better
- MSKCC study (6 patients)⁵
 - Engineered to be highly specific to the BCMA molecule
 - Many patients experienced CSR, but no neurotoxicities; ~75% of patients (who could be evaluated for response) responded to this new CAR T-cell construct

1. Yan L et al. *Blood*. 2017;130: Abstract 506.
2. Smith EL et al. *Blood*. 2017;130: Abstract 742.



Antibody-Drug Conjugate (ADC)



- 35 patients with relapsed/refractory MM (many who had previously received more than 5 different regimens) were treated with GSK2857916 via an intravenous infusion
- Results from the trial revealed that 60% of patients had a response
- The most commonly occurring side effect were corneal events (such as blurred vision, dry eye) and low platelet counts

Trudel S et al. *Blood*. 2017;130: Abstract 741.



Key Points: Immunotherapy

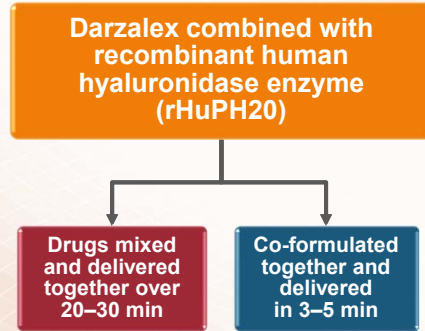
- Immunotherapy means a lot of different things, not just antibodies directed against MM cells, CAR T, and related
- We still don't know the long-term outcome for CAR T
- What are the best targets? How do we identify them?
- Everyone is excited about CAR T, but this is a strategy that is still very toxic and of very limited availability
- ADCs are getting very limited press but are very exciting; a number are already in clinical trials
- We should not be giving up on checkpoint inhibitors; this might still be the most exciting strategy



Studies in Relapsed and Refractory Myeloma



The Use of Darzalex as a Subcutaneous Injection

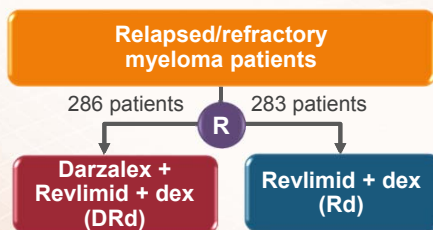


- Almost all patients discontinued treatment when the drugs were mixed and delivered together; however, all patients who received the co-formulated drugs stayed on treatment
- Both drug formulations had similar response rates, with ~40% of patients responding to the treatments
- Lower than expected rates of infusion-related reactions occurred in all groups, but especially in the group that received the co-formulated drugs

Chari A et al. *Blood*. 2017;130: Abstract 838.



Updates on Therapies in Relapsed/Refractory Myeloma: Darzalex

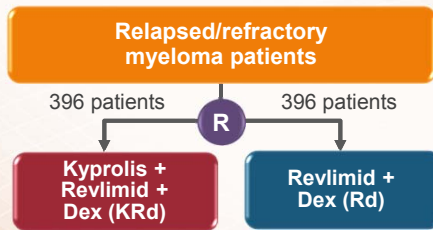


- An analysis of efficacy and safety data based on longer follow-up time
- Compared to treatment with Rd, DRd therapy:
 - Prolonged the time to disease recurrence
 - Increased the number of patients who achieved a response (including more with \geq VGPR and \geq CR)
 - Prolonged the duration of response
 - Increased the number of patients who achieved MRD negativity by 3 times

The POLLUX study.
 Dimopoulos MA et al. *Blood*. 2017;130: Abstract 739.



Updates on Therapies in Relapsed/Refractory Myeloma: Kyprolis



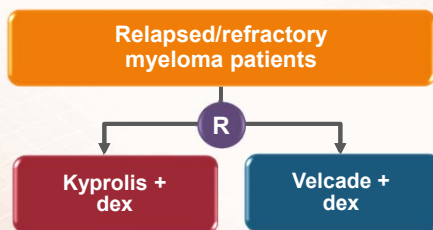
- The planned final analysis of overall survival from this study was conducted
- KRd resulted in a 21% reduction in the risk of death compared to Rd

This trial supports the use of KRd as a standard of care for relapsed/refractory patients.

The ASPIRE study.
Stewart AK et al. *Blood*. 2017;130: Abstract 743.



