High-Risk Disease

August 25, 2023

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Tech Support

1-719-234-7952

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Resources

- Resource tab includes
  - Speaker bios
  - Copy of the slide presentation
  - Exhibit Hall

Submit your questions throughout the program!

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MMRF Research Initiatives

1. MMRF Myeloma Accelerator Challenge (MAC) Grants
   - Broad, multi-institutional research grants designed to advance clinical trial concepts in the areas of
     - High-risk newly diagnosed multiple myeloma (NDMM)
     - High-risk smoldering myeloma (SMM)
   - Each research network will be funded up to $10M over 3 years
2. MMRF Horizon Adaptive Platform Trials
   - Paired with MAC grants
   - Done in collaboration with 13 MMRC sites
   - Trials in relapsed/refractory myeloma, high-risk NDMM, high-risk SMM

For more information, visit themmrf.org

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Speakers

Melissa Alsina, MD
H. Lee Moffitt Cancer Center
Tampa, Florida

Craig Hofmeister, MD, MPH
Winship Cancer Institute of Emory University
Atlanta, Georgia

Nicholas Lenoir
Patient
Spring Hill, Florida

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What Is High-Risk Multiple Myeloma?

Craig Hofmeister, MD, MPH
Winship Cancer Institute of Emory University
Atlanta, Georgia

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The Meaning of *Risk* Depends on the Context

What the doctor says	What is meant by the word *risk*
"You have high-**risk** monoclonal gammopathy of undetermined significance; please come back in 3 months for a blood test."	**Risk** means the odds of developing multiple myeloma.
"Because of your **high**-risk **disease**, we will always need to treat you with 3- or even 4-drug cocktails."	High-**risk** means less likely to respond to drugs and for a shorter time is more treatment resistant. Low **risk** is easier to treat and patients on average live longer.
"Your only lytic **lesion** is in your skull, so your myeloma bone disease is low **risk**."	If you only have a few bones known to be affected by myeloma, and they are not weight-bearing, you have a lower **risk** for fracture.

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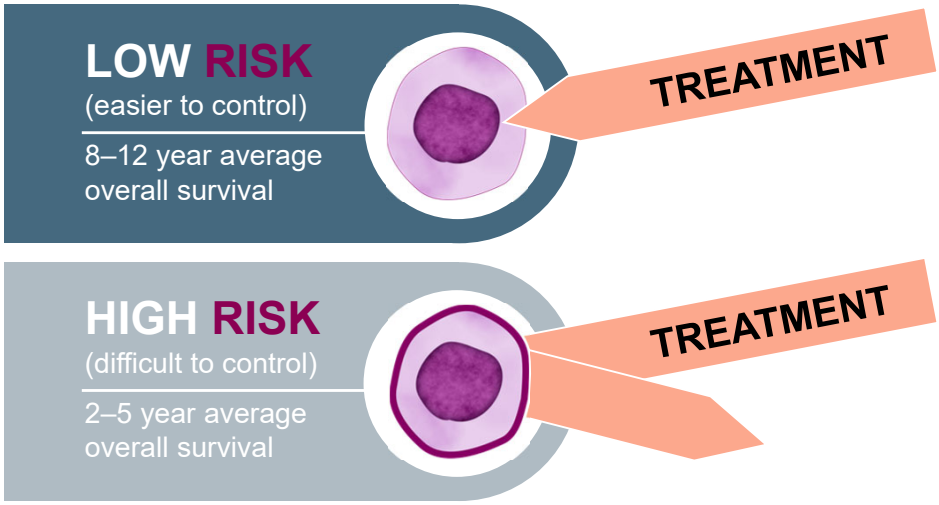
Risk in the Setting of Multiple Myeloma Describes How Quickly the Disease Will Become Resistant to Treatment



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Know the Risk *of Your Multiple Myeloma*

Introducing the SECOND Staging System: the International Staging System (ISS)

Stage	Criteria	Survival (yrs) when published
1	ß2M <3.5 mg/L and serum albumin ≥3.5 g/dL	5
2	Not stage I or III	3.5
3	ß2M ≥5.5 mg/L	2

ß2M, beta-2 microglobulin. It and albumin are both standard blood tests.

Greipp PR et al. *J Clin Oncol*. 2005;23:3412.

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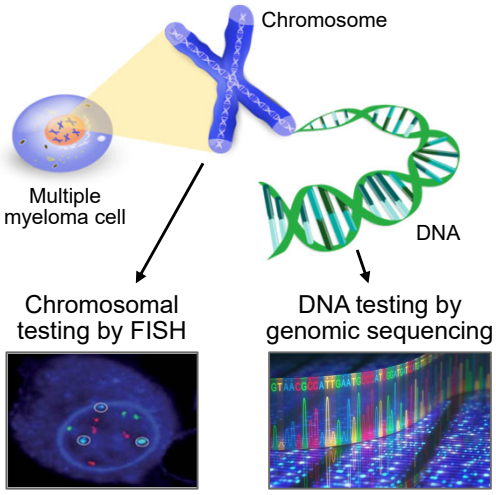
The DNA in the Patient's Myeloma Cells Is the Other Half of the Story of "What Kind of Myeloma"

- Genetic changes in myeloma cells may affect prognosis and treatment selection
- Using samples from the bone marrow: specific tests look at these genetic changes
- Some tests are used routinely and look at the ***chromosomal*** changes (FISH)
- Newer tests assess changes in the ***DNA*** (gene expression profiling and next-generation sequencing)
- All patients in the MMRF CoMMpass study had **genomic sequencing** from diagnosis to relapse



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Know the Risk *of Your Multiple Myeloma*

Introducing the THIRD Staging System: the Revised International Staging System (R-ISS)

Stage	Criteria	Genetics	Survival (yrs)
 1	ß2M <3.5 mg/L and serum albumin ≥ 3.5 g/dL	No del(17p) Normal LDH No t(4;14) No t(14;16)	**8–12**
2	Not stage 1 or 3		**7**
 **3**	ß2M ≥5.5 mg/L	t(4;14) or t(14;16) or del(17p) or High LDH	**2–5**

ß2M, beta-2 microglobulin. It and albumin are both standard blood tests.

