MULTIPLE MYELOMA Research Foundation

Multiple Myeloma Highlights From the 2022 American Society of Hematology (ASH) Annual Meeting

December 20, 2022

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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!

MM RF

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The Work of the MMRF

The MMRF does three things in relentless pursuit of its mission to accelerate a cure for each and every myeloma patient.

1

We accelerate new treatments

Bringing next-generation therapies to patients faster

2

We drive precision medicine

Using data to deliver better answers and more precise treatments for patients

3

We empower patients

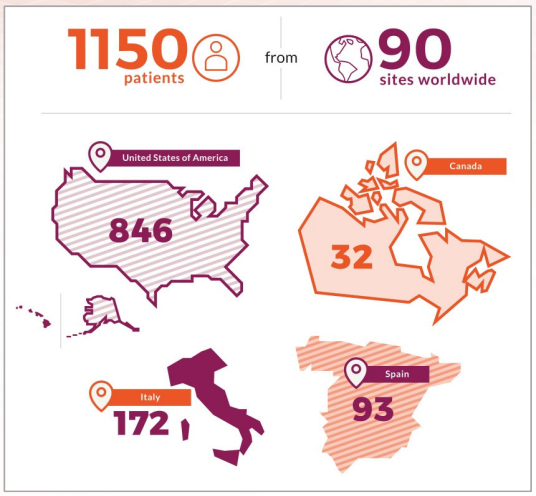
Putting them on The Right Track and guiding them to the right team, tests, and treatments to extend their lives

5

MMRF CoMMpass Study: Advancing Personalized Medicine Research

- Landmark study focusing on the genomics of myeloma
- Goals
  - Learn which patients respond best to which therapies
  - Identify new targets and new hypotheses
- Newly diagnosed patients will be followed for at least 8 years

All participants undergo a type of detailed genetic testing called *genomic sequencing.*



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CoMMpass Is a Trial of Discovery

- CoMMpass data has
  - Provided the myeloma community with information on
    - Frequency of genetic abnormalities
    - How genetic abnormalities play a role in myeloma
      - Drive multiple myeloma cell growth and survival
      - Contribute to drug resistance
      - May predict which patients respond to which therapy
    - Genetic abnormalities that help refine risk assessment
  - Led to conception of the MyDRUG trial

All patients in CoMMpass had genomic sequencing from diagnosis to relapse. The resulting data provides detailed genetic profiles for every myeloma patient at every stage of their disease!

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The MMRF CureCloud®: a 5,000-patient research study

MMRF CureCloud®

Together, we can make a difference for every patient with multiple myeloma.

We are making progress in the fight against myeloma because of contributions from patients like you.
People with multiple myeloma are living longer than ever before — but there's still no cure for most patients. Medical advances have been possible because patients have participated in clinical studies.

The MMRF CureCloud® study aims to identify more personalized treatments for every myeloma patient, faster.
The fastest way to find these treatments is to make information from every myeloma patient available to cancer researchers.

Myeloma is different in every patient — we need to learn more to see what's best for each patient.

It's easy and convenient to participate from home — at no cost to you or your doctor.

Unlike other studies, in the CureCloud you will not need to:
- ✖ Take any experimental medication or change your current medications.
- ✖ Go for any extra doctor's visits or see a different doctor.

Sign up online or in a CureCloud participating clinic and confirm your eligibility.
- ✔ Get a home blood test (genomic test*).
- ✔ We'll collect your medical records.

You'll help researchers find better treatments while learning more about your myeloma.
Information contributed by you and other patients will help researchers find better therapies for every myeloma patient, faster. We'll share with you anything we find out about your myeloma from your blood test and medical records.

Your data is strictly protected — the information you provide is held in a very secure database.

**Genomic test: analysis of myeloma DNA in your blood to see if there are any changes.*

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How does the MMRF CureCloud work?

You'll get a blood test at home.

- After you sign up, you will receive a CureCloud bloodwork kit..
- A trained medical professional will come to your home to draw your blood.

We'll collect your medical records.

- When you sign up, you'll provide the names and contact information for the doctors who have treated your myeloma and any clinics or hospitals where you've had tests (bone scans, MRI, etc.).
- We'll contact them and collect your records.

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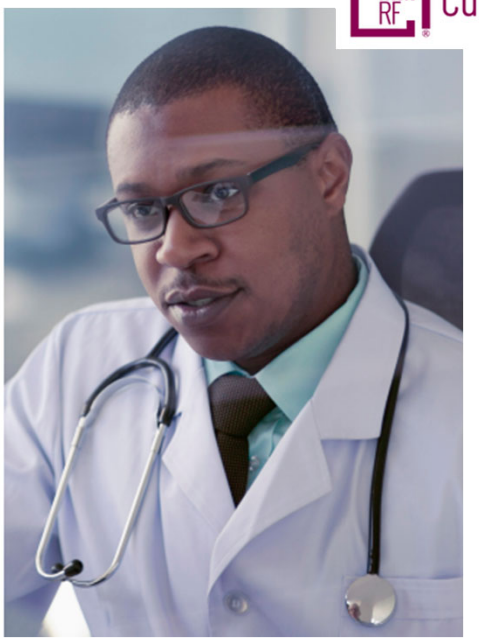
What happens to my information?

Your information is shared anonymously — to help the entire myeloma community.
The information you contribute is made anonymous and will be available to the myeloma community. Researchers will be able to use this information to learn more about myeloma, helping to find new medicines or even, someday, a cure. In the future, patients and their doctors will be able to access this data to find specific treatment options that are right for them.

You'll learn more about *your* myeloma.
Once we've collected your medical records, you'll have access to a private, personal dashboard with all the medical information related to your myeloma*.

With all your information at hand, you'll be able to have better conversations with your myeloma care team.

