TREATING MULTIPLE MYELOMA WITH T-CELL DIRECTED THERAPY: BISPECIFIC ANTIBODIES

May 24, 2023

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WELCOME AND INTRODUCTIONS

Lesley Hoerst, BSN, RN
Senior Manager, Professional Education Programs
The Leukemia & Lymphoma Society

This activity is supported by Janssen Oncology.

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LEARNING OBJECTIVES

After completing this activity, the participant should be better able to:

- **Explain treatment options and provide an overview of the latest developments in therapy for patients with myeloma, focusing on refractory disease**
- **Interpret the clinical significance of new and emerging data regarding T-cell therapy**
- **Identify patients who are candidates for bispecific antibody therapy**
- **Explain the HCP's role in preparing the patient for therapy, administering treatment, and monitoring for and managing side effects**
- **List education and support resources for patients and caregivers and how to access them**

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SPEAKER

Saad Z. Usmani, MD, MBA, FACP

Chief, Myeloma Service
Memorial Sloan Kettering Cancer Center
New York, NY

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DISCLOSURES

- **Research funding:** Amgen, Array Biopharma, BMS, Celgene, GSK, Janssen, Merck, Pharmacyclics, Sanofi, Seattle Genetics, SkylineDX, Takeda.
- **Consulting:** Abbvie, Amgen, BMS, Celgene, EdoPharma, Genentech, Gilead, GSK, Janssen, Oncopeptides, Sanofi, Seattle Genetics, SecuraBio, SkylineDX, Takeda, TeneoBio.
- **Speaker:** Amgen, BMS, Janssen, Sanofi.

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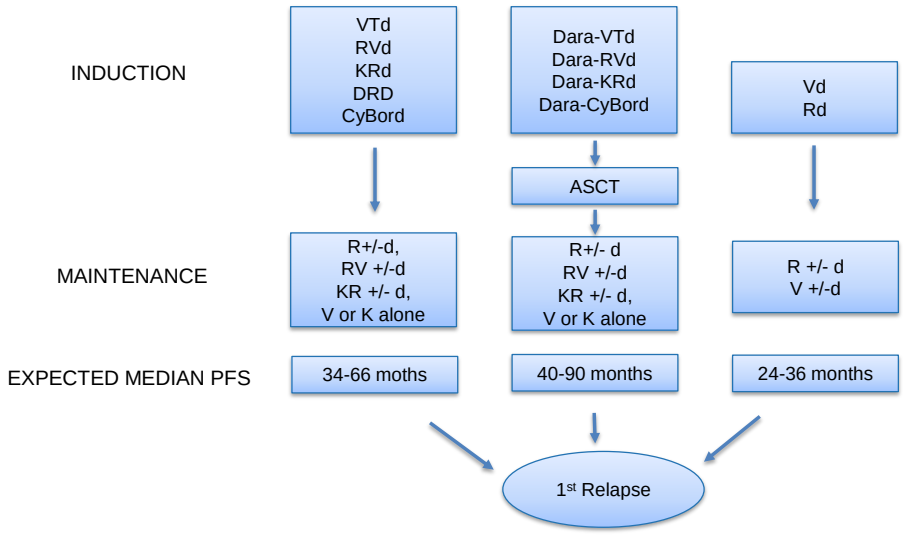
JOURNEY TO THE FIRST RELAPSE



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FACTORS IN SELECTING RELAPSED THERAPY

Patient	Disease	Treatment

• Age
• Performance status
• Renal insufficiency
• Poor marrow reserve
• Neuropathy
• Comorbidities
  • Cardiac disease
  • Diabetes
	• Risk Status
	• Cytogenetics
	• del [17p], t(4;14), t(14;16)
	• Rapidity of relapse
	  • Rate of rise
	  • Organ damage
	  • Extramedullary disease
	  • Plasma cell leukemia
		• Previous therapy
		  • Depth
		  • Duration
		• Route of administration
		• Single or combination
		• Cost
		• Toxicity
		  • Myelosuppression
		  • Neuropathy
		  • Thrombosis
		• Risk of SPM

SPM: secondary primary malignancy

Dimopoulos MA, et al. *Nat Rev Clin Oncol* 2015;12(1):42-54; Baz R, et al. *Support Care Cancer* 2015;23(9):2789-2797; Agarwal A et al. *Clin Lymphoma Myeloma Leuk.* 2017;17(2):69-77.