Palumbo A et al. *J Clin Oncol.* 2015;33:2863.

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Multiple Myeloma Prognosis and Risk

Many blood test and bone marrow biopsy test results can determine a patient's risk for myeloma that is aggressive (high risk) or not (standard risk) based on the R-ISS

Standard risk

- Serum β2M level <3.5 mg/L
- Serum albumin level ≥3.5 g/dL
- No high-risk chromosomal abnormality*
- Normal LDH level

All other possible combinations of the test results means that a patient is **R-ISS stage II**

High risk

- Serum β2M level ≥5.5 mg/L
- High-risk chromosomal abnormality* or high LDH level

*High-risk chromosomal abnormality by FISH: del(17p) and/or t(4;14) and/or t(14;16)

R-ISS, Revised International Staging System; β2M; beta-2 microglobulin; LDH, lactate dehydrogenase; FISH, fluorescence in situ hybridization

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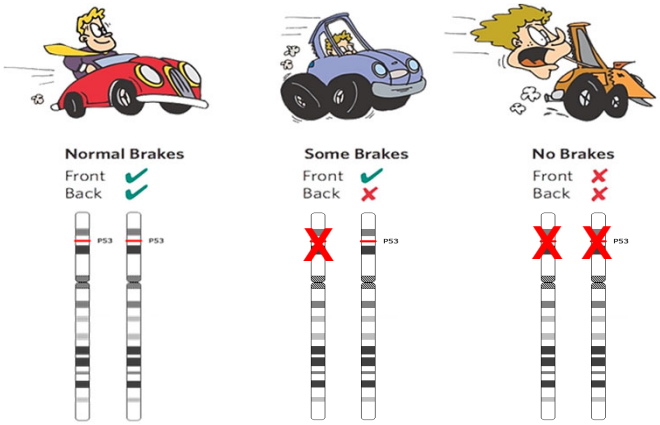
MMRF CoMMpass Findings: Identifying Double-Hit Multiple Myeloma

- Identification of high-risk disease is evolving from FISH testing to genetic mutation analysis
- CoMMpass has identified the ***highest-risk group***, known as double-hit multiple myeloma

<u>Key CoMMpass finding</u>:
FISH testing alone cannot identify whether patients have double-hit myeloma.

The concept of double-hit myeloma



Having no brakes is a bad thing but having half the brakes is okay.

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The Meaning of *Stage* Depends on the Context

When a patient with lung, colon, breast, or prostate cancer hears...	...that means
"You have early **stage** cancer."	You likely have **stage** 1 or 2 cancer, it is isolated to a small part of the affected organ, and there is a better than 50% chance of cure.
"Your cancer is metastatic."	Your cancer is spread throughout your body, and curative surgery is not an option. We found this cancer late in its course after it spread. Your survival is shorter than if we had found this cancer significantly earlier.

In most cancers, ***stage*** is a synonym for ***control***.

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The Meaning of Stage Depends on the Context 😟

When I say ***stage*** to a myeloma patient	What does that mean
"We expect you to have easier-to-treat myeloma."	You have stage 1 myeloma
"As with 60% of my myeloma patients, I don't know whether you have easier- or harder-to-treat myeloma."	You have stage 2 myeloma
"We expect you to have harder-to-treat myeloma."	You have stage 3 myeloma.

In myeloma, ***stage*** is a synonym for ***risk***.

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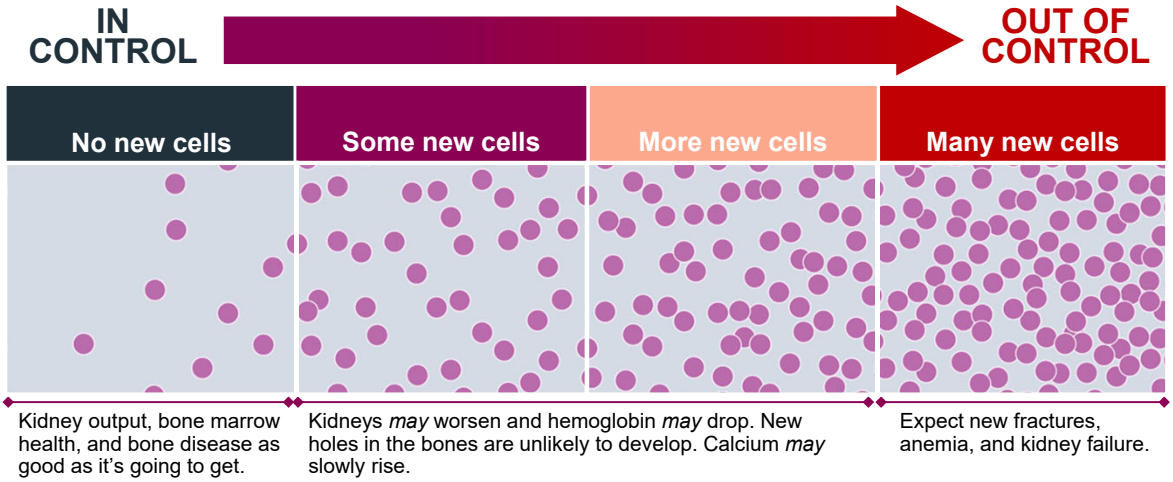
How are *stage* and *risk* different from control?



