Non-BCMA Bispecific Antibodies

October 11, 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

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

Ajai Chari, MD
University of California, San Francisco
San Francisco, California

Suzanne Trudel, MD, FRCPC
University of Toronto
Princess Margaret Hospital
Toronto, Ontario, Canada

Nicholas Lenoir
Patient
Spring Hill, Florida

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Myeloma Targets Beyond BCMA

Ajai Chari, MD
University of California, San Francisco
San Francisco, California

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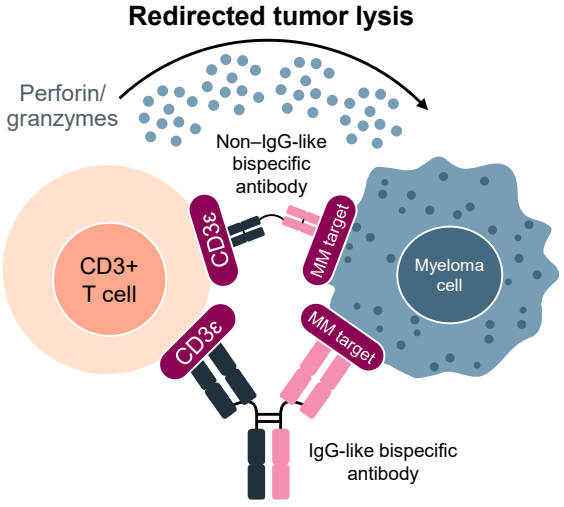
Bispecific Antibodies

- Bispecific antibodies are also referred to as *dual-specific antibodies, bifunctional antibodies,* or *T cell–engaging antibodies.*
- 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; three approved for use in myeloma!
- Availability is off-the-shelf, allowing for immediate treatment.



Cohen A et al. *Clin Cancer Res.* 2020;26:1541.
Singh A et al. *Br J Cancer.* 2021;124:1037.

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Myeloma Cell Targets for Bispecific Antibodies

BCMA

- Highly expressed only on the surface of plasma cells
- Myeloma patients have significantly higher serum BCMA levels than healthy individuals

GPRC5D

- Highly expressed on myeloma cells in the bone marrow
- Lowly expressed on hair follicles but not on other healthy cells
- Expression on myeloma cells is independent of BCMA

FcRH5

- Selectively expressed on B cells and plasma cells

GPRC5D, G protein-coupled receptor family C group 5 member D; FcRH5, Fc receptor-homolog 5

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Bispecific Antibodies Under Investigation

Target (MM cell × T cell)	Bispecific antibody	Status
BCMA × CD3	Tecvayli (teclistamab)	✓ Approved
	Elrexfio (elranatamab)	✓ Approved
	Linvoseltamab	Clinical studies
	Alnuctamab	Clinical studies
	ABBV-383	Clinical studies
GPRC5D × CD3	Talvey (talquetamab)	✓ Approved
	Forimtamig (RG6234)	Clinical studies
FcRH5 × CD3	Cevostamab	Clinical studies

Overall response rates 60% to 70% in heavily pretreated myeloma patients

High proportion of patients achieving VGPR or CR

GPRC5D, G protein-coupled receptor family C group 5 member D; FcRH5, Fc receptor homolog 5; VGPR, very good partial response; CR, complete response

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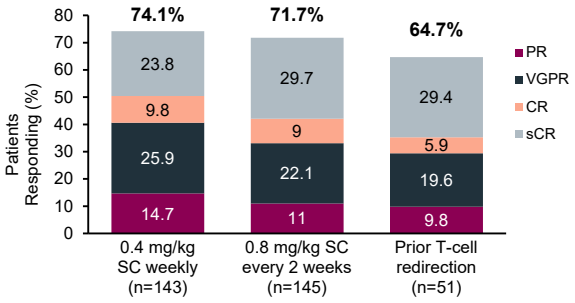
Talvey in Patients With Relapsed/Refractory Multiple Myeloma

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

288 patients—with or without prior T cell–redirecting therapies—received treatment with Talvey at 2 different doses (0.4 mg/kg every week and 0.8 mg/kg every other week) subcutaneously.



Now approved for patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody!