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WHICH FACTOR IS NOT AS IMPORTANT IN SELECTING RELAPSED THERAPY?

A. **Caregiver support**

B. **Performance status**

C. **Cytogenetics**

D. **Previous therapy**

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WE HAVE MANY OPTIONS!

Lenalidomide combinations

- Carfilzomib, lenalidomide, dexamethasone (KRd)
- Ixazomib, lenalidomide, dexamethasone (IRd)
- Elotuzumab, lenalidomide, dexamethasone (EloRd)
- Daratumumab, lenalidomide, dexamethasone (DRd)

Carfilzomib combinations

- Daratumumab, carfilzomib, dexamethasone (DKd)
- Isatuximab, carfilzomib, dexamethasone (IRd)
- Carfilzomib, dexamethasone (Kd) with or without cyclophosphamide

Pomalidomide combinations

- Carfilzomib, pomalidomide, dexamethasone (KPd)
- Elotuzumab, pomalidomide, dexamethasone (EloPd)
- Daratumumab, pomalidomide, dexamethasone (DPd)
- Isatuximab, pomalidomide, dexamethasone (IsaPd)

Other notable combinations

- Selinexor, bortezomib, dexamethasone (SVd)
- Off-label use of venetoclax, dexamethasone for translocation (11;14) (VenD)

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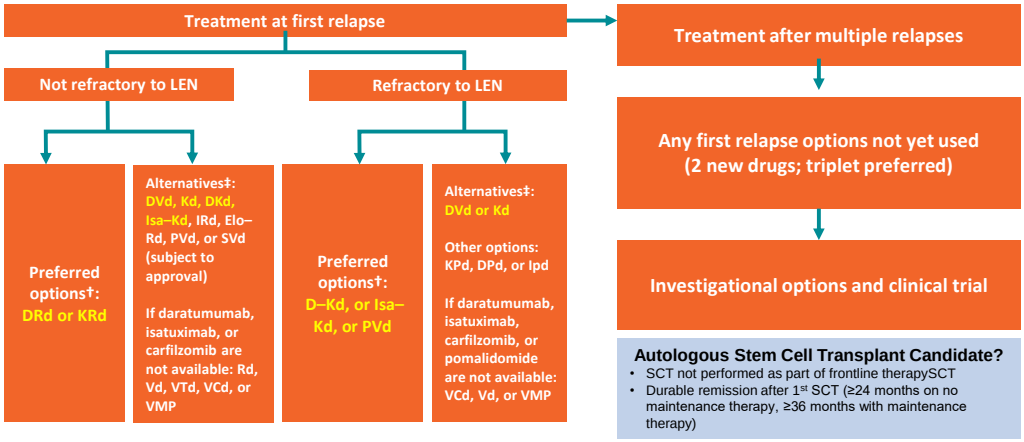
IMWG GUIDELINES：TREATMENT AT RELAPSE



Moreau P et al.*Lancet Oncol* 2021; 22: e105–18.

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BISPECIFIC MONOCLONAL ANTIBODIES

- Concept originated in the early 1960s. [Nisnoff A et al. Science 1960;132:1770-1].
- Human trials:
  - 1990: GBM, specificity for glioma antigen and T-cell receptor
  - 1995: NHL, CD19 x CD3, no clinical response and first recognition of CRS
  - 1997: HL, CD30 x CD16 (NK cell activating) showed clinical responses
  - 2001: Blinotumumab, a CD19x CD3 bispecific antibody enters clinical trials – trial terminated due to CRS
  - 2004: Blinatumomab phase I escalation trial begins in 2004 with first clinical responses at 15 mg/m2/day dosing.
  - 2006-2008: Compassionate use program begins for heavily pre-treated pediatric ALL, clearance of CD19+ peripheral blood and BM at very low doses.
  - 2014: Blinotumumab becomes the first FDA and EMA approved bispecific construct for the treatment of relapsed and refractory (r/r) ALL. Full Approval in 2017.
  - 2022: > 200 Bispecific constructs in development, 7 that are FDA/EMA approved.