And control is usually measured by monoclonal protein and light chains

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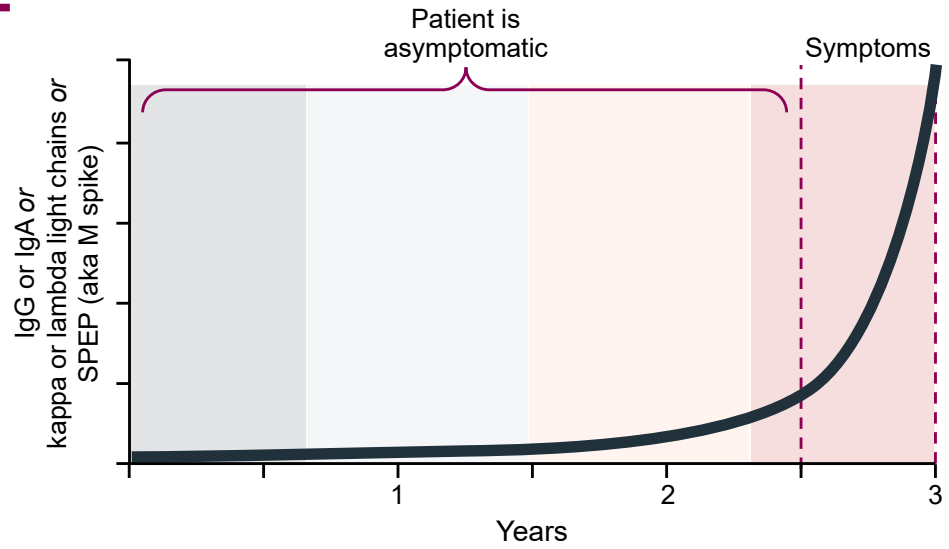
Can we enumerate *control*? Yes! Numbers rule.



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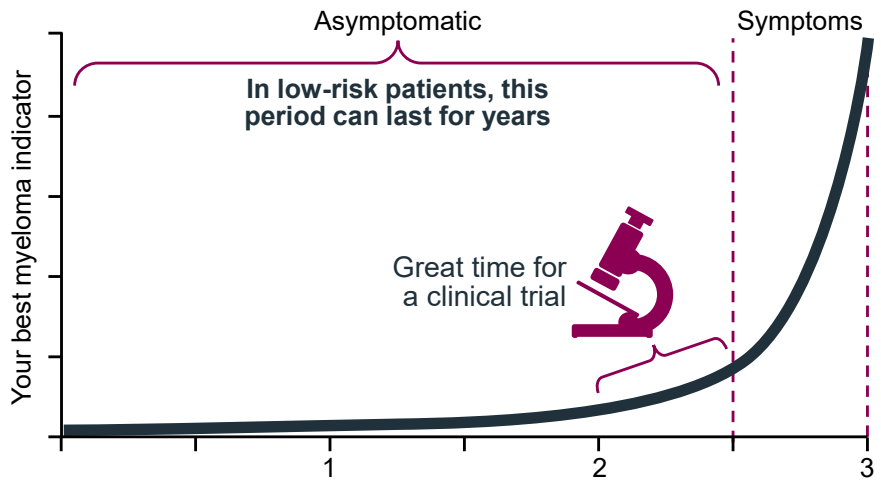
Do you relapse differently if you are low risk?



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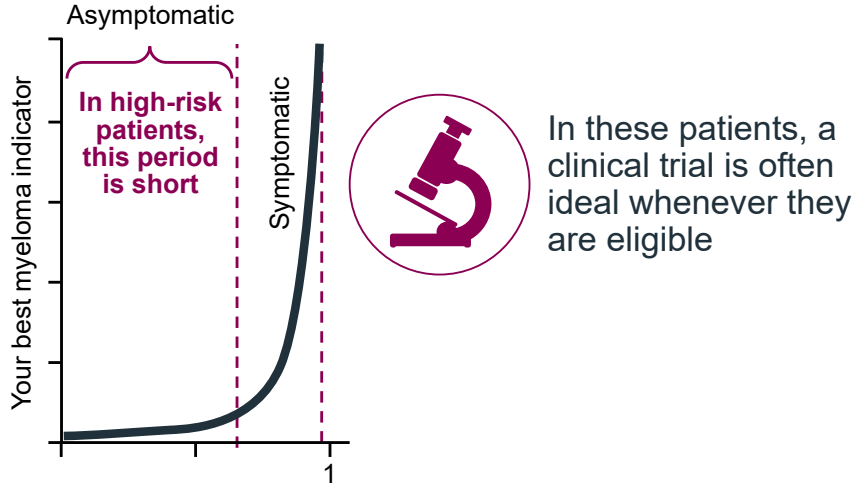
Do you relapse differently if you are high risk?



In these patients, a clinical trial is often ideal whenever they are eligible

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Despite recent improvements in treatment, high-risk patients have not experienced the same benefit as patients with standard risk.

Therefore, the treatment of high-risk patients is a very important focus of research.

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How Do We Treat High-Risk Multiple Myeloma?

Melissa Alsina, MD
H. Lee Moffitt Cancer Center
Tampa, Florida

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Approach to Treatment: Risk-Adapted Therapy

Risk-adapted therapy
Aims to treat patients with the therapy that will work best for them while decreasing the side effects from treatment

Patients with **standard-risk** myeloma are given best proven effective treatment to control their myeloma and **achieve deepest response possible**.

Patients with **high-risk** myeloma are given a best proven effective treatment against their specific form of myeloma. Usually stronger combinations, longer duration. **Achieving deep response is critical.**

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Summary of High-Risk Subsets in Contemporary Newly Diagnosed Multiple Myeloma Trials

Study	Treatment arms	Total number of patients	*High risk* definition	Number of high-risk myeloma patients
SWOG-1211[1]	RVd vs RVd-Empliciti	100	GEP^{hi}, del17p, t(14;16), t(14;20), Amp1q21, elevated LDH, pPCL	RVd = 52 RVd-Elo = 48
SWOG-0777[2]	RVd vs Rd	525	del17p, t(14;16), or t(4;14)	Combined n=44
MAIA[3]	DRd vs Rd	737	del17p, t(14;16), or t(4;14)	DRd = 48 Rd = 44
ALCYONE[4]	D-VMP vs VMP	706	del17p, t(14;16), or t(4;14)	D-VMP = 53 VMP = 45
CASSIOPEIA[5]	Darzalex-VTd vs VTd	1,085	del17p or t(4;14)	Dara-VTd = 82 VTd = 86
STAMINA[6]	Tandem transplant vs ASCT/RVD vs ASCT	758	ISS 3, del13, del 17p, t(4;14), t(14;16), t(14;20)	Tandem = 72 ASCT/RVD = 76 ASCT = 75

The high-risk myeloma definition is not uniform across the contemporary randomized phase 3 trials and accounts for a small subset of study populations.

