MULTIPLE MYELOMA Research Foundation

Understanding Next in Class Novel Therapies in Multiple Myeloma: *New Classes and Targets*

March 23, 2016

Welcome and Introductions

Joan Levy, PhD
Multiple Myeloma Research Foundation
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Recent Drug Approvals

Drug*	Class	FDA Approval
Farydak® (panobinostat)	HDAC inhibitor	February 23, 2015
Darzalex™ (daratumumab)	Antibody	November 16, 2015
Ninlaro® (ixazomib)	Proteasome inhibitor	November 20, 2015
Empliciti™ (elotuzumab)	Antibody	November 30, 2015

* All of the approvals above are for the treatment of relapsed/refractory multiple myeloma

HDAC, histone deacetylase inhibitor.

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Faculty

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Myeloma Overview

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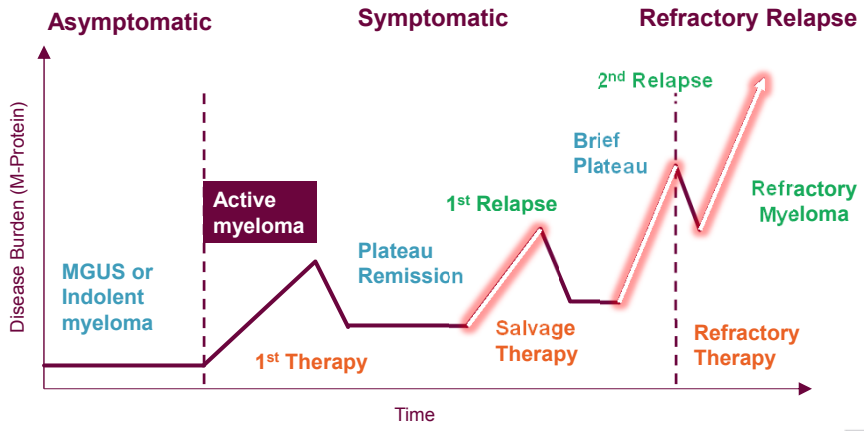
Multiple Myeloma Disease Course



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Focus on Relapsed and Refractory Multiple Myeloma

Relapsed	Refractory
• When the cancer returns after treatment, usually after a period of remission or response • Since there is no cure for multiple myeloma, it is likely that patients will relapse at some point during their disease • With therapy, relapsed patients can achieve a second response	• When myeloma is not responsive to therapy • May occur in patients who never see a response from their first treatment therapies • May occur in patients who do initially respond to treatment, but do not respond to treatment after a relapse

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Proteasome Inhibitors

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Proteasome Inhibitors

Drug	Description
Velcade® (bortezomib)	• IV infusion approved for refractory (2003), relapsed (2005), and newly diagnosed MM (2008) • SQ injection approved in 2012
Kyprolis® (carfilzomib)	• IV infusion • Approved as a single agent (2012), as DOUBLET with dexamethasone (2016), and TRIPLET with Revlimid plus dexamethasone (2016)
Ninlaro® (ixazomib)	• Once-weekly pill • Approved TRIPLET with Revlimid and dexamethasone (2015)
Marizomib	• IV infusion • Currently in clinical trials
Oprozomib	• Once-weekly pill • Currently in clinical trials

IV, intravenous; MM, multiple myeloma; SQ, subcutaneous.
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Weekly Carfilzomib: CHAMPION-1 Study

- Phase I/II study of weekly carfilzomib 70 mg/m^2
- Promising response rates and PFS
  - 77% overall response rate; 63% response rate in patients refractory to bortezomib
  - Median duration of response: 16.3 months
  - Median PFS: 14.3 months
- Tolerable safety profile
- Next steps: Phase III ARROW study will compare once-weekly vs twice-weekly carfilzomib

PFS, progression-free survival.
Berenson J et al. *Blood*. 2015; 126(23): Abstract 373.
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High-Dose Carfilzomib: Phase III ENDEAVOR Study

- ENDEAVOR compared high-dose carfilzomib (56 mg/m^2) plus dexamethasone with bortezomib plus dexamethasone
- Response and PFS was better with carfilzomib
  - In patients with 1 prior line of therapy:
    - Overall response rate was better with carfilzomib (82%) than bortezomib (66%)
    - PFS was better with carfilzomib (22.2 months) than bortezomib (10.1 months)
  - In patients with 2 or more prior lines of therapy:
    - Overall response rate was better with carfilzomib (72%) than bortezomib (60%)
    - PFS was better with carfilzomib (14.9 months) than bortezomib (8.4 months)
- More patients in the carfilzomib group developed high blood pressure and cardiac failure

PFS, progression-free survival.