**Information will only be collected from the myeloma doctors you provide when you sign up.*



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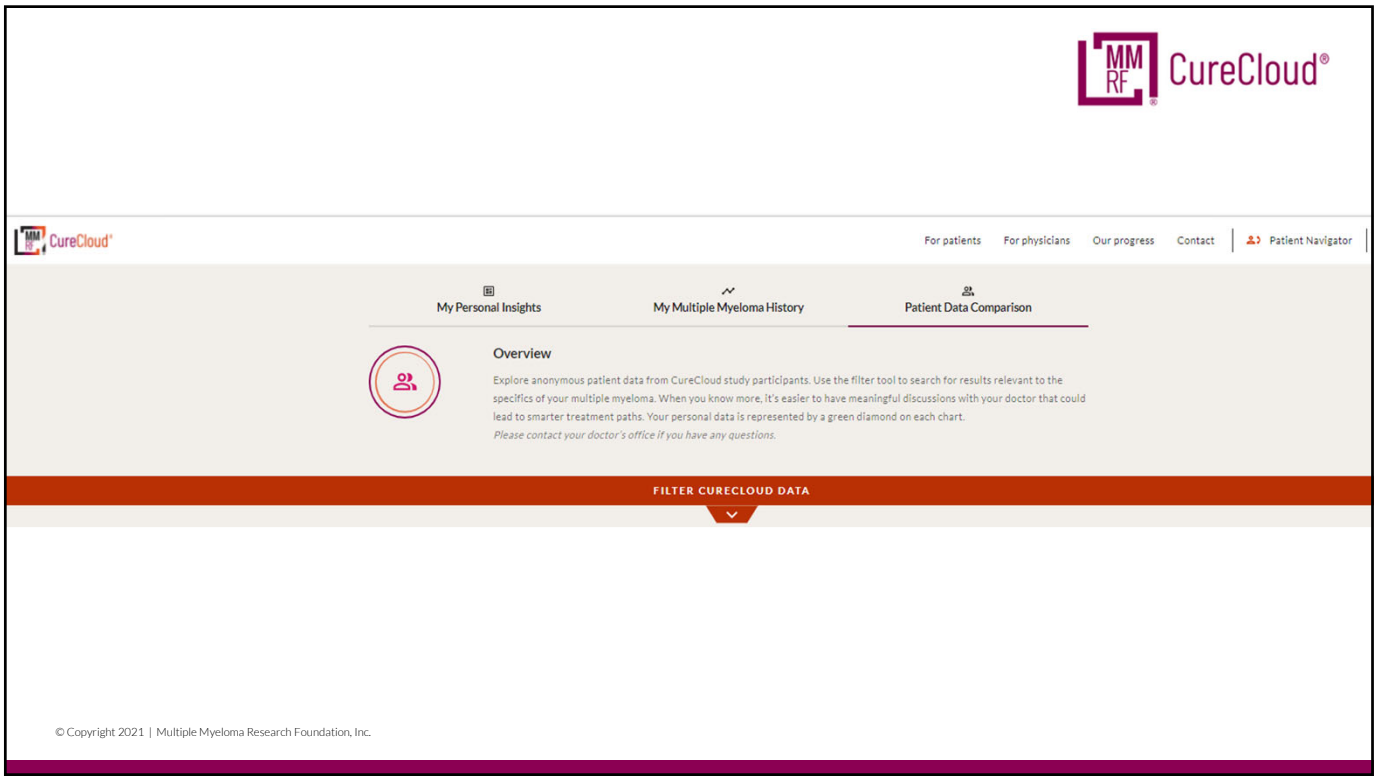

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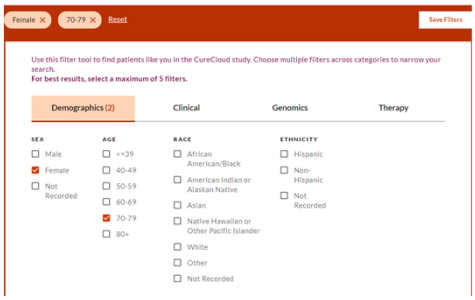
A Patient's Own Data–Compared With Data From Many Others

- Clinical data with patient's data represented (green diamond)
- Patient can filter data by characteristics like age, sex, and race to see patients like themselves



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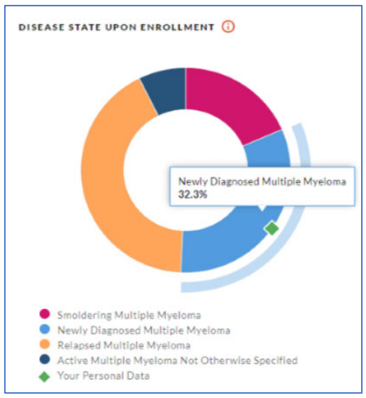

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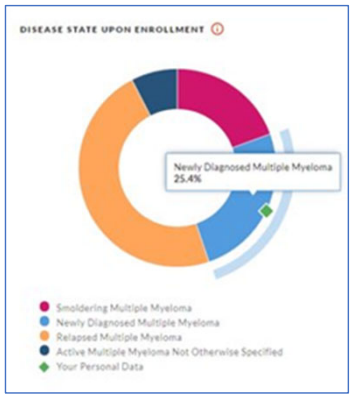

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A Patient's Own Data–Compared With Data From Many Others

- Clinical data with patient's data represented (green diamond)
- Patient can filter data by characteristics like age, sex, and race to see patients like themselves

CureCloud®

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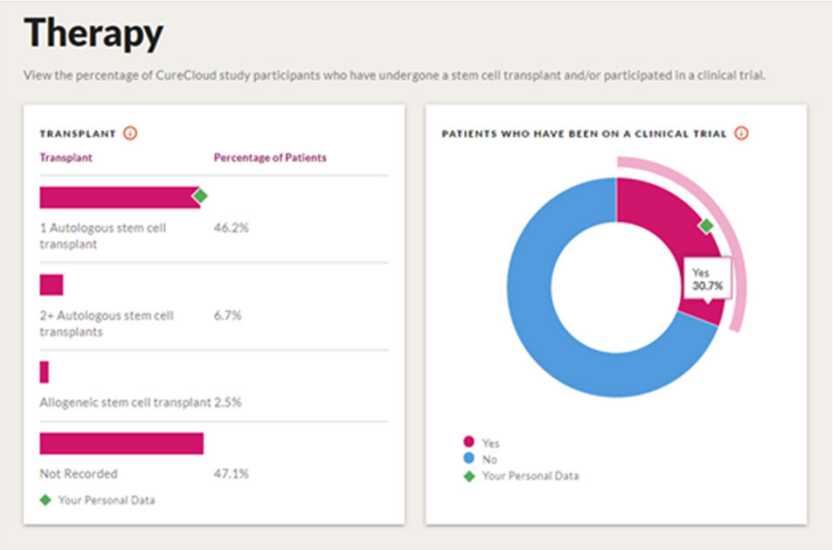
A Patient's Own Data–Compared With Data From Many Others

- Treatment data with patient's data represented (green diamond)
- Patient can filter data by characteristics like age, sex, and race to see patients like themselves

CureCloud®



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MULTIPLE MYELOMA Research Foundation

Thank you

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Speakers

Malin Hultcrantz, MD PhD
Memorial Sloan Kettering Cancer Center
New York, New York

Joshua R. Richter, MD
Tisch Cancer Institute/Icahn School
of Medicine at Mount Sinai
New York, New York

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Topics To Discuss

Precursor Conditions and Disease Monitoring

- iStopMM study and MGUS observations
- Treating high-risk SMM
- Mass spectrometry as a new measurement tool

Updates on Newly Diagnosed MM

- Frailty
- High risk disease
- Maintenance therapy

Updates on Relapsed/Refractory MM

- Current CAR T-cell therapy
- Isatuximab-based therapies
- Bispecific antibodies
- New drugs on horizon

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Updates on Precursor Conditions, Monitoring, and Newly Diagnosed Multiple Myeloma

Malin Hultcrantz, MD, PhD
Memorial Sloan Kettering Cancer Center
New York, New York

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Nationwide Screening Studies to Identify Patients With Myeloma Precursor Conditions

Iceland

iStopMM
Iceland Screens, Treats or Prevents Multiple Myeloma

United States and Canada

THE PROMISE STUDY

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Learning More About MGUS

iStopMM Study

148,704 individuals 40 years of age or older in Iceland enrolled

↓

75,422 screened for M protein and abnormal free light chain

↓

3,358 individuals with MGUS

3.9% of individuals screened have MGUS (5% in individuals over 50 years of age)

MGUS subtypes: 57% IgG; 21% IgM; 12% IgA. IgA prevalence rises slowly with age and plateaus after age 70.

Risk categories*: 43% low; 40.4% low-intermediate; 16.3% high-intermediate; and 0.3% high.

No evidence of MGUS progression following SARS-CoV-2 vaccination (in 1,814 individuals vaccinated) irrespective of the number of doses administered and the type of vaccine used.†

iStopMM data set used to create a prediction model to identify patients with MGUS that have ≥10% bone marrow plasma cells. This model may help clinicians determine which of their MGUS patients may defer a bone marrow biopsy.‡

*Based on the 2/20/20 risk stratification model where three risk factors are associated with progression to active myeloma: (1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow.