IMiD, immunomodulatory drug; PI, proteasome inhibitor

Schinke CD et al. *J Clin Oncol*. 2023;41. Abstract 8036.

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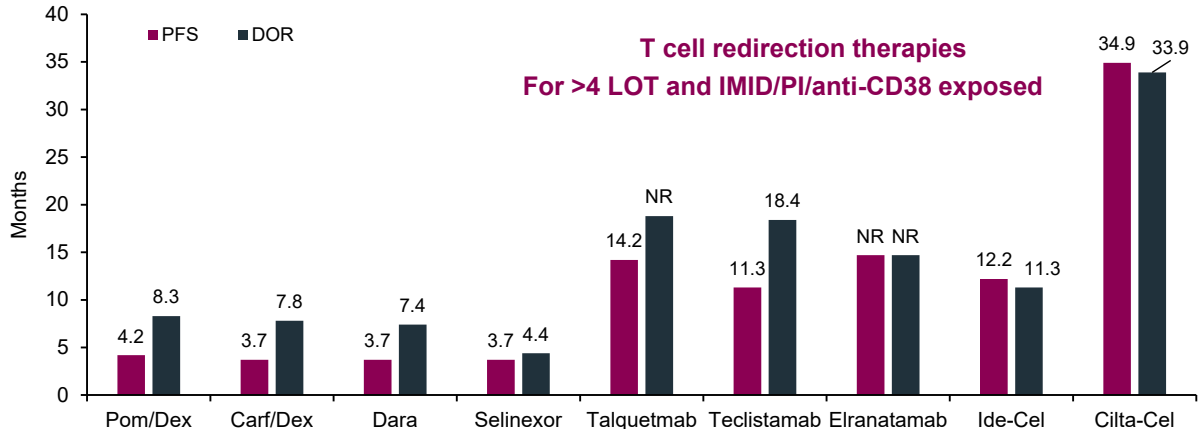
PFS and Duration of Response of Recently Approved Therapies in Relapsed/Refractory Myeloma



LOT, line of therapy; IMID, immunomodulatory drug; PI, proteasome inhibitor; PFS, progression-free survival; DOR, duration of response.

This is not a head-to-head comparison and cross-trial comparisons should not be interfered from these data.

Data represent two populations, PFS includes all patients, DOR includes responding patients only

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Expected Toxicities With Bispecific Antibodies

Cytokine release syndrome (CRS)

Infections

Cytopenias

Neurotoxicity (ICANS)

Off-target effects (with GPRC5D targeted agents)

Cytokeratin changes/rash
Dysgeusia

ICANS, immune effector cell-associated neurotoxicity syndrome

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Talvey in Patients With Relapsed/Refractory Myeloma

Most frequent adverse events, %	0.4 mg/kg		0.8 mg/kg	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Anemia	44.8	31.5	45.5	27.6
Neutropenia	35.0	30.8	28.3	22.1
Thrombocytopenia	27.3	20.3	29.7	18.6
Non-hematologic				
CRS	79.0	2.1	74.5	0.7
Taste disorder (dysgeusia)*	72.0	NA	71.0	NA
Infections	58.7	19.6	66.2	14.5
Skin related*	55.9	0	73.1	0.7
Nail related	54.5	0	53.8	0
Weight decreased	41.3	2.1	41.4	5.5
Fatigue	24.5	3.5	27.6	0.7

*Taste- and skin-related side effects led to discontinuations in 5 patients

Schinke CD et al. *J Clin Oncol*. 2023;41. Abstract 8036.

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GPRC5D-Associated Side Effects

Affected area	Symptoms and effects	Management
Skin	Rash, skin peeling	Relatively benign, not painful, self-limiting, and manageable with emollients
Nails	Nail thinning and loss	Mostly aesthetic but take time to resolve
Oral	Difficulty swallowing, dry mouth, taste changes	Can lead to weight loss; have longer duration and can affect quality of life. Most successfully managed with dose modification. Supportive measures may be used (eg, NaCl mouth rinse, artificial saliva spray, diet modification)

Myeloma patients respond well to treatment, and GPRC5D-associated side effects improve over time, becoming more tolerable; notable reduction in side effects is seen with dose modification

Catamero D et al. *Clin Lymphoma Myeloma Leuk*. 2023;xx. Abstract NSP-03.