Moreau P et al. *Blood*. 2015; 126(23): Abstract 729.

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Ixazomib Dose Comparison

- Study comparing 2 doses of ixazomib (4 mg vs. 5.5 mg) plus weekly dexamethasone in patients with relapsed MM who had not previously received a proteasome inhibitor
- Early results (median follow up of 10 months):
  - Overall response rate is better for the 5.5 mg ixazomib group (51%) than the 4 mg group (31%)
  - Ixazomib was well-tolerated at both doses
    - Fewer patients required dose reductions in the 4 mg group (17%) than the 5.5 mg group (43%)

MM, multiple myeloma.

Kumar SK et al. *Blood*. 2015;126(23):3050.

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All-Oral Triplet: Ixazomib, Lenalidomide and Dexamethasone

- Phase III study comparing ixazomib, lenalidomide, and dex (triplet) with lenalidomide and dex
  - Patients had 1-3 prior lines of therapy and were not refractory to prior lenalidomide or proteasome inhibitor therapy
- Better response, duration of response, and PFS with triplet therapy
  - Overall response rate: 78.3% vs. 71.5%
  - Duration of response: 20.5 months vs. 15.0 months
  - PFS: 20.6 months vs. 14.7 months
- All-oral triplet therapy well tolerated

dex, dexamethasone; PFS, progression-free survival.

Moreau P, et al. *Blood*. 2015;126(23):727.

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Triplet Therapy: Ixazomib, Pomalidomide and Dexamethasone

- Phase I/II study comparing ixazomib plus pomalidomide and dex (triplet) with pomalidomide plus dex (doublet)
  - Patients had received ≥2 prior lines of therapy and were refractory to an IMiD and a proteasome inhibitor
- Phase I results
  - 13 patients completed >1 cycle of triplet therapy
  - Best ORR: 62% (7 PR, 1 VGPR)
- Next steps: comparing the triplet and doublet treatments

dex, dexamethasone; IMiD, immunomodulatory drug; ORR, overall response rate; PR, partial response, VGPR, very good partial response.

Voorhees PM, et al. *Blood*. 2015;126(23):375.

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Marizomib, Pomalidomide, and Dexamethasone

- Study in heavily pretreated patients
  - Including patients with high-risk genetics and refractory to prior carfilzomib treatment
- Highly active triplet
  - Partial responses: 64%
  - Partial + minimal responses: 79%
- Manageable toxicities

Spencer A, et al. *Blood*. 2015; 126(23):4220.

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Oprozomib, Pomalidomide, and Dexamethasone

- Study in heavily treated patients
  - Patients had ≥2 prior treatment cycles with bortezomib and either lenalidomide or thalidomide
  - Best treatment schedule: oprozomib 210 mg twice weekly (2/7)
- Early data
  - Confirmed responses: 86%
  - Duration of response: 29-287 days
- Well tolerated

Shah JJ, et al. *Blood*. 2015; 126(23):378.

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HDAC Inhibitors

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HDAC Inhibitors

Drug	Description
Farydak® (panobinostat)	• Oral non-selective HDAC inhibitor • Approved in combination with bortezomib and dexamethasone (2015)
Ricolinostat	• Oral selective HDAC6 inhibitor • Currently in clinical trials
ACY-241	• Oral selective HDAC6 inhibitor • Currently in clinical trials

HDAC, histone deacetylase inhibitor.

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Panobinostat Combinations

Ongoing Studies in Relapsed/Refractory Disease

- Panobinostat, lenalidomide, bortezomib dexamethasone
- Panobinostat, lenalidomide, dexamethasone
- Panobinostat, thalidomide, bortezomib, dexamethasone-panobinostat maintenance
- Panobinostat, carfilzomib
- Panobinostat, ixazomib, dexamethasone
- Panobinostat, everolimus

Laubach JP, et al. *Clin Cancer Res*. 2015;21(21):4767-4773.