Love TJ et al. *Blood*. 2022;140. Abstract 103.
†Palmason R et al. *Blood*. 2022;140. Abstract 105.
‡Eythorsson E et al. *Blood*. 2022;140. Abstract 107.

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Therapeutic Intervention for High-Risk SMM

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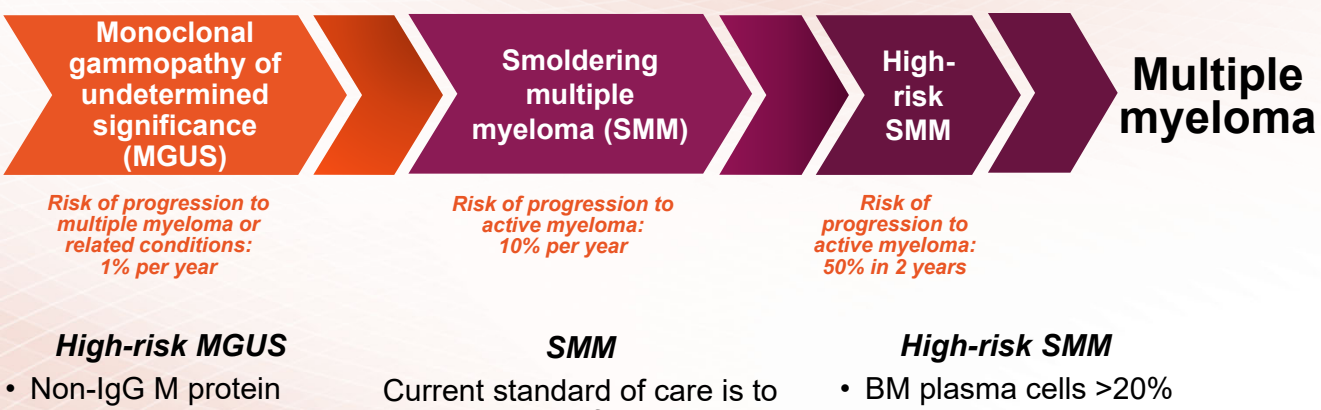

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Multicenter, Open-Label, Phase 2 Trial of Kyprolis-Revlimid-dex for High-Risk SMM Patients

GEM-CESAR Study

High-risk* smoldering multiple myeloma patients

90 patients

Induction — Kyprolis + Revlimid + dex (KRd)

ASCT

Consolidation — KRd

Maintenance — Revlimid

- At 70 months, 94% of patients have not progressed to multiple myeloma; 48% have biochemically progressed (rescue therapy with DPd resulted in 80% overall response rate)
- The presence of SLiM criteria and MRD at the end of maintenance predicted progression.
- The achievement of MRD negativity after maintenance and 4 years after ASCT predicted sustained MRD negativity.

Encouraging results for a curative approach to high-risk SMM.

*According to the Mayo and/or Spanish models.

Mateos MV et al. *Blood*. 2022;140. Abstract 118.

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Four-Drug Combination Strategy for High-Risk SMM Patients

ASCENT Study

High-risk* smoldering multiple myeloma patients

87 patients

Induction — Darzalex + Kyprolis + Revlimid + dex (Dara-KRd)

Consolidation — Dara-KRd

Maintenance — Darzalex + Revlimid

- Best overall response rate was 97% (92% ≥VGPR); 84% of patients achieved MRD negativity.
- Grade ≥3 hematologic toxicity in 18% of patients; non-hematologic toxicity in 51% of patients.
- 89.9% of patients are progression-free at 3 years.

High response rates with a transplant-free regimen. Longer follow up will answer possible cure with early intervention.

*Based on the 2/20/20 risk stratification model where three risk factors are associated with progression to active myeloma: (1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow; or a total score of ≥9 on IMWG scoring system.

Kumar SK et al. *Blood*. 2022;140. Abstract 757.

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Disease Monitoring

Mass Spectrometry

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Minimal Residual Disease Detection and Monitoring in the Blood by Mass Spectrometry

MRD is currently measured using a bone marrow sample; myeloma cells are detected using one of two methodologies: (1) flow cytometry or (2) next-generation sequencing.

Mass spectrometry (MS) is being evaluated as a method to assess MRD or M protein in the blood as a potentially more sensitive test to detect MRD in patients after therapy.

The phase 3 trials GEM2014MAIN and GMMG-MM5 are providing critical information on the use of this new technology compared to results from bone marrow biopsy samples.[1-3]

Sustained MRD negativity as determined by MS is prognostic for improved outcome, whereas MRD positivity is associated with worse outcome and is a potential marker for earlier treatment intervention.[4]

MS is more sensitive than measuring the M-spike (SPEP and IFE)

MS has a high concordance with bone marrow based MRD methods and can guide the need for bone marrow biopsies

1. Puig N et al. *Blood*. 2022;140. Abstract 866.
2. Notarfranchi L et al. *Blood*. 2022;140. Abstract 865.
3. Mai EK et al. *Blood*. 2022;140. Abstract 968
4. Claveau JS et al. *Blood*. 2022;140. Abstract 970.

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Newly Diagnosed Multiple Myeloma

Exploring Frailty

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Frailty Status Over Time

SEER-Medicare–linked database

Newly diagnosed myeloma patients ≥65 years receiving novel drugs between 2007–2014

4,617 patients identified

- **Non-frail** — 5%
- **Prefrail** — 25%
- **Mildly frail** — 32%
- **Moderately frail** — 23%
- **Severely frail** — 16%

Frailty status followed for 3 years

- Frailty categorization changed in 93% of patients (78% improved, 72% deteriorated)
- Current frailty status was a better predictor of overall survival than frailty at diagnosis.

Frailty categorization changes during myeloma disease course, necessitating the need for re-measurment.

Mian HS et al. *Blood.* 2022;140. Abstract 171.

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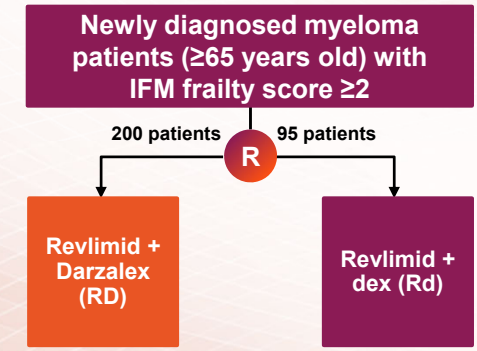
Dexamethasone-Sparing Regimen for Frail Patients

IFM2017-03 Trial



No dexamethasone!

- Deeper responses observed with RD vs Rd at 4, 8, and 12 months (≥VGPR rates 41% vs 26%; 68% vs 48%; 71% vs 55%, respectively).
- Favorable safety profile without increased infection or pneumonia with RD vs Rd

Encouraging results for a dexamethasone-sparing strategy for frail multiple myeloma patients.

Manier S et al. *Blood.2022;140*. Abstract 569.