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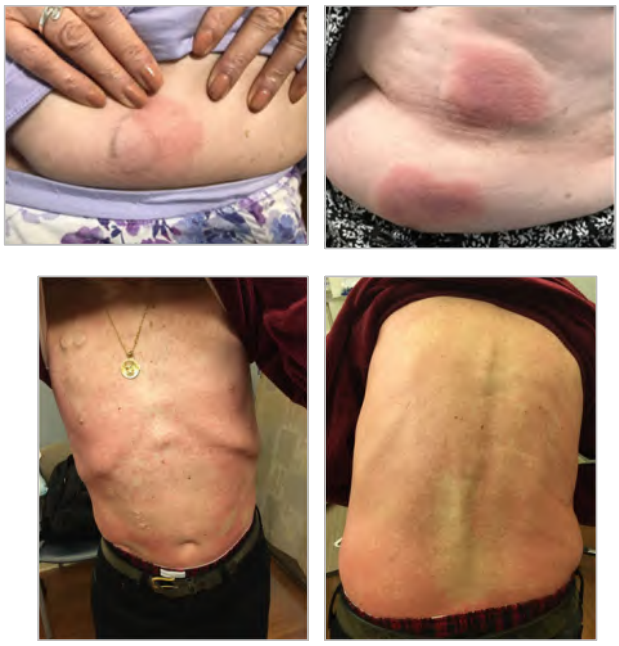

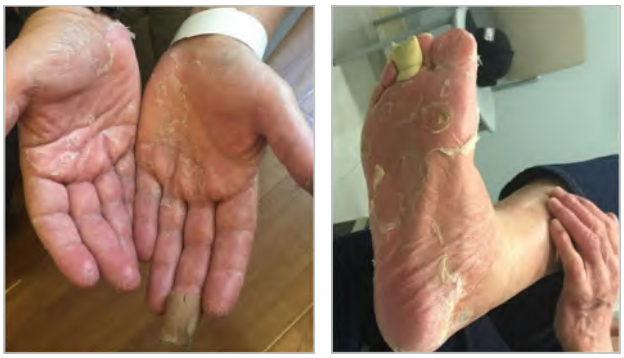

Products applied twice daily
- Ammonium lactate 12% cream
- Triamcinolone 0.1% cream
- Emollients

- Oral antihistamines as needed

5 patients who had grade 3 rash

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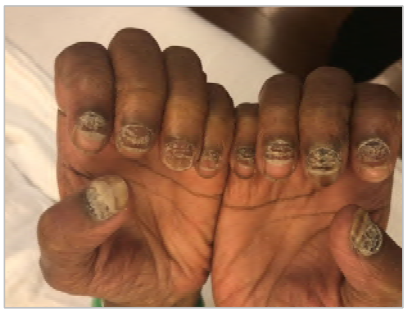
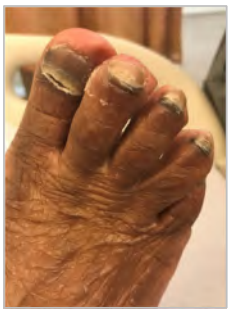
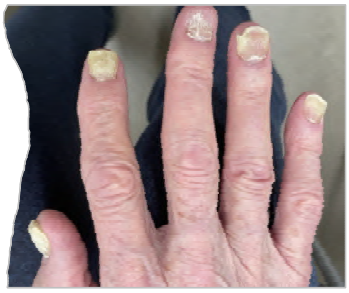
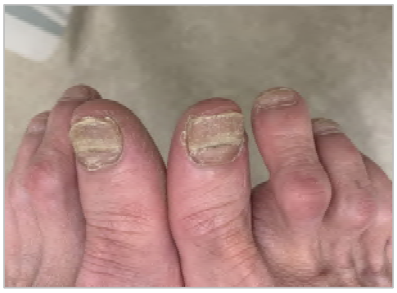

- Starts ~C2, lasts for months
- Avoid frequent/long durations of water immersion
- Frequent application of emollients (Vaseline/Aquaphor)
- Vitamin E oil
- File to smooth the edges and corners of the nail plates
- Clear nail polish or nail hardeners
- Biotin supplements may be helpful