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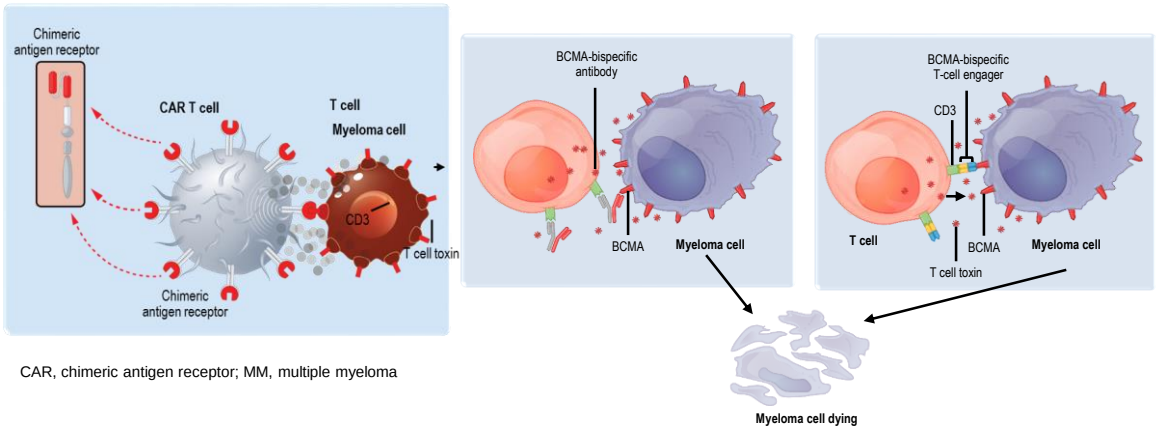
THIS IS THE AGE OF IMMUNE THERAPY IN MM THERAPEUTICS – OUR COLLECTIVE AIM IS CURE.



CAR, chimeric antigen receptor; MM, multiple myeloma

Adapted from Cho S-F et al. *Front Immunol*. 2018;9:1821.

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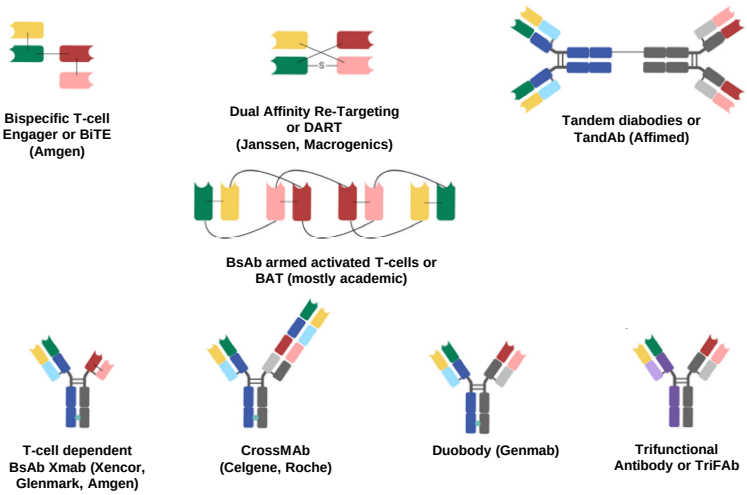
BISPECIFIC ANTIBODIES (BSABS) – MANY DIFFERENT PLATFORMS



Bispecific T-cell Engager or BiTE (Amgen)

Dual Affinity Re-Targeting or DART (Janssen, Macrogenics)

Tandem diabodies or TandAb (Affimed)

BsAb armed activated T-cells or BAT (mostly academic)

T-cell dependent BsAb Xmab (Xencor, Glenmark, Amgen)

CrossMAb (Celgene, Roche)

Duobody (Genmab)

Trifunctional Antibody or TriFAb

Adapted from Lejeune M et al. *Front Immunol* 2020 11:762.