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Newly Diagnosed Multiple Myeloma

High-Risk Disease

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High-Risk Disease Definitions

Revised International Staging System (R-ISS)[1]

R-ISS Stage I
- ISS[2] stage I
  - Serum β2M level <3.5 mg/L
  - Serum albumin level ≥3.5 g/dL
- No high-risk CA*
- Normal LDH level

R-ISS Stage II
- All other possible combinations

R-ISS Stage III
- ISS[2] stage III
  - Serum β2M level ≥5.5 mg/L
- High-risk CA* or high LDH level

*Deletion 17p and/or t(4;14) and/or t(14;16)

Mayo Clinic Stratification for Myeloma & Risk-Adapted Therapy (mSMART)[3]

High risk
- Genetic abnormalities*
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - del 17p
  - p53 mutation
  - Gain 1q
- R-ISS Stage 3
- High plasma cell S-phase
- GEP: high-risk signature
- *Double-hit myeloma*: any two high-risk genetic abnormalities
- *Triple-hit myeloma*: three or more high-risk genetic abnormalities

Standard risk
- All others including:
  - Trisomies
  - t(11;14)
  - t(6;14)

*By FISH or equivalent

Additional Features

- **Disease features**
  - Other cytogenetic and genetic abnormalities
  - Plasma cell leukemia
  - Extramedullary disease
  - Renal failure
- **Patient features**
  - Comorbidities
  - Frailty
- **Response features**
  - Lack of response to therapy
  - Short first PFS

1. Palumbo A et al. *J Clin Oncol.* 2015;33:2863. **2.** Griepp PR et al. *J Clin Oncol.* 2005;23:3412. **3.** Mikhael J et al. *Mayo Clin Proc.* 2013;88:360.

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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 consecutive high-risk* newly diagnosed myeloma patients treated with KRd (n=87) and VRd (n=67) at Memorial Sloan Kettering Cancer Center from 2015 to 2019
- 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]

- Study to evaluate the efficacy of Darzalex-cyclophosphamide-Velcade-Revlimid-dex (Dara-CyVRd) induction followed by ASCT and 2 rounds of consolidation with Dara-VR (with or without dex) in 107 ultra high-risk† patients with multiple myeloma and plasma cell leukemia (PCL)
- By end of second consolidation, 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 and 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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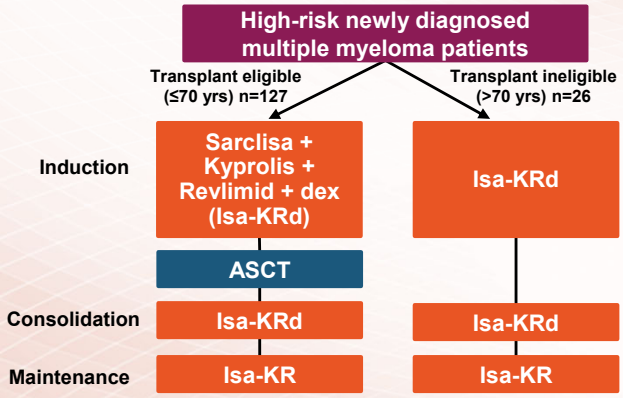
Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

GMMG-CONCEPT Study



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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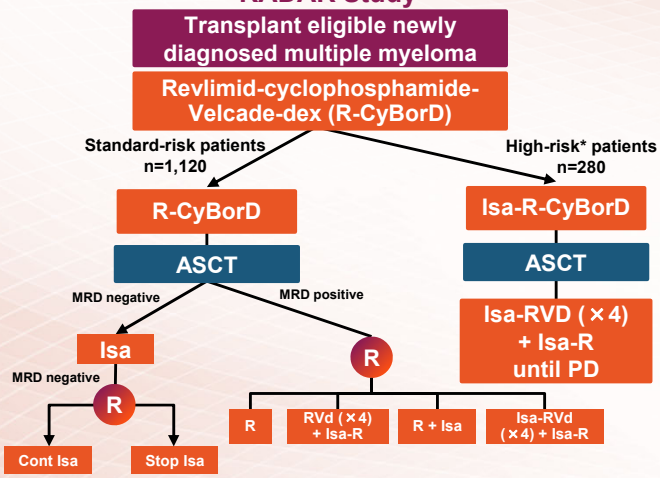
Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

RADAR Study



Innovative study design to tailor treatment:
- Deescalate for MRD neg patients
- Deepen response for MRD positive patients
- Manage ultra-HR disease

*At least 2 of t(4;14), t(14;16), del(17p), 1q+, 1p-

Yong K et al. *Blood.* 2022;140. Abstract 762.

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Newly Diagnosed Multiple Myeloma

Maintenance Therapy

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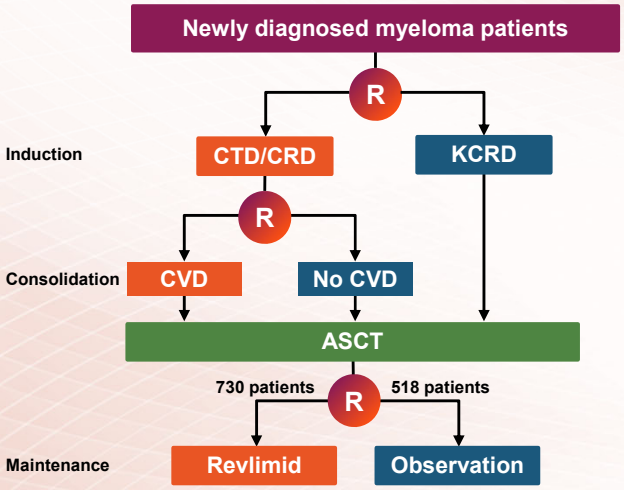
Maintenance Duration

Myeloma XI Study



Median PFS (mos)	At Time of Randomization to Maintenance Therapy (median follow up 44.7 mos)
	All Patients*
Revlimid	64
Observation	32
Hazard Ratio	0.52
P Value	<0.001

*PFS benefit across all patient subgroups on Revlimid maintenance therapy: standard risk; molecular high risk which included the presence of del(17p), gain(1q), t(4;14), t(14;16), or t(14;20); MRD positive; and MRD negative.

More evidence for the benefit of longer duration of Revlimid maintenance in patients who are MRD positive than MRD negative. And evidence of ongoing benefit beyond 2–3 years for patients with both standard- and high-risk disease.

Pawlyn C et al. *Blood*. 2022;140. Abstract 570.

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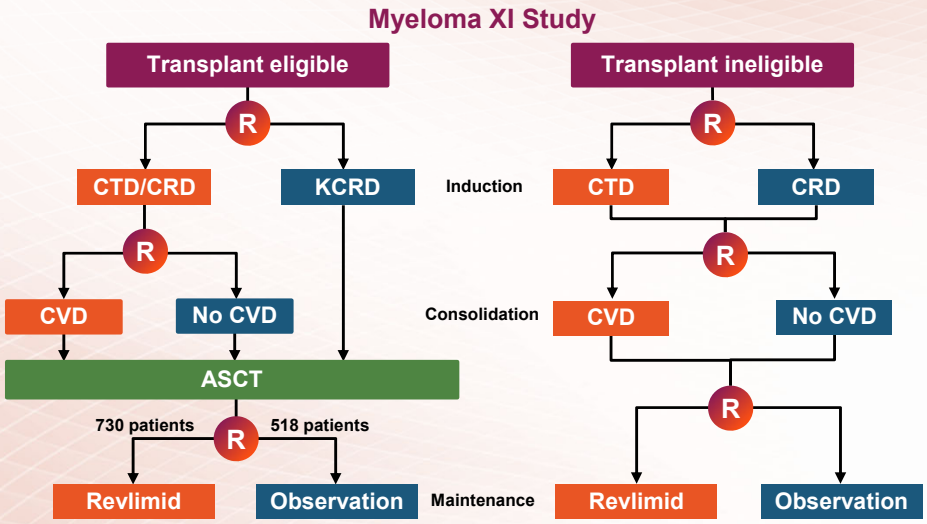
Second Primary Malignancies With Revlimid



Transplant eligible:
- 5.5% developed an SPM overall
- SPM incidence was 12.2% at 7 years in lenalidomide maintenance arm compared to 5.8% in the observation arm

Transplant ineligible:
- 9.9% developed an SPM overall
- SPM incidence was 17.1% at 5 years in lenalidomide maintenance arm compared to 10% in the observation arm

Double-exposure to lenalidomide (induction and maintenance) is associated with higher incidence of SPM and is more marked in transplant-ineligible patients.