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Ricolinostat Triplet Regimens

- Ricolinostat, pomalidomide, dexamethasone
  - Median follow-up: 12 weeks
  - Overall response rate: 29%
- Ricolinostat, bortezomib, dexamethasone
  - Median follow-up: 3 months
  - Overall response rate: 39%
- Ricolinostat, lenalidomide, dexamethasone
  - Median follow-up: 6 months
  - Overall response rate: 55%

1. Raje N, et al. *Blood*. 2015; 126(23):4228. 2. Vogl N, et al. *Blood*. 2015; 126(23):1827.
3. Yee A, et al. *Blood*. 2015; 126(23):3055.

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ACY-241

- Phase I trial ACY-241 alone followed by triplet therapy with ACY-241 plus pomalidomide and dexamethasone
  - Patients had ≥2 prior treatment cycles of lenalidomide and a PI
- Very early data after 1-3 cycles of treatment
  - ACY-241 monotherapy and combination therapy well tolerated
  - Evidence of anti-tumor activity

Niesvizky R, et al. *Blood*. 2015;126(23):3040.

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Antibody Therapies

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Antibody Therapy

Drug	Target	Description
Darzalex™ (daratumumab)	CD38	• IV infusion • Approved as a single agent in relapsed/refractory multiple myeloma
Empliciti™ (elotuzumab)	SLAMF7	• IV infusion • Approved in combination with Revlimid and dexamethasone
Keytruda® (pembrolizumab)	PD-1	• Approved to treat melanoma and metastatic non-small cell lung cancer • NOT APPROVED in multiple myeloma
Isatuximab (SAR650984)	CD38	

IV, intravenous.

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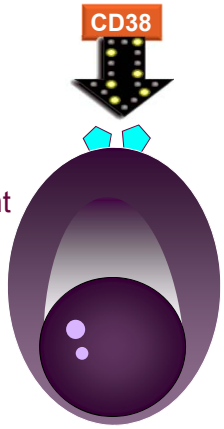
Daratumumab

- Darzalex (daratumumab) is a monoclonal antibody that targets CD38
- Current approved use for daratumumab:
  - Patients who have had ≥3 lines of treatment
  - Patients who are refractory to a PI and an IMiD
  - Approved for use as a single agent



IMiD, immunomodulatory drug; PI, proteasome inhibitor.

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Daratumumab Monotherapy in Heavily Treated Patients

- Study of daratumumab monotherapy
  - Combined analysis of GEN501 and SIRIUS trials
  - GEM501: ≥2 lines of treatment
  - SIRIUS: ≥3 lines or refractory to both PI and IMiD
- Early data (median follow-up: 14.8 months)
  - Overall response rate: 31%
  - Median duration of response: 7.6 months
  - Overall survival: 19.9 months

IMiD, immunomodulatory drug, PI, proteasome inhibitor.
Usmani S, et al. *Blood*. 2015; 126(23):29.
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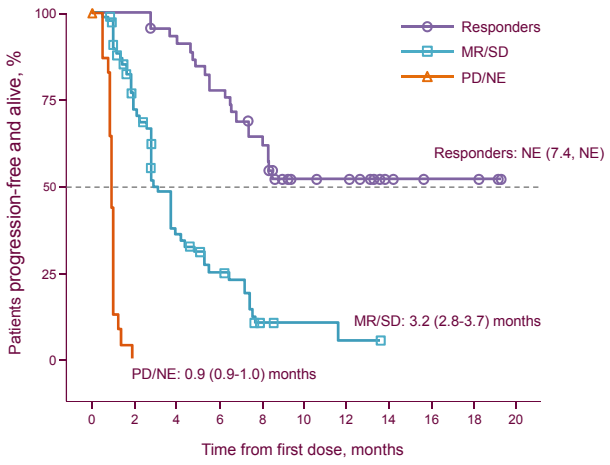
Daratumumab Monotherapy in Heavily Treated Patients

Progression-Free Survival



MR, minimal response; NE, not evaluable; PD, progressive disease; SD, stable disease.
Usmani S, et al. *Blood*. 2015; 126(23):29.
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Triplet Therapy: Daratumumab, Pomalidomide, Dexamethasone

- Phase I study in relapsed/refractory MM
  - Patients had ≥2 prior therapies, including ≥2 cycles bortezomib or lenalidomide but no prior pomalidomide
- Triplet shows promising activity
  - Overall response rate: 71%
  - Response in double-refractory patients: 67%
- Well tolerated
  - Similar to pomalidomide and dexamethasone doublet
- Next steps: Phase III trial

MM, multiple myeloma.
Chari A, et al. *Blood*. 2015; 126(23):508.