1. Usmani SZ et al. *Lancet Haematol*. 2021. **2.** Durie B et al. *Lancet*. 2017. **3.** Facon T et al. *N Engl J Med*. 2018. **4.** Mateos MV et al. *N Engl J Med*. 2018. **5.** Moreau P et al. *Lancet*. 2019. **6.** Staudtmaeur E et al. *J Clin Oncol*. 2018.

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Darzalex Meta-Analysis in High-Risk Multiple Myeloma

Six phase 3 trials comparing standard treatment regimens with or without Darzalex in newly diagnosed[1-3] or relapsed/refractory[4-6] myeloma patients with high-risk cytogenetics

High risk defined as the presence of t(4;14), t(14;16), or del(17p).

Addition of Darzalex to backbone regimens improved PFS of patients with high-risk cytogenetic features in both frontline and relapsed settings.

PFS benefit for high-risk patients was greater in relapsed setting compared to frontline.

PFS benefit for standard-risk patients was similar in both relapsed and frontline settings.

Results were similar regardless of backbone regimens.

Giri S et al. *JAMA Oncol*. 2020;6:1.

1. MAIA Trial. Facon T et al. *N Engl J Med*. 2019;380:2104. **2.** CASSIOPEIA Trial. Moreau P et al. *Lancet*. 2019;394:29. **3.** ALCYONE Trial. Mateos MV et al. *Lancet*. 2020;395:132. **4.** POLLUX Trial. Dimopoulos MA et al. *N Engl J Med*. 2016;375:1319. **5.** CASTOR Trial. Palumbo A et al. *N Engl J Med*. 2016;375:754. **6.** CANDOR Trial. Usmani SZ et al. *Blood*. 2019;134. Abstract LBA-6.

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Treatment Regimens for High-Risk Disease Features

Kyprolis-Revlimid-dex (KRd) vs Revlimid-Velcade-dex (RVd) retrospective chart review[1]

- 154 high-risk* newly diagnosed myeloma patients treated with KRd or RVd
- Patients receiving KRd vs RVd had:
  - Greater depth of response
  - Significant improvement in PFS (especially those who received early ASCT)
- R-ISS stage II and III (compared to stage I) were significant predictors for progression or death
- More than 6 cycles of treatment was associated with longer PFS and OS

*High-risk cytogenetic abnormalities defined as 1q+ (gain or amp), t(4;14), t(14;16), t(14;20), and/or del(17p) or monosomy 17.

OPTIMUM Study[2]

- 107 ultra high-risk† patients with MM and plasma cell leukemia
- Patients received Darzalex-cyclophosphamide-Velcade-Revlimid-dex (Dara-CyVRd) induction followed by ASCT and 2 rounds of consolidation with Dara-VR (with or without dex)
  - 46.7% of patients were MRD negative (10^{-5});
  - 84% of patients who were MRD negative after ASCT sustained their MRD negativity at the end of second consolidation;
  - 86% of patients were alive;
  - 77% were progression free at 30 months

†≥2 high-risk lesions: t(4;14), t(14;16), t(14;20), gain(1q), del(1p), del(17p), or SKY92 risk signature.

1. Tan C et al. *Blood*. 2022;140. Abstract 752. **2.** Kaiser MF et al. *Blood*. 2022;140. Abstract 758.

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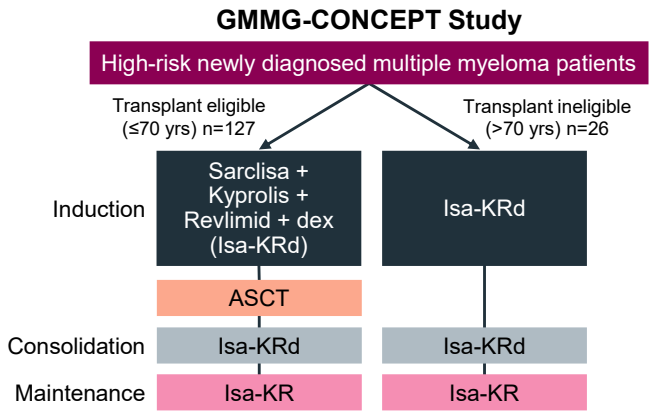
Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease



Total population cytogenetic abnormalities:
44% del(17p); 38.4% t(4;14); 15.2% t(14;16); 36% >3 copies of 1q21; 30.4% ≥2 high-risk cytogenetic abnormalities

Best response (through consolidation) (%)	Transplant eligible (n=99)	Transplant ineligible (n=26)
Overall response rate	**94.9**	**88.5**
sCR/CR	72.7	57.7
VGPR	18.2	30.8
PR	4.0	0
SD	0	0
MRD negative (1×10^{-5}) in evaluable patients	67.7	54.2

Adverse events (% grade ≥3)	Transplant eligible (n=97)	Transplant ineligible (n=25)
Hematologic		
Neutropenia	39.2	28
Leukopenia	24.7	4
Thrombocytopenia	26.8	16
Anemia	14.4	12
Non-hematologic		
Infection	27.8	28
Cardiac	2.1	20

Weisel KC et al. *Blood*. 2022;140. Abstract 759.