Jones JR et al. *Blood*. 2022;140. Abstract 754.

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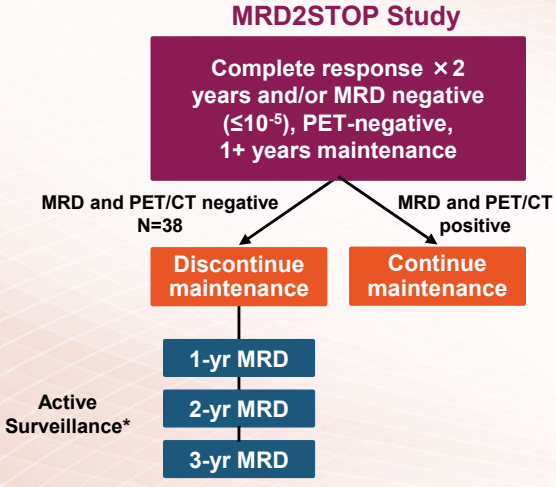
Using MRD Negativity to Guide Discontinuation of Maintenance Therapy



89% remain on study (5% with PD, 6% withdrew).

MRD resurgence occurred in 13% of patients (2 patients had resurgence of M-protein and disease progression).

MRD negativity (at 10^{-6} and 10^{-7}) is sustained even after discontinuation of maintenance therapy.

MRD-guided discontinuation of maintenance may carry significant cost savings.

*MRD assessment performed with PET, flow cytometry (10^{-5}), next-generation sequencing (10^{-6}), and CD138-selected next-generation sequencing (10^{-7})

Derman BA et al. *Blood*. 2022;140. Abstract 870.

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Key Points

- MGUS from the iStopMM trial: 3.9% of individuals over the age of 40 years
  The majority of individuals have low risk of progression.
- Mass spectrometry is being evaluated as a blood-based method for disease monitoring.
- Trials designs for high-risk smoldering and multiple myeloma show promising results.
- Individualizing maintenance therapy based on MRD monitoring.
- Focus on frailty and quality of life.

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Questions & Answers

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Updates on Relapsed/Refractory Multiple Myeloma

Joshua Richter, MD
Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai
New York, New York

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Relapsed/Refractory Multiple Myeloma

Sarclisa Combinations

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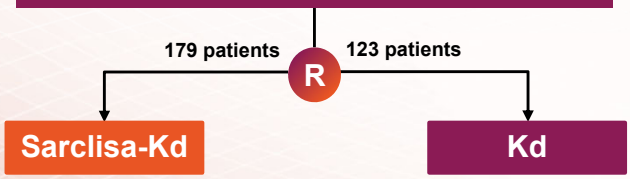
Sarclisa After Early or Late Relapse

IKEMA Study

Patients with relapsed/refractory myeloma who received 1-3 prior therapies, no prior therapy with Kyprolis and not refractory to prior anti-CD38 antibody



Data evaluated according to patients who experienced an early* versus late† relapse.

	Early Relapse		Late Relapse	
	Sarclisa -Kd	Kd	Sarclisa-Kd	Kd
Median progression-free survival (months)	24.7	17.2	42.7	21.9
Overall response rate (%)	82	82.6	90.4	86.1
≥VGPR rate (%)	67.2	52.2	76	58.3
MRD negativity rate (%)	24.6	15.2	37.5	16.7
MRD-negative CR rate (%)	18	10.9	30.8	13.9

Regardless of early or late relapse, RRMM patients benefit from the use of isa-Kd with respect to depth of response and prolonged PFS.

*<12 months from initiation of most recent line of therapy (for patients who had ≥2 lines of therapy); <18 months (for patients who had 1 prior line of therapy) and <12 months from ASCT
†≥12 months from initiation of most recent line of therapy (for patients who had ≥2 lines of therapy; ≥18 months for patients who had 1 prior line of therapy)

Facon T et al. *Blood*. 2022;140. Abstract 753.

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Relapsed/Refractory Multiple Myeloma

CAR T-Cell Therapy: How It's Going

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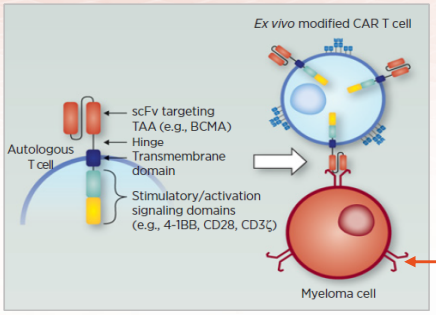
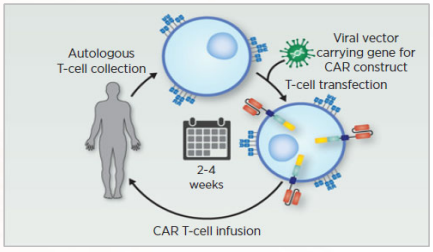
CAR T-Cell Therapy

- Genetically modified T cells designed to recognize specific proteins on myeloma cells
- CAR T cells are activated once in contact with the myeloma cell and can destroy the myeloma cell
- CAR T cells can persist for long periods of time in the body
- CAR T cells are created from a patient's own blood cells, but the technology is evolving to develop "off-the-shelf" varieties (allo-CART)





Approved:
- **Abecma (ide-cel)**
- **Carvykti (cilta-cel)**

CAR, chimeric antigen receptor; MM, multiple myeloma
Cohen A et al. *Clin Cancer Res.* 2020;26:1541.

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CAR T-Cell Therapy Insights

Prognostic Value of Depth of Response Following CAR T-Cell Therapy[1]
- Achieving sustained, undetectable MRD after Abecma is associated with prolonged PFS
- Only MRD status—not complete response (CR) status—predicted early relapse 1 month after Abecma.
- However, both MRD and CR status at 12 months were required to identify patients with longer PFS

Real-World Outcome With Abecma After BCMA-Targeted Therapy[2]
- Eleven US academic centers conducted a retrospective analysis on the real-world outcome for patients treated with Abecma after previously receiving BCMA-targeted therapy
- Prior BCMA-targeted treatment is associated with inferior PFS and a trend toward inferior outcomes for patients receiving Abecma within 6 months of having received prior BCMA-targeted therapy
- Warrants further investigation into the optimal timing of Abecma infusion

Outcomes and Options Following Relapse From CAR T[3]
- A retrospective analysis of 78 patients with RRMM who received BCMA-targeted CAR T-cell therapy
- Patients who had previously been refractory to a specific drug class re-responded after CAR-T relapse.
- Median OS after progressing on CAR T was 14.8 months and 18 months for patients who received subsequent BCMA CAR T or BCMA bispecific antibodies within 6 months of progressing on CAR T

Assessment of Cytopenias from CAR T[4]
- Retrospective review of data from 90 patients 4 months after CAR T-cell infusion
- Patients with poor hematologic recovery (28%) compared with adequate recovery (72%) were older, more heavily pretreated, and more likely to have received ≥1 ASCT

Abecma in Earlier Lines of Treatment[5]
- KarMMa-2 phase 2 multicenter study of Abecma in 37 patients with RRMM with high-risk disease*
- Results show a benefit to Abecma in earlier line of treatment

*Early relapse after frontline therapy or inadequate response after frontline ASCT

1. Paiva B et al. *Blood*. 2022;140. Abstract 868. **2.** Ferreri CJ et al. *Blood*. 2022;140. Abstract 766. **3.** Reyes KR et al. *Blood*. 2022;140. Abstract 250.
4. Thibaud S et al. *Blood*. 2022;140. Abstract 249. **5.** Usmani S et al. *Blood*. 2022;140. Abstract 361.