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Talvey Use in Practice

Administered subcutaneously according to step-up dosing schedule and then weekly or every 2 weeks thereafter

Patients are to be hospitalized for 48 hours for monitoring of side effects after they have completed their step-up dosing, at a REMS-certified facility

REMS, risk evaluation and mitigation strategy

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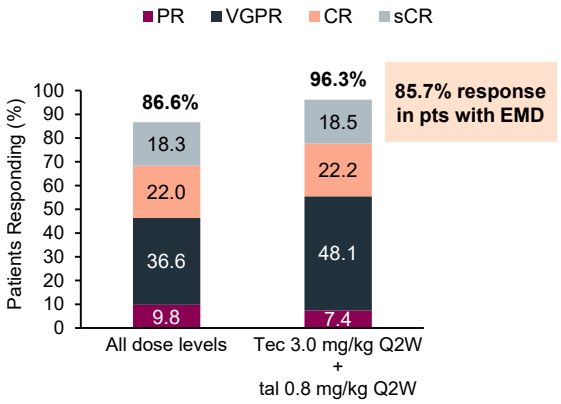
Talvey Combinations: Tecvayli + Talvey in Patients With Relapsed/Refractory MM



85.7% response in pts with EMD

Most frequent adverse events (%)	All dose levels (n=93)		Tec + Tal at RP2R dose levels (n=34)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Neutropenia	65.6	61.3	55.9	44.1
Anemia	50.5	34.4	32.4	23.5
Thrombocytopenia	43.0	29.0	32.4	23.5
Non-hematologic				
CRS	76.3	3.2	73.5	0
Dysgeusia	61.3	–	47.1	–
Pyrexia	50.5	2.2	38.2	2.9
Skin toxicity	53.8	0	52.9	0
Nail disorders	46.2	0	41.2	0

Progression-free survival, 20.9 months; duration of response, not yet evaluable.

PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; CRS, cytokine release syndrome; EMD, extramedullary disease
RedirecTT-1 Study. Cohen YC et al. *J Clin Oncol*. 2023;41. Abstract 8002.

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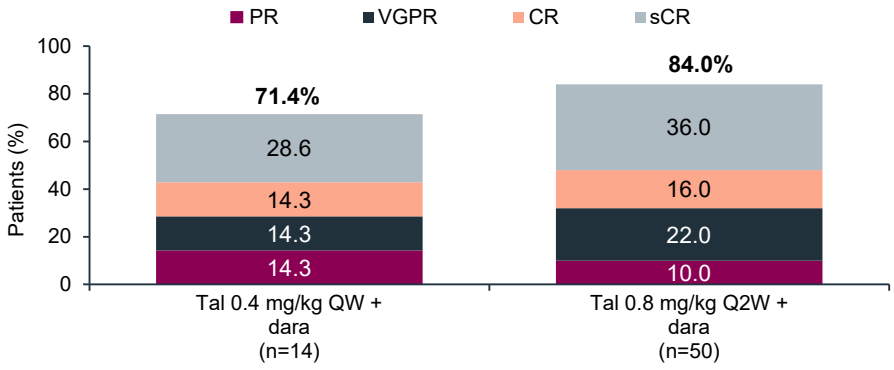
Talvey Combinations; Talvey + Darzalex in Patients With 3 or More Prior Lines of Therapy



Progression-free survival, 19.4 months; duration of response, 20.3 months.

PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response
TRIMM-2 Study. Dholaria BR et al. *J Clin Oncol*. 2023;41. Abstract 8003.