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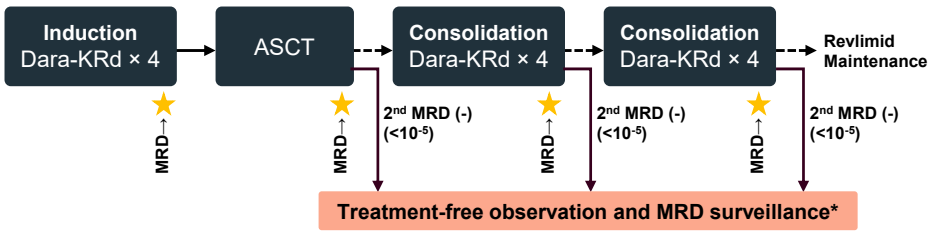
Phase 2 MASTER Trial of Dara-KRd With MRD Response-Adapted Therapy in NDMM

Eligibility
- NDMM
- ECOG PS ≥ 2
- Measurable paraprotein in serum or urine,
- Adequate organ function

Exclusion
- Prior/recent malignancy, CV event, cerebrovascular event, HIV, active hepatitis
- No upper age limit or hematologic parameters.
- ≤1 cycle of tx containing Velcade, cyclophosphamide, and dex were eligible

Study design contained enrichment for patients with **high-risk cytogenetic abnormalities**; patients w/ t(4;14); t(14;16); or del(17p) would account for ≥35% of participants.

Dara-KRd
- Darzalex 16 mg/m^2 days 1,8,15 C 3-6; day 1 C >6
- Kyprolis (20) 56 mg/m^2 Days 1,8,15
- Revlimid 25 mg Days 1-21
- Dexamethasone 40 mg PO Days 1,8,15,22



Primary end point: MRD negativity (10^{-5})

Patients with 2 consecutive MRD-negative assessments entered treatment-free MRD surveillance
Costa LJ, et al. *J Clin Oncol*. 2022;40:2901.

★ MRD assessment by NGS
*24 and 72 weeks after completion of therapy

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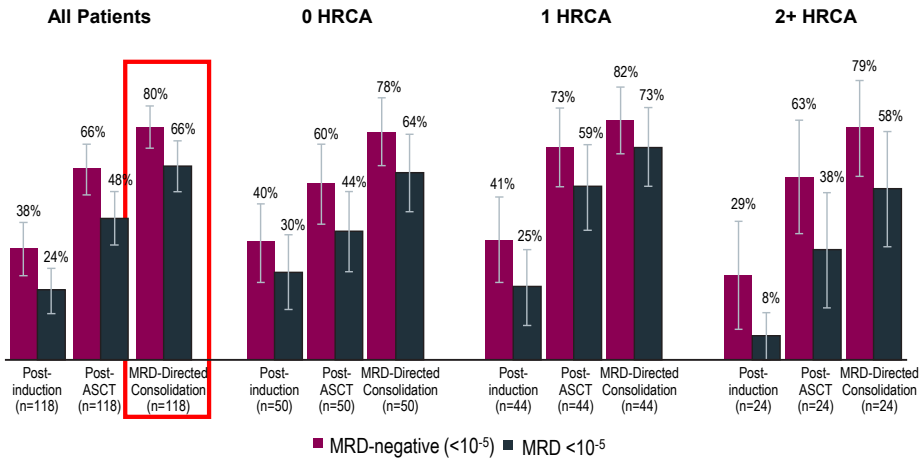
Phase 2 MASTER Trial of Dara-KRd With MRD Response-Adapted Therapy in NDMM: Results

- 80% of patients reached MRD negativity
- 71% reached two consecutive MRD-negative assessments during therapy, entering treatment-free surveillance
- Response ≥PR 98%
  - 86% ≥CR



HRCA, high-risk cytogenetic abnormalities.
Costa LJ, et al. *J Clin Oncol*. 2022;40:2901-2912.

Median follow-up, 25.1 mo

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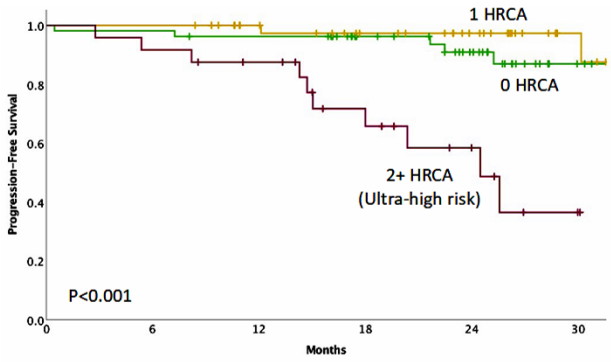
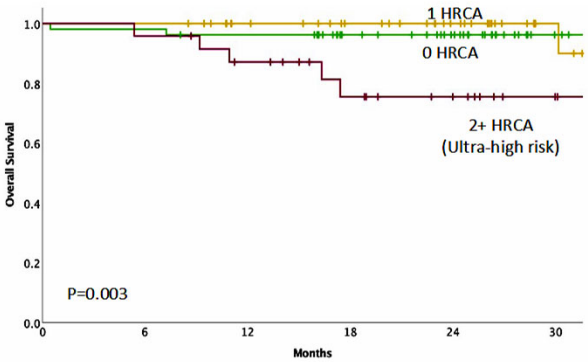
MASTER Trial: PFS and OS



2-year PFS	0 HRCA	91%
	1 HRCA	97%
	2+ HRCA	58%



2-year OS	0 HRCA	96%
	1 HRCA	100%
	2+ HRCA	76%

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)
Costa LJ, et al. *J Clin Oncol*. 2022;40:2901-2912.