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Relapsed/Refractory Multiple Myeloma

Bispecific Antibodies

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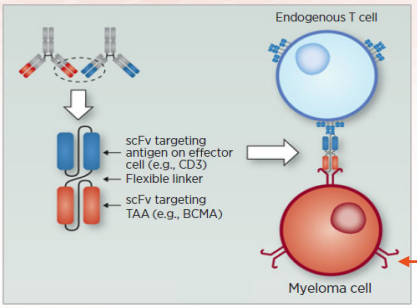
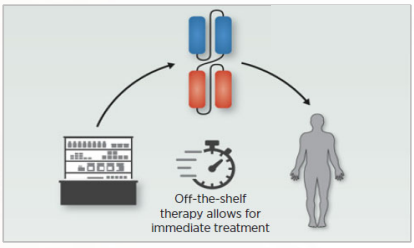
Bispecific Antibodies

- Bispecific antibodies are also referred to as dual-specific antibodies, bifunctional antibodies, or T-cell–engaging antibody
- Bispecific antibodies can target two cell surface molecules at the same time (one on the myeloma cell and one on a T cell)
- Many different bispecific antibodies are in clinical development
- Availability is off-the-shelf allowing for immediate treatment



BCMA, GPRC5D, or FcRH5



Examples:
- **Tecvayli (teclistamab)**
- **Elranatamab**
- TNB-303B (ABBV-383)
- Linvoseltamab
- Cevostamab
- **Talquetamab**

Cohen A et al. *Clin Cancer Res.* 2020;26:1541.

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Bispecifics Discussed at ASH

Bispecific Antibody	Target (on MM cell × T cell)
Tecvayli (teclistamab)	BCMA × CD3
Elranatamab	BCMA × CD3
Linvoseltamab	BCMA × CD3
Alnuctamab	BCMA × CD3
ABBV-383	BCMA × CD3
Talquetamab	GPRC5D × CD3
Forimtamig (RG6234)	GPRC5D × CD3
Cevostamab	FcRH5 × CD3

GPRC5D, G protein-coupled receptor family C group 5 member D

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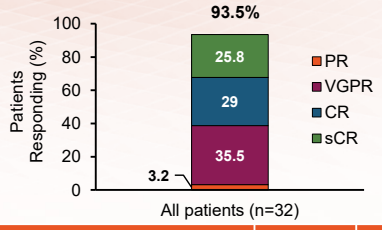
Tecvayli in Combination With Darzalex and Revlimid

Phase 1b study (MajesTEC-2) in RRMM with 1–3 prior lines of therapy (including an IMiD and a PI).

32 patients—who had received at least 2 prior lines of therapy—received treatment with the triplet with Tecvayli at 2 different doses (0.72 mg/kg and 1.5 mg/kg) subcutaneously.



Most Frequent Non-Hematologic Adverse Events, %	Any Grade	Grade 3/4
CRS	81.3	0
Fatigue	46.9	6.3
Infections (≥1)	90.6	37.5
COVID-19	37.5	12.5
Upper respiratory	31.3	0
Pneumonia	25	15.6
COVID pneumonia	12.5	3.1
Sepsis	9.4	9.4
Pneumonia pseudomonal	6.3	6.3
CMV	6.3	6.3

IMiD, immunomodulatory drug; PI, proteasome inhibitor

1. Searl E et al. *Blood*. 2022;140. Abstract 160.

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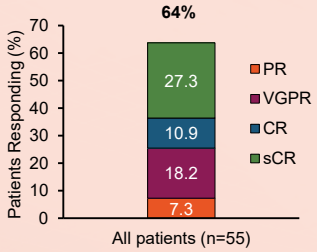
Elranatamab in Patients With Relapsed/Refractory Multiple Myeloma

Updated Efficacy and Safety Results with Elranatamab (MagnetisMM-1 Study)[1]

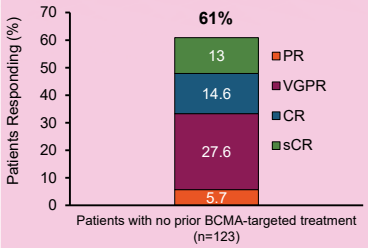
Phase 1 study in RRMM
(91% triple-class refractory)



Median duration of response 17.1 months.

MagnetisMM-3 Study of Elranatamab[2]

Phase 2 study in RRMM refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 antibody—no prior BMCA-targeted treatment



Elranatamab to be investigated alone and in combination with other drugs in phase 3 studies.

IMiD, immunomodulatory drug; PI, proteasome inhibitor

1. Raje N et al. *Blood*. 2022;140. Abstract 158. **2.** Bahlis NJ et al. *Blood*. 2022;140. Abstract 159.

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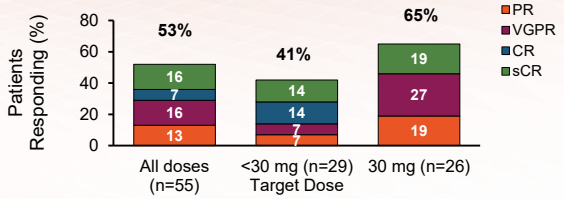
Phase 1 Study of Alnuctamab in Patients With Relapsed/Refractory Multiple Myeloma

Intravenous Formulation Results

	IV Alnuctamab (n=70)
Median follow up (months)	8.0
Overall response rate (%)	39
Median duration of response (months)	33.6
Responses ongoing (%)	48
Median progression-free survival (months)	
All patients	3.1
Responders	36.4
Nonresponders	1.7

Subcutaneous Formulation Results



Most Frequent Adverse Events, %	Any Grade	Grade 3/4
Hematologic		
Anemia	38	25
Neutropenia	37	32
Thrombocytopenia	24	9
Non-hematologic		
CRS	53	0
Infections	34	9
ICANS	3	0
ALT increase	12	6

Wong SW et al. *Blood*. 2022;140. Abstract 162.

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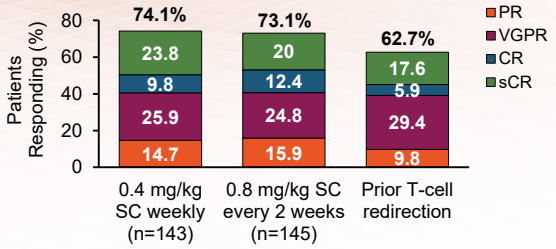
Talquetamab in Patients With Relapsed/Refractory Multiple Myeloma

Phase 1/2 study (MonumenTAL-1) in RRMM

288 patients—with no prior T-cell redirecting therapies—received treatment with talquetamab at 2 different doses (0.4 mg/kg every week and 0.8 mg/kg every other week) subcutaneously.

Data from this trial was recently used to submit a Biologics License Application to the U.S. Food and Drug Administration for the treatment of patients with relapsed or refractory multiple myeloma.