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PROS/CONS OF BISPECIFICS

Pros:

- Off the shelf
- Low grade cytokine release syndrome (CRS)
- Low incidence of neurotoxicity (NT)
- Many targets: BCMA, GPRC5D, FCRH5
- Ability to combine with other mechanisms of actions

Cons:

- Not every patient is responding to BsAbs.
- Continuous therapy model associated with infection risk
  - Hypogammaglobulinemia requiring IVIg administration
  - VZV/PJP Prophylaxis
- Logistic challenges for community at large during first cycle of monitoring and managing CRS/NT

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WHAT IS ONE PRO TO BISPECIFIC THERAPY?

A. High incidence of neurotoxicities and CRS

B. Off the shelf

C. Cannot combine with other agents

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TECLISTAMAB – 1ST EMA/FDA APPROVED BSAB FOR MM

Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study *Lancet* 2021; 398: 665-74

Saad Z Usmani, Alfred L Garfall, Niels W C J van de Donk, Hareth Nahi, Jesus F San-Miguel, Albert Oriol, Laura Rosinol, Ajai Chari, Manisha Bhutani, Lionel Karlin, Lotfi Benboubker, Lixia Pei, Raluca Verona, Suzette Girgis, Tara Stephenson, Yusri Elsayed, Jeffrey Infante, Jenna D Goldberg, Arnob Banerjee, Maria-Victoria Mateos, Amrita Krishnan

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 11, 2022 VOL. 387 NO. 6

Teclistamab in Relapsed or Refractory Multiple Myeloma

P. Moreau, A.L. Garfall, N.W.C.J. van de Donk, H. Nahi, J.F. San-Miguel, A. Oriol, A.K. Nooka, T. Martin, L. Rosinol, A. Chari, L. Karlin, L. Benboubker, M.-V. Mateos, N. Bahlis, R. Popat, B. Besemer, J. Martínez-López, S. Sidana, M. Delforge, L. Pei, D. Trancucci, R. Verona, S. Girgis, S.X.W. Lin, Y. Olyslager, M. Jaffe, C. Uhlar, T. Stephenson, R. Van Rampelbergh, A. Banerjee, J.D. Goldberg, R. Kobos, A. Krishnan, and S.Z. Usmani

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SUMMARY OF BCMA BISPECIFIC ANTIBODIES

	Teclistamab (n=165)	Linvoseltamab (n=167)	ABBV-383 (n=118)	Elranatamab (n=123)	Alnuctamab (n=68)
Route	SC	IV	IV	SC	SC
Dose and schedule	1.5mg/kg/QW	Q1W x 16w W≥16: Q2W	Q3W	76mg/Q1W C≥7: Q2W if PR	Q1W x 8 w Q2W C3-C7 C≥7 Q4W
Median prior LoT	5 (2-14)	6 (2-17)	5 (1-15)	5 (2-12)	4 (3-11)
Triple refractory	77.6%	90%	61%	96%	63%
CRS, G≥3	72.1%, 0.6%	47.9%, 0.6%	54%, 3%	57.7%, 0%	53%, 0%
Neurotoxicity, G≥3	3%, 0	4%, 0	NR, 6 pts	4, 3.4	2 pts, 3%
Infections, G≥3	76.4%, 44.8%	NR	32%, 17%	66.7%, 35%	34%, 9%
ORR (%)	63%	75% 200-800 mg	60%/81%* *at ≥40 mg	61%	53%
≥CR (%)	39.4%	16%	20%/30%*	27.6%	23%
Median PFS (m) (95% CI)	11.3 m (8.8-17.1)	Not reported	Not reported	NE (10.4-NE)	Not reported
Median DoR (m) (95% CI)	18.4 m (14.9-NE)	Not reached	Not reported	NE (12.0-NE)	Not reported
MRD – (10^{-5})	26.7%	4/10	Not reported	90.9% (n=22)	16/20

