BISPECIFIC THERAPY: ADVANCING PATIENT CARE THROUGH TARGETED TREATMENT

March 11, 2025

Jointly provided by The Leukemia & Lymphoma Society and Postgraduate Institute for Medicine

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WELCOME AND INTRODUCTIONS

Elise Curry, BA, BSN, RN, OCN
Clinical Trial Nurse Navigator,
Clinical Trial Support Center
The Leukemia & Lymphoma Society

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LEARNING OBJECTIVES

- Describe the underlying science and mechanisms of bispecific therapies
- Identify current and emerging indications for bispecific therapies for hematologic malignancies
- Assess the clinical evidence on the efficacy, safety, and potential side effects of bispecific therapies
- Develop strategies for incorporating bispecific therapies into clinical practice
- Describe the treatment process and mechanisms to improve patient understanding, care, and involvement
- Discuss challenges and potential future advancements in bispecific antibody development

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CE DESIGNATION

Joint Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and The Leukemia & Lymphoma Society. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Continuing Medical Education

The Postgraduate Institute for Medicine designates this CME activity for a maximum of 1 *AMA PRA Category 1 Credit*(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Registered Nursing Credit Designation

Approval for nurses has been obtained by the National Office of The Leukemia & Lymphoma Society under Provider Number CEP 5832 to award 1.0 continuing education contact hour through the California Board of Registered Nursing.

Approval for Nurses has been obtained by The Leukemia & Lymphoma Society under provider number 50-12996, Expires: 10/31/2026, to award 1.0 continuing education contact hour through the Florida Board of Nursing.

Continuing Physician Assistant Education

Postgraduate Institute for Medicine has been authorized by the American Academy of PAs (AAPA) to award AAPA Category 1 CME credit for activities planned in accordance with AAPA CME Criteria. This activity is designated for 1 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation.

Interprofessional Continuing Education

This activity was planned by and for the healthcare team, and learners will receive 1 Interprofessional Continuing Education (IPCE) credit for learning and change.

IPCE CREDIT™

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SPEAKERS

Luciano Costa, MD, PhD
Professor of Medicine
Mary and Bill Battle Professor of Multiple Myeloma
The University of Alabama at Birmingham
Birmingham, AL

Peter Martin, MD
Professor of Medicine
Chief of the Lymphoma Program
Weill Cornell Medicine
New York, NY

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DISCLOSURE INFORMATION

- **Luciano Costa** reports Grant/Research Support from BMS, Johnson & Johnson, Pfizer, AbbVie, Caribou, Genentech, and Gracel, and Consultant/Advisory Board for BMS, Johnson & Johnson, Pfizer, AbbVie, Caribou, Genentech, Regeneron, Adaptive Biotechnologies, and AstraZeneca.
- **Peter Martin** reports Consultant/Advisory Board for Abbvie, AstraZeneca, Beigene, BMS, Genentech, Janssen, Pepromene, and Merck
- **Elise Curry** reports Patient advisory board member for Viracta Pharmaceuticals with compensation provided to LLS.

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METHOD OF PARTICIPATION

Learners must participate in the entire activity and complete and submit the evaluation form to earn credit. Once completed, the certificate will be generated. If you have questions regarding the receipt of your certificate, please contact us via email at ProfEducation@LLS.org.

There are no fees for participating in or receiving credits for this activity.

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Bispecific Antibodies in Multiple Myeloma

Luciano J. Costa, MD, PhD
Mary and Bill Battle Professor of Multiple Myeloma
University of Alabama at Birmingham
Birmingham, AL

O'NEAL COMPREHENSIVE CANCER CENTER
UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
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Therapeutic bispecific T-cell engagers in use in myeloma share the following characteristic:

a) They all bind to BCMA in the malignant plasma cell.
b) They all have weight-based dosing.
c) They are all administered subcutaneously.
d) They do not require step-up dosing.
e) They can only be administered inpatient.