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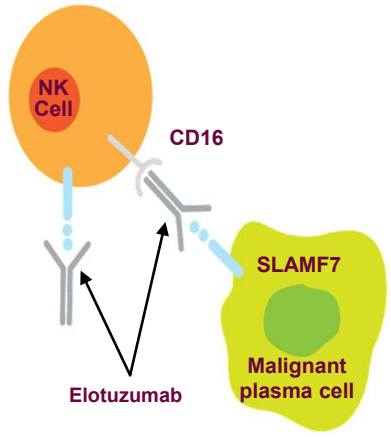
Elotuzumab

- Empliciti (elotuzumab) is a monoclonal antibody that recognizes a protein (SLAMF7) that myeloma and natural killer (NK) cells produce
- Approved as combination therapy (ELd, elotuzumab, Revlimid (lenalidomide), dexamethasone) in patients who have received 1-3 prior therapies



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

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ELOQUENT-2 Update

- The ELOQUENT-2 trial compared the effectiveness of elotuzumab, lenalidomide, and dexamethasone (ELd) with lenalidomide and dexamethasone (Ld) in patients with relapsed, refractory multiple myeloma
  - 3-year follow-up data were presented at ASH 2015
- Patients receiving ELd had a 30% reduction in the risk of disease progression or death compared with those treated with Ld

ELd: elotuzumab plus lenalidomide/dexamethasone; Ld: lenalidomide/dexamethasone.

1. Lonial S, et al. *New Engl J Med*. 2015;373:621-631. 2. Dimopoulos MA, et al. *Blood*. 2015;126(23):28.

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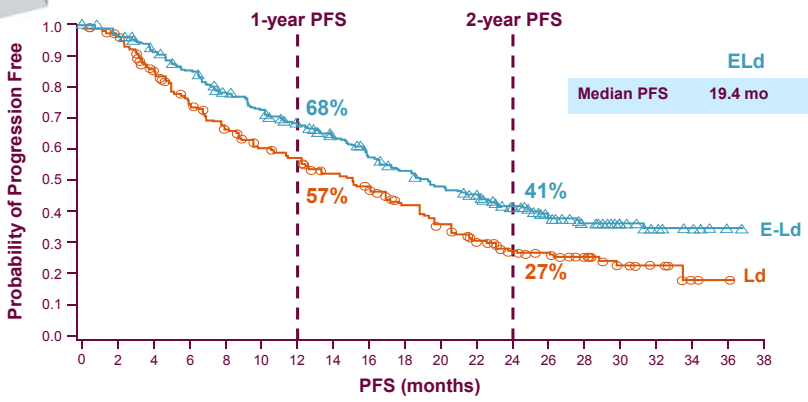
ELOQUENT-2 Update: Progression-Free Survival



	ELd	Ld
Median PFS	19.4 mo	14.9 mo

ELd–treated patients had a 30% reduction in the risk of disease progression or death vs Ld; treatment difference at 1 and 2 years was 11% and 14%, respectively

ELd: elotuzumab plus lenalidomide/dexamethasone; Ld: lenalidomide/dexamethasone.

1. Lonial S, et al. *New Engl J Med*. 2015;373:621-631. 2. Dimopoulos MA, et al. *Blood*. 2015;126(23):28.

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Immunomodulatory Drugs

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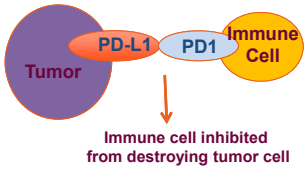
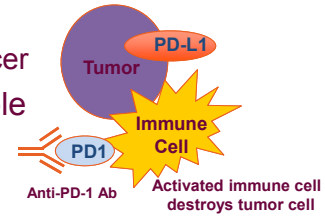
Pembrolizumab

- Keytruda (pembrolizumab) is a monoclonal antibody that targets the programmed cell death 1 (PD-1) receptor
- Approved uses for pembrolizumab:
  - Advanced melanoma
  - Metastatic non-small cell lung cancer
- Currently in clinical trials for multiple myeloma





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Triplet Therapy: Pembrolizumab, Lenalidomide, Dexamethasone

- Phase I study of pembrolizumab, lenalidomide, and dexamethasone in heavily treated R/R MM
  - Patients had ≥2 prior treatments including a PI and IMiD
- Early data (median follow-up: 9.5 months)
  - Overall response rate: 76%
  - Response in lenalidomide-refractory patients: 56%
  - Median duration of response: 9.7 months
- Combination well tolerated
  - Safety consistent with individual drug profiles

MM, multiple myeloma; IMiD, immunomodulatory drug; PI, proteasome inhibitor; R/R, relapsed/refractory.