Updates on Therapies in Relapsed/Refractory Myeloma: Kyprolis

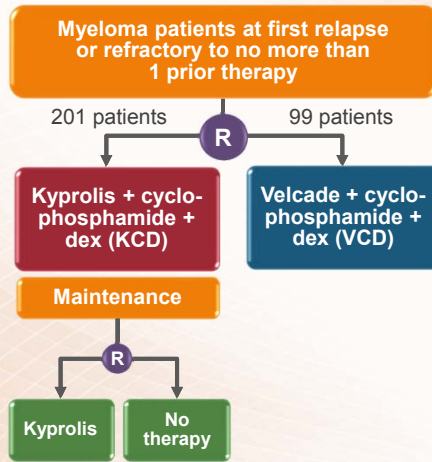


- RNA sequencing data from patients on the trial revealed a set of 13 genes whose expression could be used to categorize patients that would derive greatest clinical benefit from Kd
- This set of genes will be further validated in other independent studies

The ENDEAVOR study.
Pelham RJ et al. *Blood*. 2017;130: Abstract 839.



Kyprolis or Velcade Combined With Cyclophosphamide and Dexamethasone



Responses	KCD	VCD
≥VGPR (%)	40.2	31.9
Overall response rate (≥PR, %)	84.0	68.1
MRD negative (%)	16.4	12.5

- Overall response rate with KCD is superior to VCD possibly due to better tolerability

The MUK *five* study.
 Yong K et al. *Blood*. 2017;130: Abstract 835.



Key Points: Relapsed/Refractory Studies

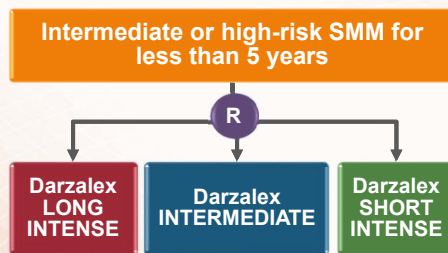
- To me it looks like carfilzomib and daratumumab are the two most active agents to date
 - We need to make practitioners and patients more comfortable with their use.
 - The SQ dara studies will go a long way in this regard
- Many other new drugs coming along as well



Smoldering Multiple Myeloma (SMM)



Darzalex for Intermediate or High-Risk SMM

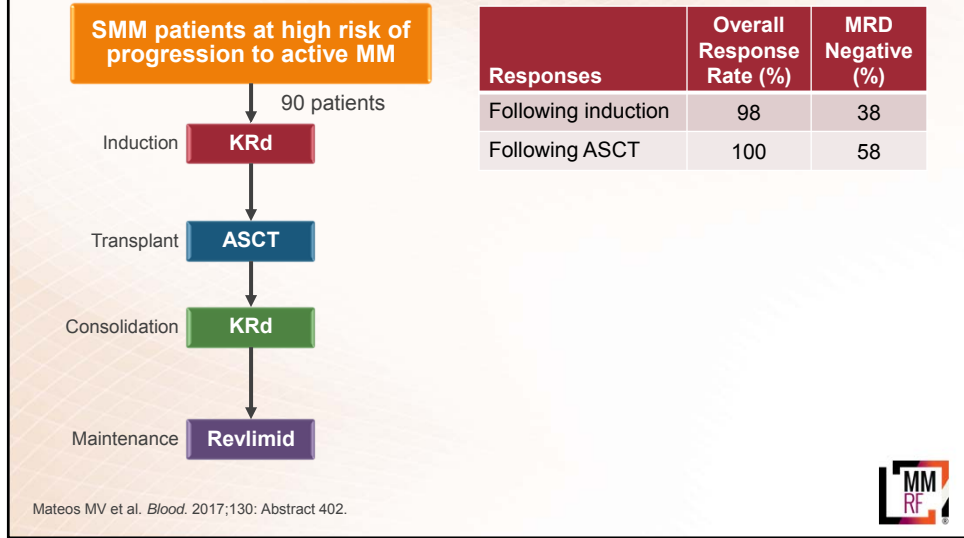


- Response rates tended to be higher in the group that received the long intense dosing schedule compared to the other schedules
- Darzalex was well tolerated

Hofmeister CC et al. *Blood*. 2017;130: Abstract 510.



Strategy for High-Risk Smoldering Myeloma Using Kyprolis/Revlimid/Dexamethasone (KRd)



Key Points: Smoldering Myeloma



- I am not sure that I believe we have come to the stage where we should be treating patients, many of who will never progress to symptomatic disease and others who might not for long periods of time.
- Efforts are ongoing at the MMRF and elsewhere to try to pinpoint which smoldering patients will progress to symptomatic disease. Until that answer is discovered, caution is advised regarding treatment of smoldering patients.

Questions & Answers



Closing





Resources for You!

MMRF Patient Support Center

Have questions about the trials or information you heard today?

Call our MMRF Nurse Patient Navigators.

Our MMRF Nurse Patient Navigators can guide you through your multiple myeloma journey every step of the way. Call Mon–Fri, 9:00 am–7:00 pm ET

 **Call now**

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