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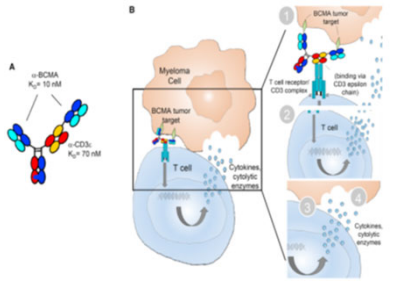
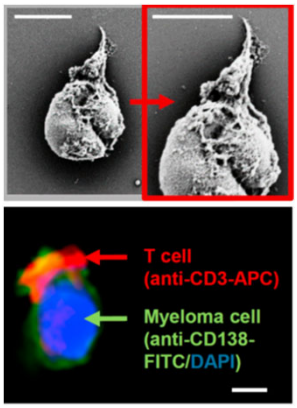
The Immunologic Synapsis





- Target clustering
- CD45 phosphatase exclusion from the synapsis
- TCR firing including ZAP70 translocation

Seckinger A et al. *Cancer Cell*. 2017;31:396-410.

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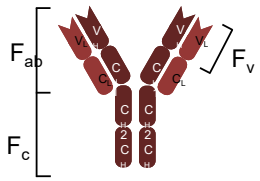

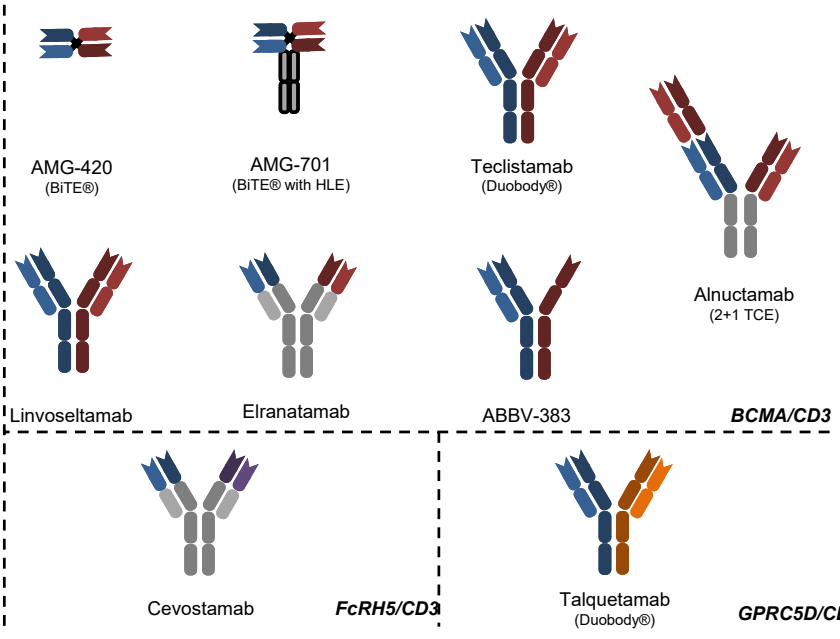

Image created by the speaker.

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Acute Immune-related Toxicities: CRS and ICANS

Cytokine Release Syndrome

Signs/symptoms of mass inflammation
- **Fever** – cardinal sign
- **Hypoxia and/or hypotension** – presence and severity guide CRS grading system
- Accompanying symptoms vary

Management
- **Rule out infection**
- **Tocilizumab** – first line; anti-IL6
- **Corticosteroids** – add if refractory
- Critical care interventions at higher grades

ICANS

Neurologic and cognitive signs
- **ICE score decline** – cardinal sign
- **Altered consciousness and seizure** – presence and severity guide ICANS grading system

Management
- **Frequent neurological assessment**
- **Corticosteroids** – first line
- Critical care interventions at higher grades

ICE, immune effector cell encephalopathy.
Santomasso BD et al. *J Clin Oncol.* 2021;39:3978-3992.