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Future Direction With Talvey

- Phase 2 pilot study of Tecvayli + Darzalex and Talvey + Darzalex in patients with high-risk* newly diagnosed multiple myeloma, with an early rescue intervention guided by minimal residual disease (MRD) assessment (GEM-TECTAL)

*One or more of the following high-risk features: del(17p), t(4;14), t(14;16), or 1q amplifications detected by fluorescence in situ hybridization, Revised International Staging System stage 3, and presence of extramedullary disease

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MULTIPLE MYELOMA Research Foundation | 25th ANNIVERSARY

Additional Non-BCMA Bispecific Antibodies

Suzanne Trudel, MD, FRCPC
University of Toronto
Princess Margaret Hospital
Toronto, Ontario, Canada

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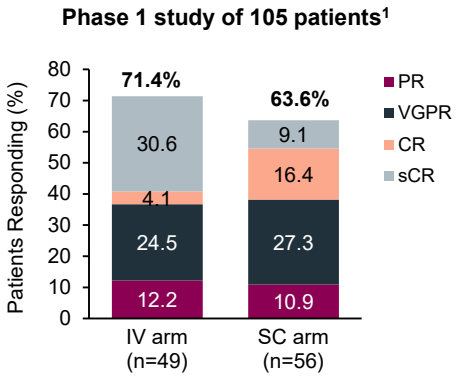
Forimtamig a GPRC5D × CD3 Bispecific Antibody in Patients With Relapsed/Refractory Multiple Myeloma



Subgroup analysis[2]	Number of patients	Overall response rate (%)
Age ≥65 years	52	71.2
>4 Prior lines of therapy	49	63.3
Triple-class refractory	81	60.5
Penta-drug refractory	45	57.8
Prior BCMA-targeted therapy	29	51.2
Antibody-drug conjugate	19	47.7
Bispecific antibody	5	42.9
CAR T cells	5	66.7
High risk cytogenetics (include del(17p), t(4;14), t(14;16))	33	63.4
1q21 gain	15	86.7
ISS III	24	70.8
Soluble BCMA >327 ng/mL	54	55.6
Soluble BCMA <327 ng/mL	55	80.0
Extramedullary disease	28	50.0

1. Carlo-Stella CA et al. *Blood*. 2022;140. Abstract 161.
2. Harrison SJ et al. *Clin Lymphoma Myeloma Leuk*. 2023. Abstract OA-05.

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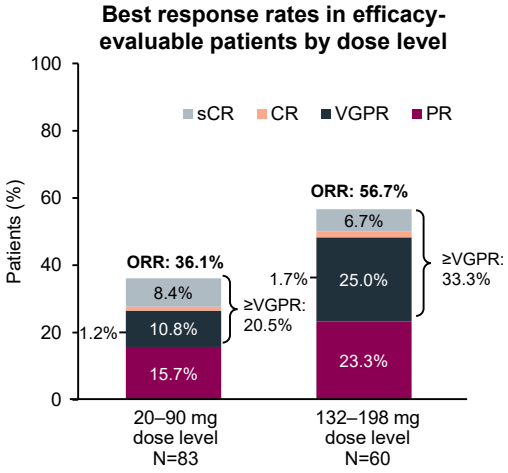
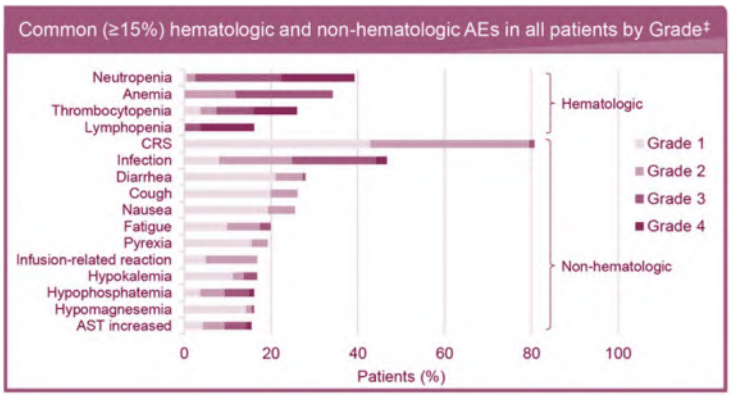
Cevostamab a FcRH5 × CD3 Bispecific Antibody in Patients With Relapsed/Refractory Multiple Myeloma





Trudel S et al. *Blood*; 2021;138. Abstract 157.