Most Frequent Adverse Events, %	0.4 mg/kg Any Grade	0.4 mg/kg Grade 3/4	0.8 mg/kg Any Grade	0.8 mg/kg Grade 3/4
Hematologic				
Anemia	44.8	31.5	39.3	24.8
Neutropenia	34.3	30.8	28.3	22.1
Lymphopenia	28	25.9	26.2	25.5
Thrombocytopenia	27.3	20.3	26.9	16.6
Infections	57.3	16.8	50.3	11.7

IMiD, immunomodulatory drug; PI, proteasome inhibitor

Chari A et al. *Blood*. 2022;140. Abstract 157.

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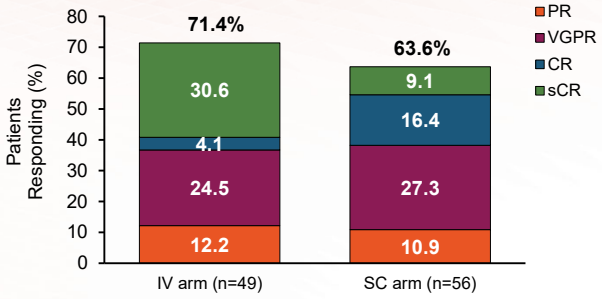
Forimtamig (RG6234) in Patients With Relapsed/Refractory Multiple Myeloma

Phase 1 study in RRMM

105 patients received treatment with RG6234 in 2 different formulations (intravenous and subcutaneous).



Carlo-Stella C A et al. *Blood*. 2022;140. Abstract 161.

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Expected Toxicities With T-Cell Activating Therapies (CAR T and Bispecific Antibodies)

Cytokine release syndrome (CRS)

Infections

- Viruses: CMV, EBV
- PCP/PJP
- Ongoing discussions regarding prophylactic measures
  - IVIG
  - Anti-infectives

Cytopenias

Neurotoxicity (ICANS)

- Usually occurs within first 1–2 weeks
- Frequency (all grade and grade 3–5) higher with CAR T

Off target effects (with GPRC5D targeted agents)

Cytokeratin changes/rash Dysgeusia

ICANS, immune effector cell-associated neurotoxicity syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PCP/PJP, pneumocystis pneumonia/pneumocystis jiroveci pneumonia

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Pretreatment With Tocilizumab Reduces Incidence and Severity of Cytokine Release Syndrome

Cevostamab is an FcRH5-targeted bispecific antibody under investigation in patients with RRMM.

An ongoing phase 1 study evaluating the use of tocilizumab (an IL-6 antibody) prior to the first dose of cevostamab. A single 8 mg/kg dose of tocilizumab was administered to 28 patients 2 hours prior to cevostamab.

- 35.7% of patients receiving tocilizumab experienced CRS compared to 90.9% of patients who didn't receive tocilizumab.
- Grade 3 CRS was observed in only one patient in each group and no G4/5.
- The frequency of neutropenia was higher for patients receiving tocilizumab compared with those who didn't (64.3% vs 38.6% G3/4).
- No impact on response was observed with tocilizumab pretreatment.

Trudel S et al. *Blood*. 2022;140. Abstract 567.

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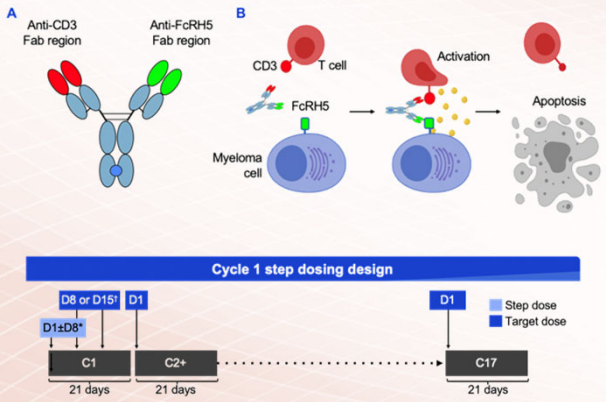
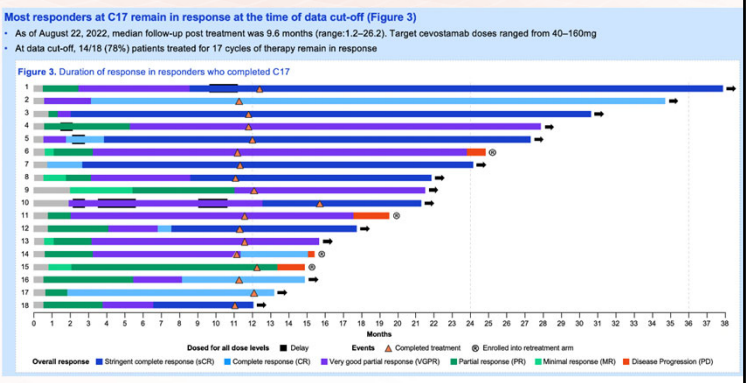
Fixed-Duration Therapy With Bispecifics Cevostamab





At the time of this presentation, no patients who achieved an sCR have relapsed!

Lesokhin AM et al. *Blood*. 2022;140. Abstract 1924.

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Relapsed/Refractory Multiple Myeloma

Drugs on the Horizon

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What's next for CAR T-cell therapy?

	BMS-986354[1]	FasT CAR-T GC012F[2]	BMS-986393[3]
Features	• Targets BCMA with a shortened manufacturing time through the NEXT-T process	• Targets BCMA *and* CD19 • Manufacturing process that takes as little as 24 hours	• Targets GPRC5D
Trial Details	• Phase 1 trial of 55 patients with RRMM with a median of 5 prior lines of therapy	• Phase 1 trial of 13 newly diagnosed high-risk MM patients ineligible for stem cell transplant	• Phase 1 trial of 17 heavily pretreated patients with RRMM, including those who relapsed from BCMA CAR-T therapy
Clinical Results	• CRS occurred in 80% of patients with only 1 patient experiencing ≥G3. • Neurotoxicity occurred in 10.9% of patients (one grade 4). • Overall response rate was 98.1% with 57.4% achieving ≥VGPR (29.6% ≥CR).	• 100% of patients achieved ≥VGPR (69% sCR) • All patients achieved MRD negativity (by EuroFlow). • CRS observed in 23% of patients (all low grade).	• Neutropenia and thrombocytopenia most frequent grade 3/4 adverse events • Additional adverse events include skin- and nail-related; dysgeusia/dysphagia; CRS; ICANS • 86% evaluable patients responded including 7 of 11 patients treated with prior BMCA-targeted treatment

1. Costa LJM et al. *Blood*. 2022;140. Abstract 566. **2.** Du J et al. *Blood*. 2022;140. Abstract 366. **3.** Bal S et al. *Blood*. 2022;140. Abstract 364.

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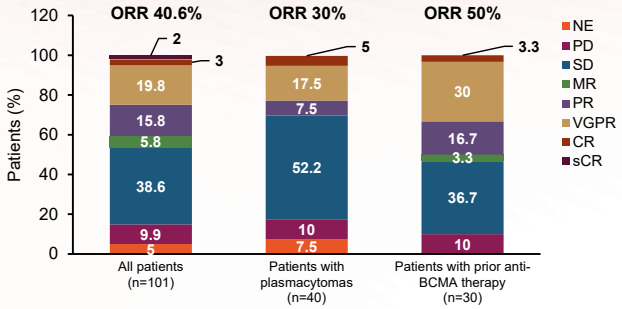
Mezigdomide: A Cereblon E3 Ligase Modulator (CELMoD)

CELMoDs are related to the immunomodulatory drugs (IMiDs) but are more potent and may overcome resistance to IMiDs

A phase 1/2 study of mezigdomide combined with dex in relapsed/refractory patients.