San Miguel J, et al. *Blood*. 2015; 126(23):505.

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Triplet Therapy: Pembrolizumab, Pomalidomide, Dexamethasone

- Phase II study of pembrolizumab, pomalidomide, and dexamethasone in R/R MM
  - Patients had ≥2 prior treatments including a PI and IMiD
- Early data (median follow-up: 9.5 months)
  - Overall response rate: 60%
  - Response in double-refractory patients: 55%
  - Median time to best response: 2 months
- Manageable safety profile

MM, multiple myeloma; IMiD, immunomodulatory drug; PI, proteasome inhibitor; R/R, relapsed/refractory.

Badros AZ, et al. *Blood*. 2015; 126(23):506.

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Other Antibodies

Antibody	Target
SAR650984	CD38
B-B4, nBTO62, DL101	CD138
Lucatumumab	CD40
IPH-2101	KIR
Atezolizumab	PDL-1

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Immunomodulatory Drugs (IMiDs)

Drug	Description
Thalomid® (thalidomide)	• Oral medication • Given alone or with dexamethasone
Revlimid® (lenalidomide)	• Oral medication • Approved in combination with dexamethasone
Pomalyst® (pomalidomide)	• Oral medication • Approved in combination with dexamethasone

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Immunomodulatory Drugs (IMiDs)

- IMiDs work against cancer cells partly by impacting the functioning of the immune system
- As a result, IMiDs:
  - Directly effect tumor cells
  - Also effect blood vessels and other substances around the tumor (called the tumor microenvironment)
- Considered the "backbone" of many treatment combinations in multiple myeloma

Immunomodulatory Drugs (IMiDs)

Today, you've heard about:

PI combinations
- Ixazomib, lenalidomide, dex
- Ixazomib, pomalidomide, dex
- Marizomib, pomalidomide, dex
- Oprozomib, pomalidomide, dex

HDAC inhibitor combinations
- Panobinostat/IMiD combinations
- Ricolinostat, pomalidomide, dex
- Ricolinostat, lenalidomide, dex
- ACY-241, pomalidomide, dex

Antibody combinations
- Daratumumab, pomalidomide, dex
- Elotuzumab, lenalidomide, dex
- Pembrolizumab, lenalidomide, dex
- Pembrolizumab, pomalidomide, dex

dex, dexamethasone,; IMiD, immunomodulatory drug, HDAC, histone deacetylase inhibitor; PI, proteasome inhibitor.

1. Moreau P, et al. *Blood*. 2015;126(23):727. 2. Voorhees PM, et al. *Blood*. 2015;126(23):375. 3. Spencer A, et al. *Blood*. 2015; 126(23):4220. 4. Shah JJ, et al. *Blood*. 2015; 126(23):378. 5. Laubach JP, et al. Clin Cancer Res. 2015;21(21):4767-4773. 6. Raje N, et al. *Blood*. 2015; 126(23): 4228. 7. Yee A, et al. *Blood*. 2015; 126(23): 3055. 8. Niesvizky R, et al. *Blood*. 2015;126(23):3040. 9. Chari A et al. *Blood*. 2015; 126(23):508. 10. Dimopoulos MA, et al. *Blood*. 2015;126(23):28. 11. San Miguel J, et al. *Blood*. 2015; 126(23):505. 12. Badros AZ, et al. *Blood*. 2015; 126(23):506.

Other Novel Therapies

Drug Class	Agents
• BTK inhibitors	• Ibrutinib, AVL-292
• CDK inhibitors	• PD0332991, SCH727965, AT7519
• BCL antagonist	• ABT263
• HSP90 inhibitors	• Ganetespib (STA-9090)
• SINE XPO1 antagonists	• Selinexor (KPT-330)
• FGFR3 inhibitor/antibodies	• TKI258, MFGR1877S
• Mutant B-Raf inhibitor	• Vemurafenib

BCL, B-cell lymphoma/leukemia; BTK, Bruton's tyrosine kinase; CDK, cyclin-dependent kinase; FGFR3, fibroblast growth factor receptor 3; HSP90, heat-shock protein 90.

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Question & Answer

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Closing Remarks

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To learn more about the MMRF, please visit:
www.multiplemyeloma.org

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