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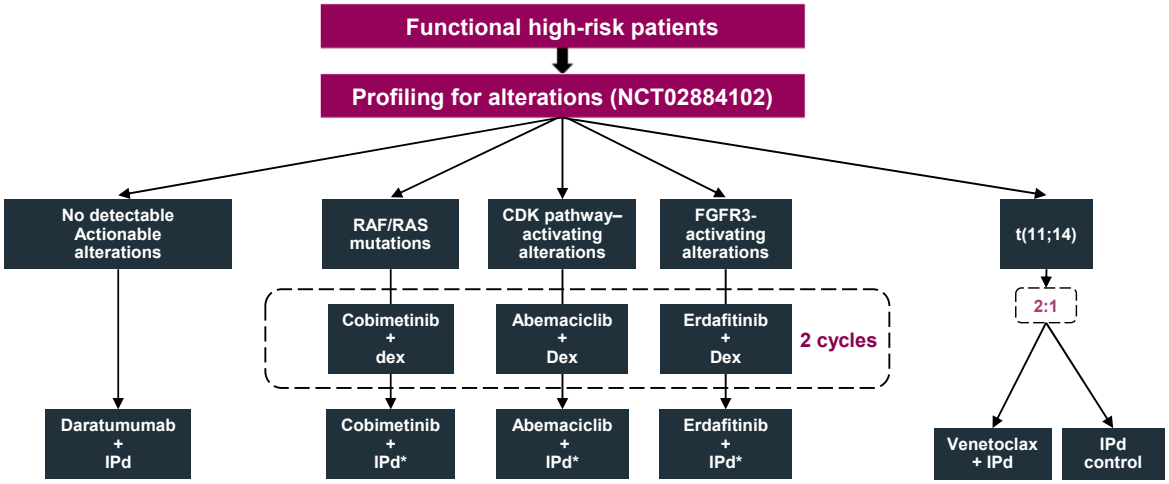
MyDRUG Study



**Assess single-agent activity after 2 cycles: after cycle 2, add backbone to single agent*

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Precision Medicine in Myeloma: MyDRUG (NCT03732703)

Case study: Man, age 59

Treatments

1st Line

- VRd/KRd induction, ASCT, Rev maintenance
- Best response: CR
- Progressed in 30 months (22 months post-ASCT/maint.)

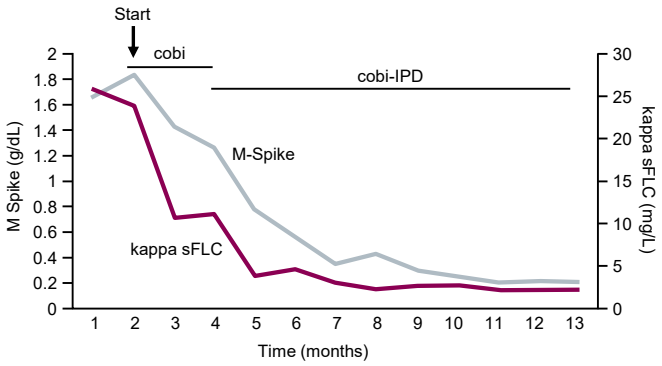
2nd Line

- EPd
- Best response: MR
- Progressed in 4 months

3rd Line

- MyDRUG

Response on MyDRUG



Genomics

- Hyperdiploid, del13q, del1p, Myc ampl.
- NRAS Q61H, 56% allelic fraction

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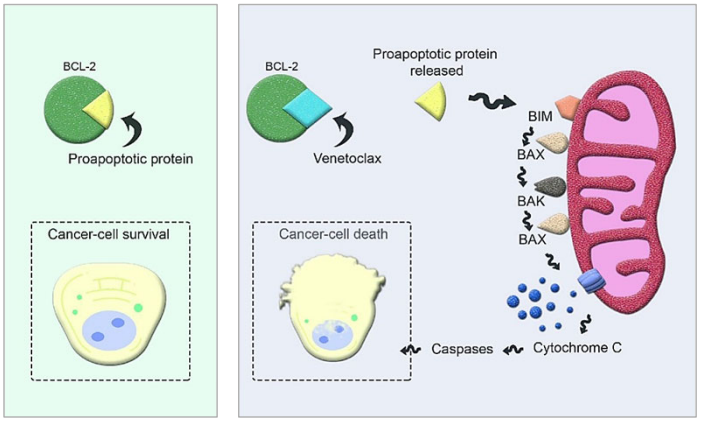
Venetoclax and t(11;14)

Venetoclax is a Bcl-2 inhibitor

- BCL2 inhibitor
- Induces cancer cell death
- t(11;14) multiple myeloma → ↑BCL2 and ↓MCL1
- t(11;14): first predictive marker in multiple myeloma, indicating susceptibility to BCL2 inhibition



Ehsan H et al. *J Hematol*. 2021;10:89.

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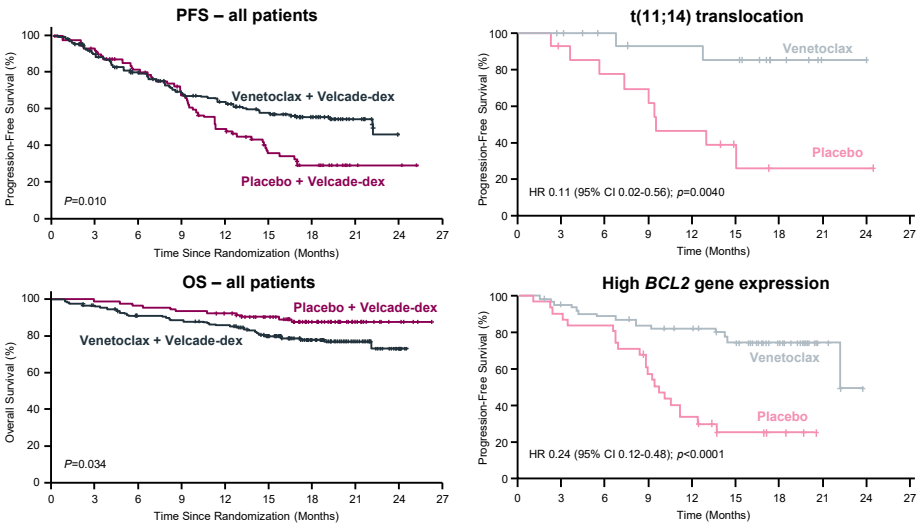
Venetoclax and t(11;14)

Venetoclax Velcade dex vs placebo Velcade dex;
1–3 prior lines

Median follow up 18.7 m mPFS
22.4 m venetoclax
11.5 m placebo

Venetoclax especially active in t(11;14) or *BCL2*^{high} MM



The BELLINI Trial. Kumar SK et al. *Lancet Oncol*. 2020;21:1630.