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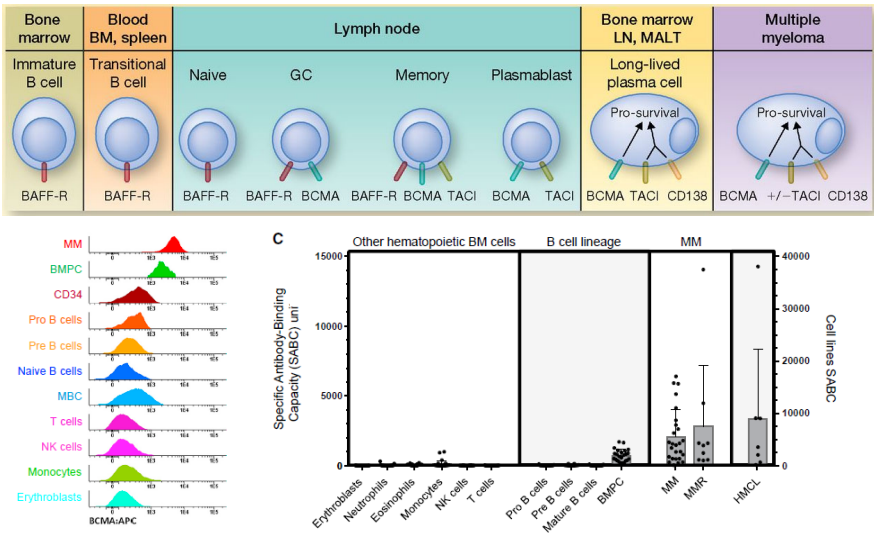
B-cell Maturation Antigen (BCMA)



Seckinger A. *Cancer Cell* 31:1, 2017.

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MajesTEC-1: Phase 1/2 Study Of Teclistamab in RRMM

N = 165
at RP2D in phase 1 and 2

Key inclusion criteria:
- ≥ 3 prior lines including PI, IMiD, and anti-CD38 mAb
- No prior BCMA-directed therapy

Baseline characteristics
- Median age 64 y
- Median 5 prior lines
- 26% high-risk cytogenetics
- 78% triple-refractory
- 30% penta-refractory

BCMA × CD3

Teclistamab administration IV or SC

Step-up interval
2 to 4 days between doses

28-d cycles until progression

0.06 mg/kg → **0.3 mg/kg** → **1.5 mg/kg** → **1.5 mg/kg weekly**

Option to switch to dosing every 2 weeks if ≥ CR for ≥ 6 months

Primary endpoint: ORR

Moreau P et al. *N Engl J Med*. 2022;387:495-505.
Sidana S et al. *HemaSphere*. 2023;7:1654-1655.

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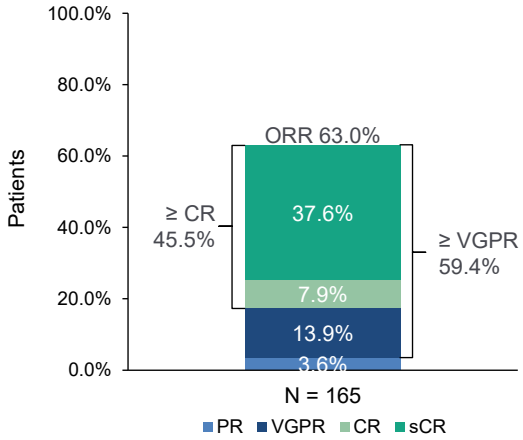
MajesTEC-1: Phase 1/2 Study Of Teclistamab in RRMM

Response Rates
Median follow-up 23 mo



63%
ORR
Primary endpoint

45.5%
≥ CRR

22 months
Median DOR

Sidana S et al. *HemaSphere*. 2023;7:1654-1655.