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Moreau P et al. NEJM 2022; Bahlis N et al. ASH 2022; Wong S et al. ASH 2022; Voorhees PM et al. ASH 2022 ;

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SUMMARY OF NON-BCMA BISPECIFIC ANTIBODIES

	Talquetamab (n=288)		Forimtamig (n=57)	Cevostamab (n=157)
Target	GPRC5d-CD3		2+1 GPRC5d-CD3	FcRH5-CD3
Route	SC (n=143)	SC (N=145)	SC	IV
Dose and schedule	0.4 mg/kg QW	0.8mg/kg Q2W	1200-7200 mcg/kg Q2W	Q3W
Median prior LoT	5 (2-13)	5 (2-17)	4 (2-14)	6 (2-18)
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Infections, G≥3	57.3%, 16.8%-	50.3%, 11.7%	45.6%, 26.4%	45%, ND
ORR (%)	74.1%	73.1%	63.6%	56.7% 132-198mg
≥CR (%)	33.6%	32.4%	25.5%	8.4%
Median PFS (m) (95% CI)	7.5 (5.7-9.4)	11.9 (8.4-NE)	NR	NR
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MRD – (10^{-5})	NR	NR	10/14	7/10

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Chari A et al. NEJM 2023; Carlo-Stella et al. ASH 2022; Trudel S et al. ASH 2021.

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SUMMARY OF BISPECIFIC ANTIBODIES – INFECTIONS

	Teclistamab n=165	Elranatamab n=123	Alnuctamab n=68 (sc)	ABBV-838 n=118	Talquetamab n=288 [0.4-0.8mg/kg]*	Cevostamab n=161	Forimtamig n=57 (SC)
Median FUP (months, m)	14.1 m	10.4 m	4.1 m	4.3 – 8.0m	14.9 – 8.6 m	8.8 m	8.0m
Overall, n (%)	126 (76.4)	82 (66.7)	23 (34)	38 (32)	57.3%-50.3%	45%	26 (45.6)
Grade 3-4, n (%)	74 (44.8)	43 (35)	6 (9)	20 (17)	16.8%-11.7%	ND	15 (26.4)
Bacterial	ND	ND	ND	ND		ND	ND
Fungal	ND	ND	ND	ND		ND	ND
Viral	ND	ND	ND	ND		ND	ND
Opportunistic infections						ND	ND
1. PJP	6 patients	6 (4.9)	ND	ND	5(3.5%)–4(2.8%)		
2. CMV	NR (*1 patients with Adenoviral pneumonia)	10 (8.1)	ND	ND	ND 3 patients		
COVID infections, n (%)						ND	
Overall	29 (17.6)	31 (25.2)	ND	ND	13(9.1) – 16(11)		12 (24.6)
Grade 3-4	20 (12.1)	14 (11.4)	ND	ND	0.7% - 2.1%		2 (3.6)
Infectious death, n (%)	16/27	NR	ND	4 pts	NR	ND	ND

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Moreau P et al. NEJM 2022; Lesokhin A et al. ASH 2022. ; Wong S et al. ASH 2022; Voorhees PM et al. ASH 2022; Chari A et al. NEJM 2023; Carlo-Stella et al. ASH 2022; Trudel S et al. ASH 2021

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PROS/CONS OF BISPECIFICS

Pros:

- Off the shelf
- Low grade cytokine release syndrome (CRS)
- Low incidence of neurotoxicity (NT)
- Many targets: BCMA, GPRC5D, FCRH5
- Ability to combine with other mechanisms of actions

Cons:

- Not every patient is responding to BsAbs.
- Continuous therapy model associated with infection risk
  - Hypogammaglobulinemia requiring IVIg administration
  - VZV/PJP Prophylaxis
- Logistic challenges for community at large during first cycle of monitoring and managing CRS/NT