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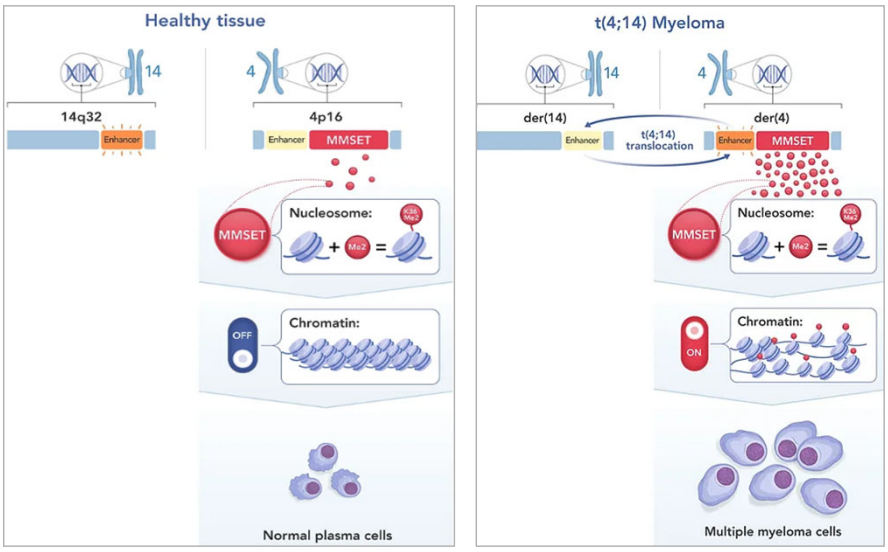
t(4;14) and MMSET

- About 15% of myeloma patients have t(4;14)
- t(4;14) → ↑MMSET
- ↑ MMSET → ↑ multiple myeloma cells



Farooki S et al. *Blood*. 2013;122. Abstract 5315.

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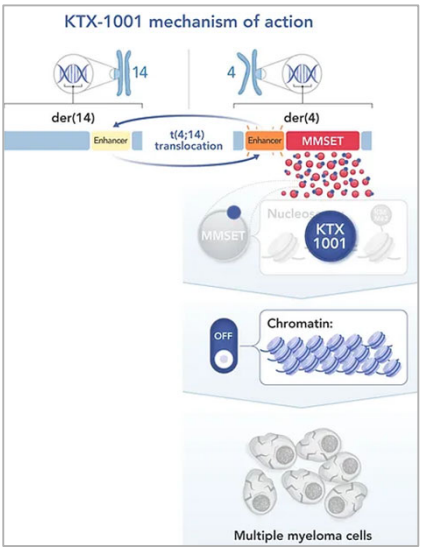
KTX-1001 and t(4;14)

- KTX-1001 inhibits MMSET, which reduces the methylation and turns off the expression of genes that multiple myeloma cells need to be cancerous
- KTX-1001 is a small molecule that is currently being evaluated in a phase 1 trial with patients with RRMM



clinicaltrials.gov/ct2/show/NCT05651932

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Additional Studies for High-Risk Myeloma

Moving the use of CAR T-cell therapy in earlier stage of disease

Study	Agent	Phase	Patient populations/ study design	*High risk* definition
KarMMa-4	Abecma	1	High-risk, newly diagnosed MM	R-ISS III
BMT-CTN 1901	Abecma	2	High-risk, newly diagnosed MM	R-ISS III; no prior progression
CARTITUDE-2	Carvykti	2	High-risk, newly diagnosed MM	R-ISS III

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Key Points

- High-risk disease is identified by the presence of patient- and disease-based factors such as frailty, extramedullary disease, cytogenetic abnormalities, or even relapses occurring earlier than expected according to the baseline factors.
- High-risk patients may not respond well to standard treatment and typically have poor outcomes.
- Proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies are the pillars of treatment.
- Goal of therapy should be to achieve deepest response possible (eg. MRD negative complete response).
- Personalized medicine approaches need to address high-risk patients.

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Patient Experience

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Questions & Answers

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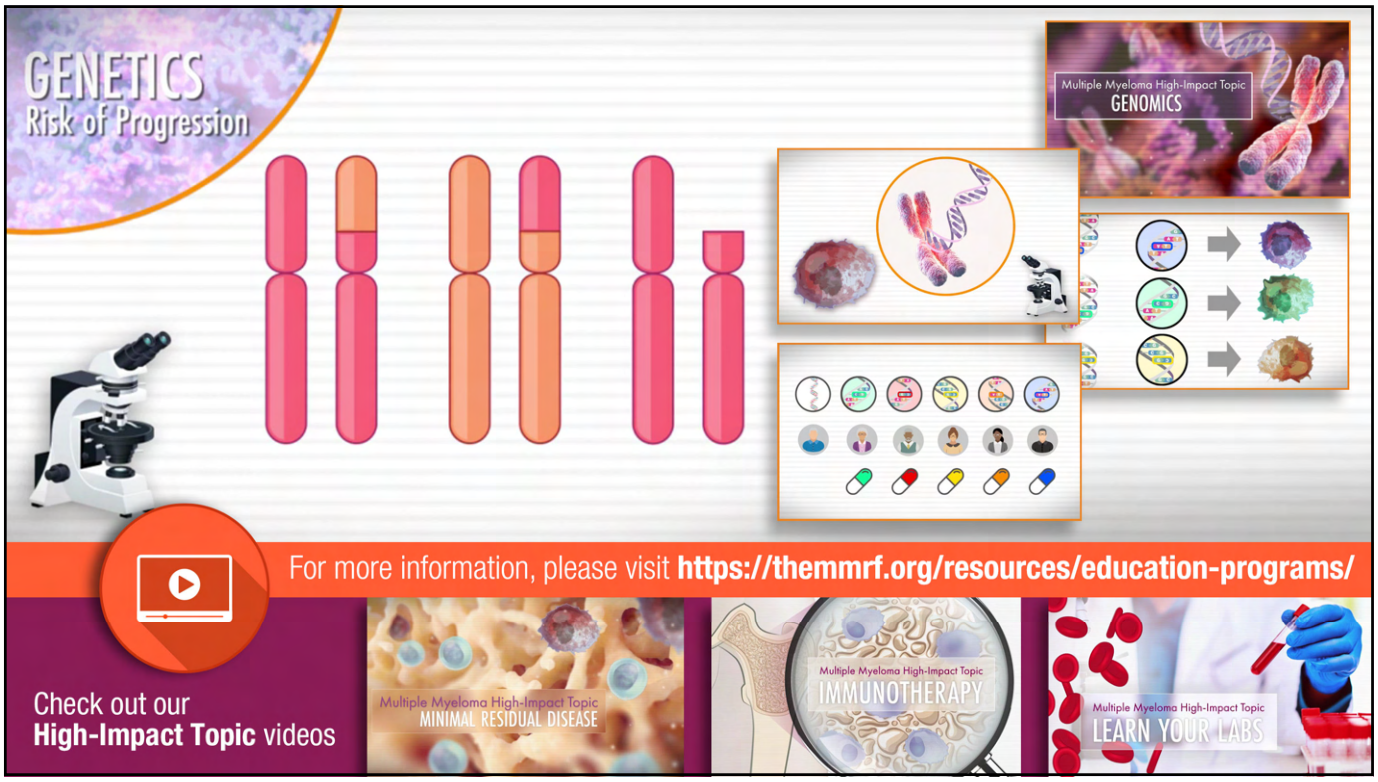