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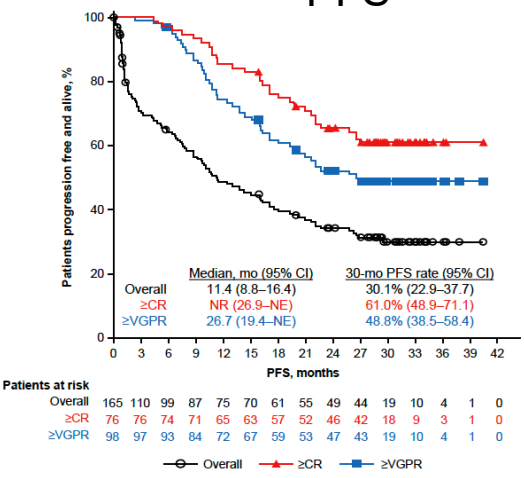
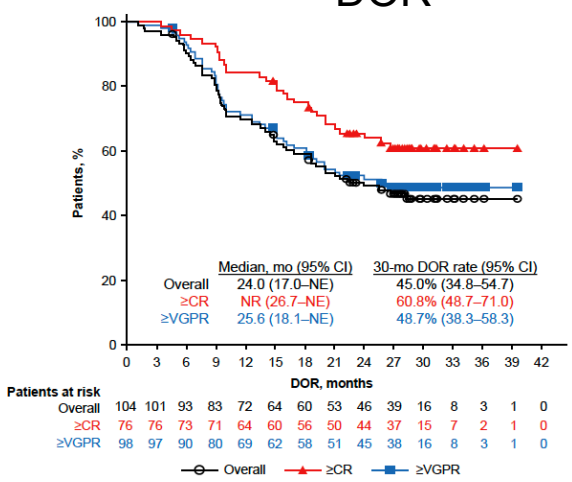
MajesTEC-1: Phase 1/2 Study Of Teclistamab in RRMM

PFS



DOR



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Popat R et al, *IMS* 2024.

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MajesTEC-1: Phase 1/2 Study Of Teclistamab in RRMM

- Most common AEs included cytopenias, infections, and CRS[1]
- CRS median onset 2 days; median duration 2 days
- 9 ICANS events in 5 patients, all grade 1/2 and resolved without dose reduction or discontinuation

Hematologic AEs,[2] N (%)	Any Grade	Grade ≥ 3
Neutropenia	118 (71.5)	108 (65.5)
Anemia	90 (54.5)	62 (37.6)
Thrombocytopenia	70 (42.4)	37 (22.4)
Lymphopenia	60 (36.4)	57 (34.5)
Leukopenia	33 (20.0)	15 (9.1)

Nonhematologic AEs,[2] N (%)	Any Grade	Grade ≥ 3
Infection	132 (80.0)	91 (55.2)
COVID-19	48 (29.1)	35 (21.2)
CRS	119 (72.1)	1 (0.6)
Diarrhea	56 (33.9)	6 (3.9)
Pyrexia	52 (31.5)	1 (0.6)
Fatigue	48 (21.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Cough	44 (26.7)	0
Injection site erythema	43 (26.1)	0
Arthralgia	42 (25.5)	1 (0.6)
Headache	40 (24.2)	1 (0.6)
Constipation	36 (21.8)	0
Hypogammaglobulinemia	34 (20.6)	3 (1.8)

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Moreau P et al. *N Engl J Med*. 2022;387:495-505.
Sidana S et al. *HemaSphere*. 2023;7:1654-1655.

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MagnetisMM-3: Phase 2 Study of Elranatamab in RRMM

N = 123

Key inclusion criteria

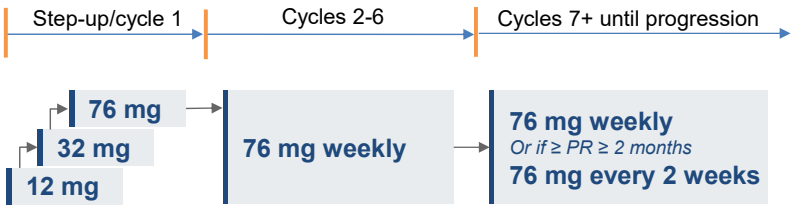
- Triple-class refractory
- No prior BCMA-directed therapy

Baseline characteristics

- Median age 68 y
- Median 5 prior lines
- 25% high-risk cytogenetics
- 42% penta-refractory