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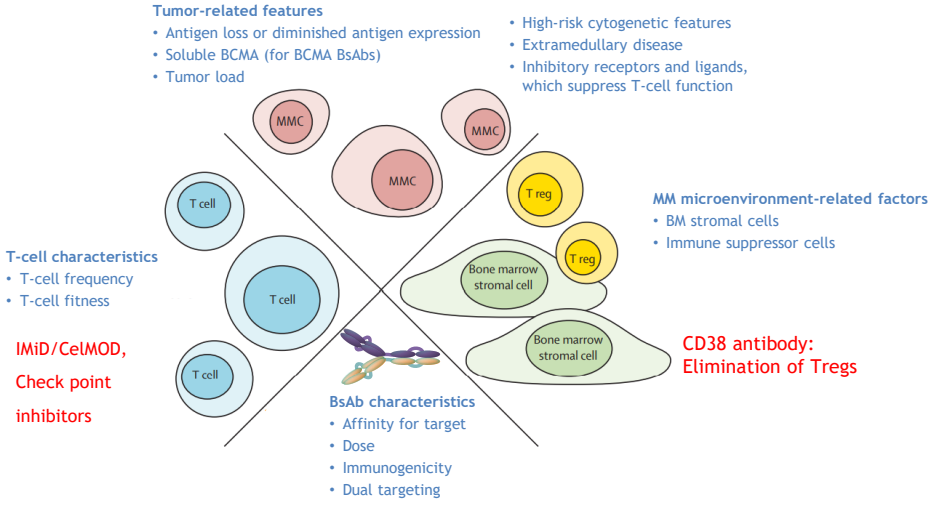
MECHANISMS OF RESISTANCE TO BSABS



BCMA, B-cell maturation antigen; BM, bone marrow; BsAb, bispecific antibody; IMiD, immunomodulatory drug; MMC, multiple myeloma cell; Tregs, regulatory T-cells

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Adapted from: van de Donk N, Themeli M, Usmani SZ. *Blood Cancer Discov* 2021;2:302–18

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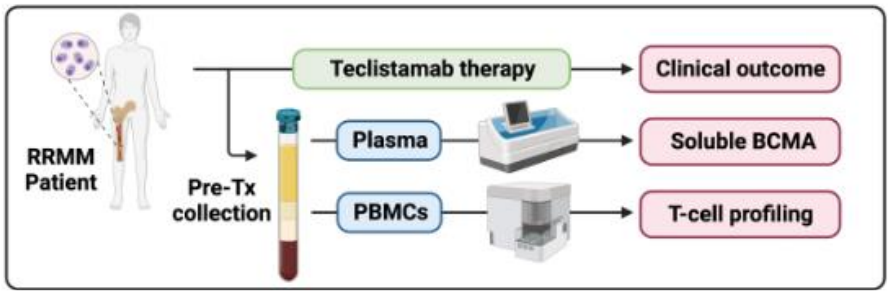
COMMERCIAL TECLISTAMAB USE AT MSKCC



Firestone R et al. ASCO 2023; Firestone R et al EHA 2023

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THE IMMUNOTHERAPY QUADRAFECTA
(BCMA CAR-T, BCMA BISPECIFIC, GPRC5D BISPECIFIC, FCRH5 BISPECIFIC)

IgA lambda plus lambda MM: Dx: 07/01/11 DS IIIA ISS unknown Cytogenetics 46, XX FISH unknown

Line 1: July 12, 2011: VelDex x 3 → VCD with VGPR followed by SCH. VRD x 3 cycles beginning January 2012
ASCT 06/05/12
Maintenance len-dex Nov 2012 –March 2014

Line 2: March 2014 VRD

Line 3: 11/24/14 Panobinostat Rd

Line 4: 7/8/15 Dara/Pom/Dex

Line 5: 2/25/16 Carfilzomib/ibrunitinb

Line 6: 12/14/16 Selinexor

Line 7: 6/10/17 VDCEP

Line 8: 7/10/17 BCNU 200 + mel 100 ASCT with pazopanib maintenance

Line 9: 1/11/18 **Talquetamab**

Line 10: 4/23/18 **BCMA CAR T**

Line 11: 8/17/20 **Teclistamab+Dara**

Line 12: 8/31/21 **Cevostamab**

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Courtesy Dr. Joshua Richter

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IMWG Guidelines in development, stay tuned!