101 patients—who had received at least 6 prior lines of therapy and 100% were triple-class refractory (one-third were previously exposed to anti-BCMA therapy—received treatment with mezigdomide-dex.



Most Hematologic Frequent Adverse Events, %	Grade 3	Grade 4
Neutropenia	21.8	53.5
Anemia	34.7	1.0
Thrombocytopenia	13.9	13.9
Febrile neutropenia	12.9	2.0

Most Frequent Non-Hematologic Adverse Events, %	Grade 3	Grade 4
Infections	28.7	5.9
Pneumonia	12.9	3.0
COVID-19	6.9	0

Richardson PG et al. *Blood*. 2022;140. Abstract 568.

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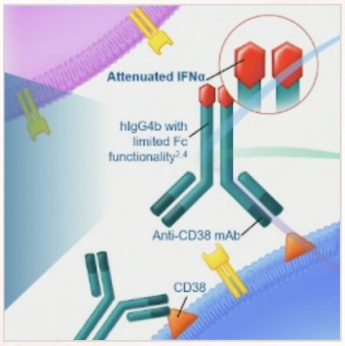
A New Class of Drug: Immunocytokines

Modakafusp alfa is an antibody that can bind to CD38 on myeloma cells that is fused to the cytokine interferon-alpha



100 patients who had a median of 7 prior lines of therapy were treated with different doses of modakafusp (19% had prior CAR T-cell therapy and 14% prior T cell engagers).

Overall response rate was 43% in patients receiving 1.5 mg/kg dose every 4 weeks (n=30); 27% of anti-BCMA exposed patients responded.

Immunocytokines are engineered to deliver cytokines (a protein produced by immune cells) that can prevent myeloma cells from dividing and to help boost myeloma-fighting immune cells.

Vogl DT et al. *Blood*. 2022;140. Abstract 565.

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Key Points

- **There is an ever increasing armamentarium of options in the relapsed setting of myeloma!**
- **There are many options in early relapse for patients progressing on lenalidomide maintenance. Isa-Kd has some of the best data in this area and can be administered in any practice.**
- **CAR T therapy continues to show impressive responses in later-line therapy and is now recapitulating that and more in earlier settings.**
- **Bispecific antibodies were stars of ASH 2022. Almost too many to keep on top of. Numerous targets and new strategies to optimize not only efficacy but toxicity.**
- **Prophylactic tocilizumab (and similar strategies) may be the key to getting bispecific antibodies into the community setting. Fixed-duration therapy is future of this approach…. ? The end to continuous therapy**

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Questions & Answers

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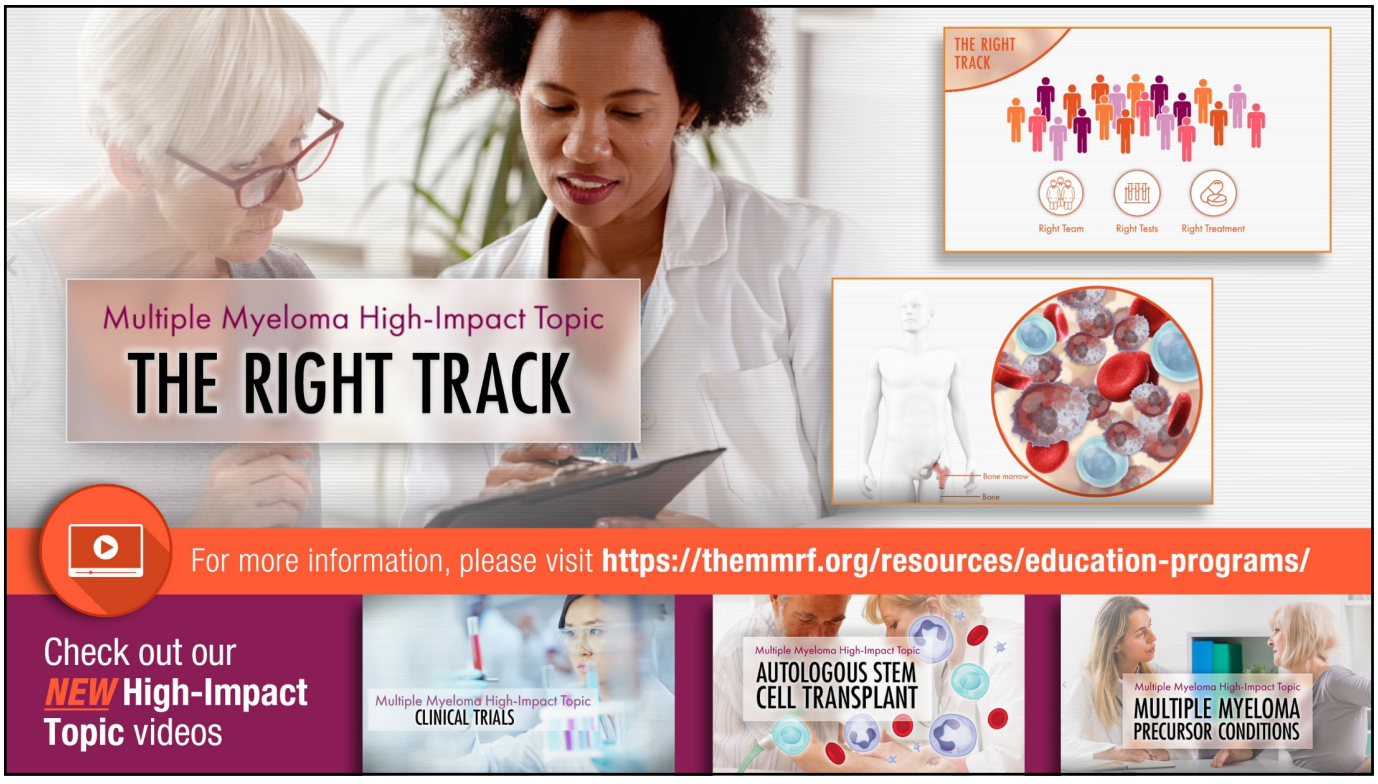

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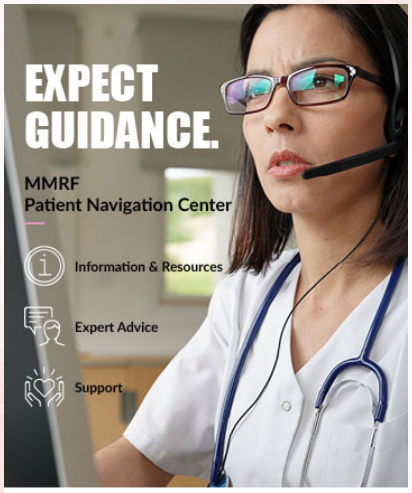
MMRF Patient Resources



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 to connect with patient navigators — who are professionals specializing in oncology — for guidance, information, and support. Patients can connect with a patient navigator via phone, email or through one of our MMRF Facebook Groups. Whenever patients have a question, our patient navigators are here to help.

MMRF Patient Navigators include:

- Grace Allison, RN, BSN, OCN, RN-BC
- Kristen Donadio, RN, BSN
- Erin Mensching, BSN, BA, RN

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

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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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Patient Education Events

For information on new programs to take place in 2023, please visit themmrf.org/resources/education-program

Happy Holidays!

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