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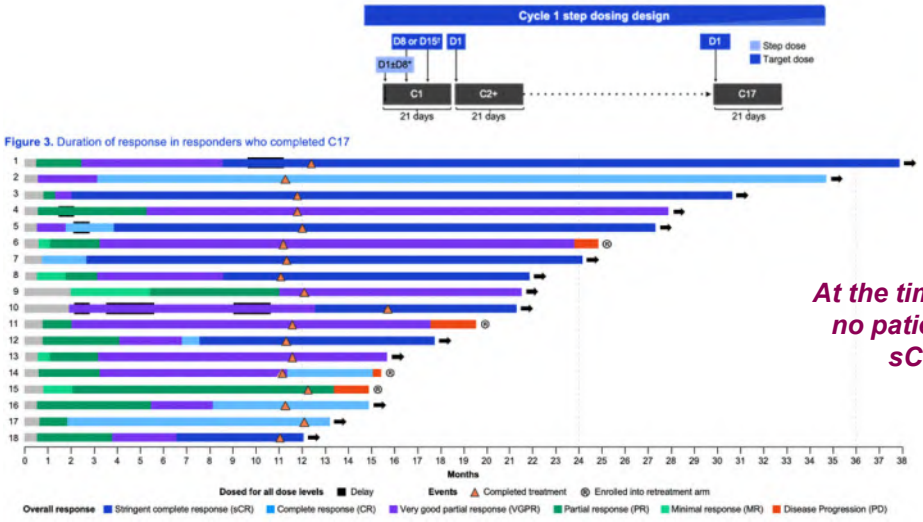
Fixed-Duration Therapy With Cevostamab



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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Expected Toxicities With Bispecific Antibodies

Cytokine release syndrome (CRS)

Infections

Cytopenias

Neurotoxicity (ICANS)

ICANS, immune effector cell-associated neurotoxicity syndrome

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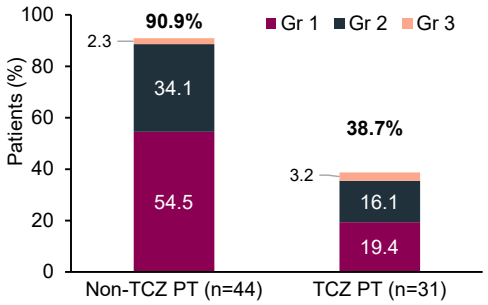
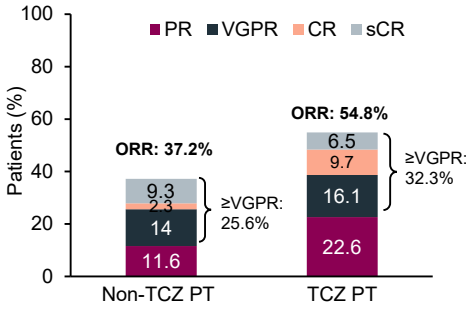
Pretreatment With Tocilizumab Reduces Incidence and Severity of Cytokine Release Syndrome With Cevostamab

Phase 1 study evaluating the use of tocilizumab (an IL-6 antibody) prior to the first dose of cevostamab.



Significantly lower rate of CRS in the TCZ PT group



TCZ PT had no negative impact on response rates

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

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Bispecific Antibodies Are Associated With an Increased Risk of Infections

A pooled analysis of 1,185 RRMM patients in 11 different clinical trials treated with single agent bispecific antibodies (with no prior use of different bispecifics)

Majority of patients (72%) treated with BCMA-targeted bispecific antibodies

	Patients (%)	
Adverse event	**All grades**	**Grade 3/4**
Neutropenia	38.6	34.8
Infections	50	24.5
CRS	59.6	NR
Pneumonia	NR	10
COVID-19	NR	11.4

Hypogammaglobulinemia occurred in 75.3% of patients with intravenous immunoglobulin used in 48%.

Death was reported in 110 patients of which 28 (25.5%) were reported to be secondary to infections.

Certain precautions should be used when using bispecific antibodies to mitigate the risk and/or identify and treat infections promptly.

NR, not reported

Lancman G et al. *Blood Adv*. March 1, 2023 [Online ahead of print].