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THE CASE FOR FIXED DURATION TREATMENT WITH BISPECIFIC ANTIBODIES

75 yo RRMM s/p 16 lines, diagnosed in 2001
Line 1: VAD induction, Mel-ASCT, PR
Line 2: Thal-Dex, PR
Line 3: Bor-Dex, PR
Line 4: Len-Dex, PR
Line 5: Bor-Dex, PR
Line 6: Cyclo-Dex, SD
Line 7: CyBorD, SD
Line 8: RVd, PR
Line 9: RVd-Cy, PR
Line 10: Bendamustine-Bor-Dex, SD
Line 11: Rd, MR
Line 12: Pom-Cy-Dex, SD
Line 13: Dara, MR
Line 14: Dara-Pom-Dex, PR
Line 15: Dara-Pom-Cy-Dex. PR
Line 16: Teclistamab in summer 2019.

- Off s/p 8 cycles due to recurrent URIs, last dosed 01/2020
- Remained off therapy until late 2022, MRD-ve by NGS and flow at 10^{-5}

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PROS/CONS OF BISPECIFICS

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WHAT IS ONE CON TO BISPECIFIC THERAPY?

A. No risk of infection

B. No challenges to monitoring for neurotoxcities and CRS

C. Not every patient is responding to bispecifics

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COMMERCIAL TECLISTAMAB USE AT MSKCC


- **Oct-Nov 2022:** P/T Committee packet for institutional approvals, SOP development, staff training, REMS registration, etc.
- **Phase I (Nov 2022-March 2023):** Inpatient monitoring , assess safety data.
- **Phase II (April 2023-onwards):** Early discharge after step-up dosing all pts, early intervention with Toci for persistent fevers.
- **Phase III (June 2023-onwards):** All outpatient dosing for selected pts
- **Dosing schedule:** Response adapted reduction in dosing frequency.

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CART VS BSAB: IT IS NOT A COMPETITION…

	CART	Bispecifics Ab
Data	Emerging Phase III data	
Cost	$$$$	$$$
Manufacturing concerns	Yes	No
Available Globally		
Non-relapse mortality		
Long-term safety data	No, NT a concern	No, infections a concern

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MSKCC MYELOMA SERVICE

Saad Z. Usmani (Chief)
High-Risk Disease , Disparities
TCE, CAR T Cells
Checkpoint Inhibitors
Developmental Therapeutics

Carlyn Tan
MM Precursor diseases
Supportive Care
Bone Health

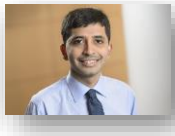
Urvi Shah
MM Precursor Disease
Nutrition & Modifiable
Risk Factors
Early Relapse

Kylee Maclachlan
MM Precursor Disease,
NDMM Trials
Genomics, Immune
Profiling

Neha Korde
NDMM Clinical Trials
Digital Wearables
Supportive Care

Alex Lesokhin
RRMM Immunotherapy
TCE, Checkpoints Inhibitors
Neoantigens
Microbiota, Immune
Profiling

Hani Hassoun
MM Supportive Care
Alliance Liaison
NDMM/RRMM Trials
Elderly and Frail



Sham Mailankody
RRMM Trials with
CAR T Cells
High-Risk Disease

Malin Hultcrantz
RRMM Trials in TCR
Antibody drug conjugates
Epidemiology

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MSKCC MYELOMA TCT PROGRAM

Sergio Giralt
Allo/Auto HCT for
MM
New Regimens
CAR T Cells

David Chung
T Cell exhaustion
Auto HCT + Vaccines
MM Immunotherapies

Gunjan Shah
HCT Toxicities
Precision Drug Dosing
CAR T Cells
Salvage Auto and Allo HCT