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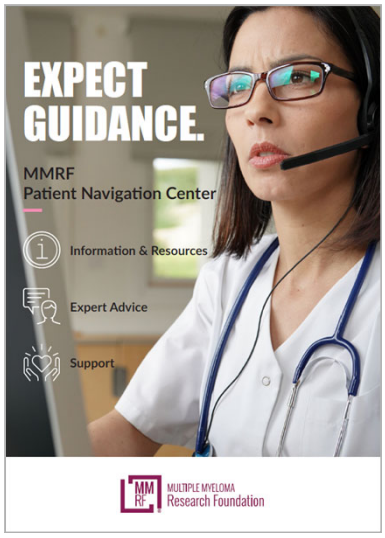
MMRF Patient Resources



MMRF Patient Navigation Center

You and your care team will have many decisions to make along your treatment journey. The Patient Navigation Center is a space for multiple myeloma patients and their caregivers to connect with patient navigators — who are professionals specializing in oncology — for guidance, information, and support. You can connect with a patient navigator via phone, or email. Whatever questions you may have, our patient navigators are here to help.

MMRF Patient Navigators include:
- Grace Allison, RN, BSN, OCN, RN-BC
- Brittany Hartmann, RN-BSN
- Erin Mensching, RN-BSN, OCN

THE RIGHT TRACK

Get on the right track for you

The MMRF's Right Track program puts you on the path to the best results for you.

Right Team
Access experts and centers that have extensive experience treating multiple myeloma.

Right Tests
Get the information, tests, and precise diagnoses to make the right treatment decisions.

Right Treatment
Work with your team to consider the best treatment plan and identify clinical trials that are right for you.

Contact the Patient Navigation Center Today

Looking for guidance? We're here to help.

Monday – Friday | 9:00AM – 7:00PM ET

Phone: 1-888-841-MMRF (6673) Online: TheMMRF.org/PatientNavigationCenter

Email: patientnavigator@themmrf.org

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Myeloma Mentors®

Myeloma Mentors® allows patients and caregivers the opportunity to connect with trained mentors. This is a phone-based program offering an opportunity for a patient and/or caregiver to connect one-on-one with a trained patient and/or caregiver mentor to share his or her patient journeys and experiences.

No matter what your disease state—smoldering, newly diagnosed, or relapsed/refractory—our mentors have insights and information that can be beneficial to both patients and their caregivers.

Contact the Patient Navigation Center at 888-841-6673
to be connected to a Myeloma Mentor or to learn more.

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To **Learn More** & **Find Your Event today**!
theMMRF.org/Events

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Upcoming Patient Education Events
Save the Date

Program	Date and Time	Speakers
High-Risk Disease FAQs *Livestream*	Wednesday, September 13 2:00 PM – 3:00 PM (ET)	Jonathan Kaufman, MD
Patient Summit *Boston, MA*	Saturday, November 11 9:00 AM – 2:00 PM (ET)	Paul Richardson, MD
Patient Summit *Virtual*	Saturday, January 13, 2024 12:00 PM – 5:00 PM (ET) 9:00 AM – 2:00 PM (PT)	Ajai Chari, MD Tom Martin, MD Sagar Lonial, MD

For more information or to register,
visit **themmrf.org/resources/education-program**

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Adaptive biotechnologies
Advancing MRD measurement. Empowering patient care.

Baxter

Bristol Myers Squibb

cure curetoday.com

GSK

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Karyopharm Therapeutics

REGENERON
SCIENCE TO MEDICINE

sanofi

Takeda ONCOLOGY

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Resources

- Resource tab includes
  - Exhibit Hall
  - Speaker bios
  - Copy of the slide presentation

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Need help with travel to a clinical study?

- The MMRF has partnered with the Lazarex Cancer Foundation to help provide more equitable access to clinical studies for multiple myeloma patients
- This partnership is one facet of the MMRF's commitment to improve diversity and representation in myeloma clinical studies
- MMRF has provided $100,000 over 2 years to Lazarex to fund travel, lodging, and food for patients (and a travel companion) so that they can participate in clinical studies that are appropriate for them
- Patients are funded according to income guidelines and will be reimbursed for allowed expenses
- For more information on this program and to be connected with Lazarex, call our Patient Navigation Center at 1-888-841-6673

It's About Living
Lazarex
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MULTIPLE MYELOMA Research Foundation | 25th ANNIVERSARY

Thank you!

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