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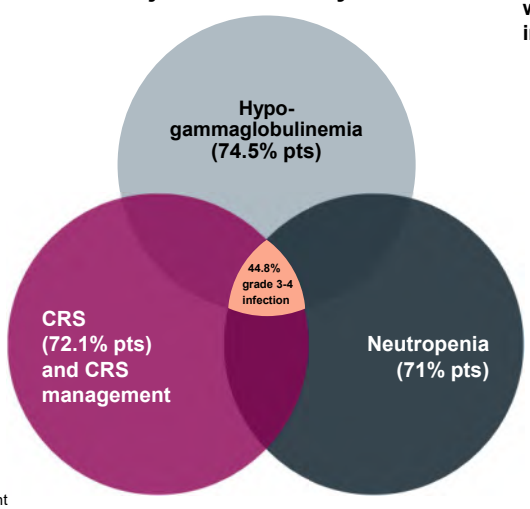
Bispecific Antibodies: Infection Risk and Current Mitigation Strategies

- **CRS can mask signs of infection**
  - Tocilizumab and steroids are used for CRS treatment and prevention but are also immunosuppressive
  - These agents can increase the risk of infections as well as masking signs of infection
- **Neutropenia is an established risk for infection**
  - Bispecific antibodies activate effector T cells and may activate immunosuppressive T regulatory cells
  - These T regulatory cells are postulated to be responsible for cytopenias seen with bispecific antibody therapy
  - Tocilizumab is known to induce neutropenia

MajesTEC-1 Safety Data



- **Hypogammaglobulinemia is linked with increased risk of severe infections, particularly:**
  - Bacterial infections
  - Respiratory tract infections
  - GI infections
  - Viral infections

CRS, cytokine release syndrome; GI, gastrointestinal; pt, patient

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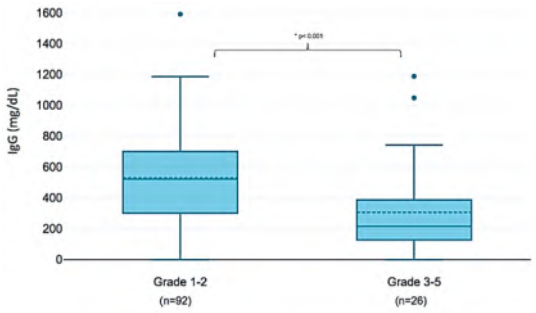
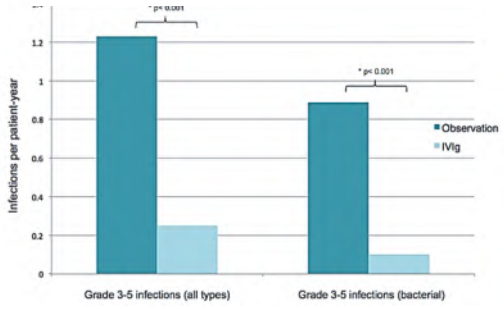
IVIG Infusion Reduces Risk of High-Grade Infections

IgG levels at time of infection and severity



Grade 3–5 infection with or without IVIg use



- Serious infections are very common, including opportunistic infections (eg, CMV, PCP)
- Infection risk continues to accumulate over time, even in deep remissions
- Profound hypogammaglobulinemia/agammaglobulinemia is universal in responders
- IVIg appears to be largely protective for severe infections

Lancman et al, *Blood Cancer Discovery* 2023

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Infection Prevention

- Avoid crowds
- Ensure handwashing, hygiene
- Growth factors
- IVIG for hypo-gammaglobulinemia
- Immunizations (no live vaccines)
- COVID-19 prevention
- Zoster and PJP prophylaxis
- Consider CMV monitoring

IVIG, intravenous immunoglobulin; PJP, *Pneumocystis jirovecii* pneumonia; CMV, cytomegalovirus

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Cevostamab Combinations: Cevostamab-Pomalyst-Dexamethasone in Relapsed/Refractory Myeloma

- Phase 1b study (CAMMA 1) in RRMM (≥2 prior lines of therapy, including ≥1 IMiD and ≥1 proteasome inhibitor)
- 8 patients received treatment with cevostamab (intravenously), Pomalyst, and dex.