Saad Z. Usmani
High-Risk Disease Biology/Trials
CAR T Cells
Auto HCT for MM

Michael Scordo
HCT Toxicities
Precision Drug
Dosing
CAR T Cells

Heather Landau
Amyloidosis
HCT Toxicities
Homebound HCT
Precision Drug Dosing
Novel Regimens for Salvage
Auto

Oscar Lahoud
Auto HCT and CAR T Cells
Post HCT Therapies

Parastoo Dahi
Auto HCT and CAR T Cells
Post HCT Therapies

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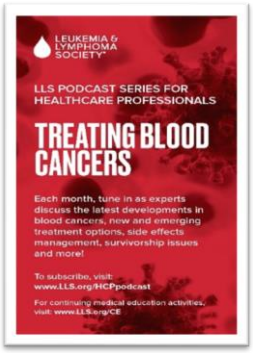
FREE LLS RESOURCES FOR HEALTHCARE PROVIDERS

- CME and CE courses: www.LLS.org/CE
- Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- Videos for HCPs: www.LLS.org/HCPvideos
- Podcast series for HCPs: www.LLS.org/HCPpodcast



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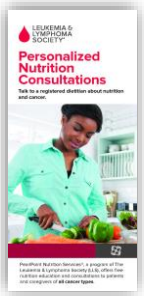
FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).
- **Clinical Trial Nurse Navigators** – RNs and NPs provide a personalized service for patients seeking treatment in a clinical trial, sift through the information and provide information to bring back to their HC team (CTSC).
  - www.LLS.org/CTSC
- **Registered Dieticians** – (LLS) provides PearlPoint Nutrition Services® to patients/caregivers of all cancer types, free nutrition education and one-on-one consultations by phone or email.
  - www.LLS.org/Nutrition
- **Reach out Monday–Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: infocenter@LLS.org
  - HCP Patient Referral Form: www.LLS.org/HCPreferral



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FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- **Webcasts, Videos, Podcasts, Booklets**:
  - www.LLS.org/Webcasts
  - www.LLS.org/EducationVideos
  - www.LLS.org/Podcast
  - www.LLS.org/Booklets
- **www.LLS.org/Myeloma**
- **Support Resources**
  - Financial Assistance: www.LLS.org/Finances
  - Other Support: www.LLS.org/Support
    - LLS Regions
    - Online Weekly Chats Facilitated by Oncology SW
    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program

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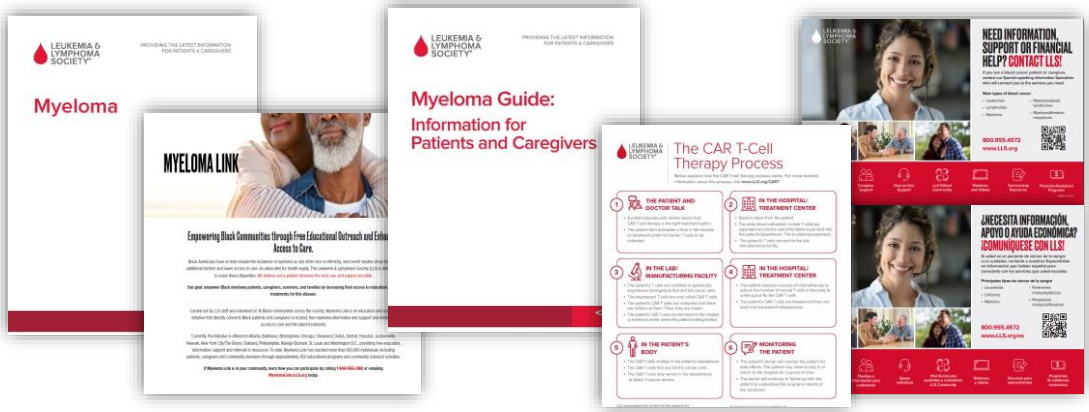
FREE LLS RESOURCES FOR YOUR PATIENTS



www.LLS.org/Myelomalink

BOOKLETS AND FACT SHEETS
English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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Q & A

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