	Cevostamab-Pom-Dex (n=8)
Overall response rate, n	8 (100%)
CR	1 (12.5%)
VGPR	3 (37.5%)
PR	4 (50%)
Adverse events (grade 3/4), n	7 (87.5%)
Neutropenia	Gr 3: 1 (12.5%) Gr 4: 3 (37.5%)
CRS	All Gr: 7 (87.5%) Gr 3: 2 (25%)

Jelinek T et al. *Clin Lymphoma Myeloma Leuk*. 2023;23. Abstract P-019.

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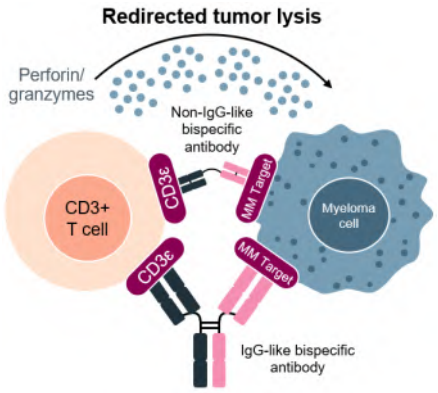
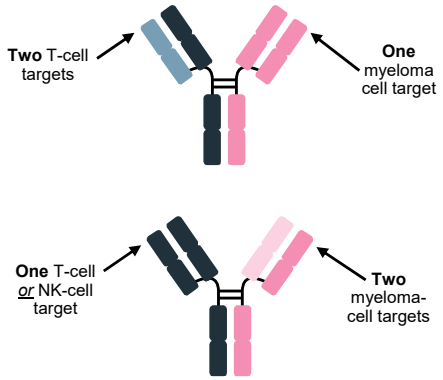
Evolution of Bispecific Antibodies

Bispecific antibodies: dual targets



Trispecific antibodies: triple targets



Lancman G et al. *Hematology Am Soc Hematol Educ Program.* 2020;2020:264.

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Key Points

- Bispecific antibodies are very active even in heavily pretreated patients.
- Side effects of bispecific antibodies include cytokine release syndrome, confusion, and low blood counts, and confusion (rare)—all of which are treatable.
- Infections have emerged as a more challenging toxicity but, with experience, strategies are forming to mitigate the risks.
- Bispecific antibodies represent an off-the-shelf immunotherapy; three bispecific antibodies have been approved since October 2022.
- Several additional bispecific antibodies are under clinical evaluation. Different bispecifics and different targets are on the way.

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Patient Experience

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Questions & Answers

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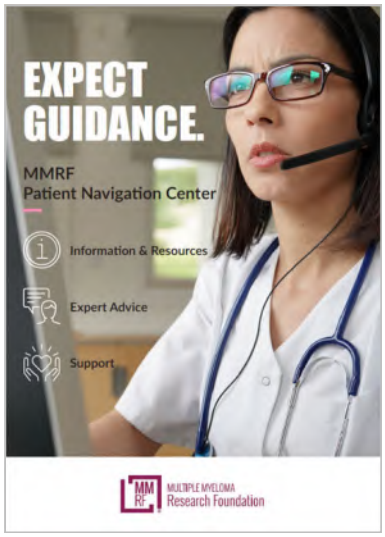
MMRF Patient Resources



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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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Learn more and find your event today!
themmrf.org/get-involved/mmrf-events

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Upcoming Patient Education Events
Save the Date

Program	Date and Time	Speakers
International Myeloma Society Annual Meeting FAQs *Livestream*	Tuesday, October 17 4:00 PM – 5:00 PM (ET)	Jesus Berdeja, MD Nick Barkemeyer, PA
Patient Summit *Virtual*	Saturday, October 21 11:00 PM – 4:00 PM (ET) 9:00 AM – 2:00 PM (MT)	Gurbakhash Kaur, MD Amrita Krishnan, MD Robert Rifkin, MD
Non-BCMA Bispecific Antibodies FAQs *Livestream*	Monday, October 30 2:00 PM – 3:00 PM (ET)	Hearn Jay Cho, MD, PhD
Patient Summit *Boston, MA*	Saturday, November 11 9:00 AM – 2:00 PM (ET)	Shonali Midha, MD Clifton Mo, MD Omar Nadeem, MD Kim Noonan, NP 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/educational-resources**

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Genentech
A Member of the Roche Group

janssen

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Resources

- Resource tab includes
  - 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

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Thank you!

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