BCMA × CD3

Elranatamab administration by SC injection



Primary endpoint: ORR

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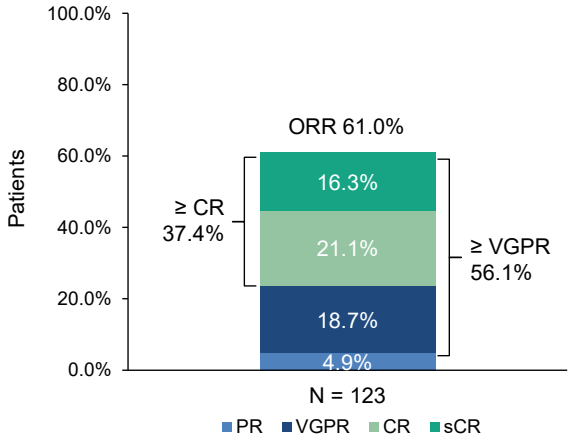
Lesokhin AM et al. *Nat Med*. 2023;29:2259-2267.

19

MagnetisMM-3: Phase 2 Study of Elranatamab in RRMM

Response Rates
Median follow-up 33.9 mo



61%
ORR
Primary endpoint

37%
≥ CRR

Median DOR not yet reached

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Lesokhin AM et al. *Nat Med*. 2023;29:2259-2267.
Prince HM et al. *ASH* 2024.

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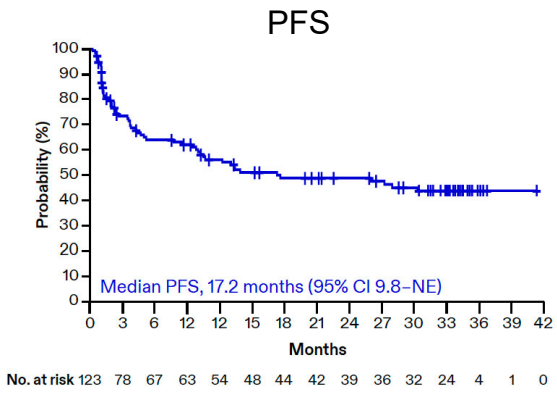
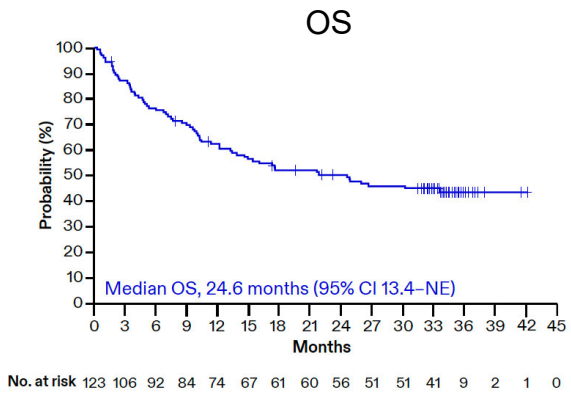
MagnetisMM-3: Phase 2 Study of Elranatamab in RRMM





Lesokhin AM et al. *Nat Med*. 2023;29:2259-2267.
Prince HM et al. *ASH* 2024.

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MagnetisMM-3: Phase 2 Study of Elranatamab in RRMM

- Most common AEs included infections, CRS, and cytopenias
- CRS median onset 2 days, median duration 2 days
- ICANS occurred in 3.4% of patients, all grade 1/2

	N = 123	
Hematologic AEs, N (%)	Any Grade	Grade ≥ 3
Anemia	60 (48.8)	46 (37.4)
Neutropenia	60 (48.8)	60 (48.8)
Thrombocytopenia	38 (30.9)	29 (23.6)
Lymphopenia	33 (26.8)	31 (25.2)

	N = 123	
Nonhematologic AEs, N (%)	Any Grade	Grade ≥ 3
Infection	82 (66.9)	49 (39.8)
COVID-19	36 (29.3)	19 (15.4)
CRS	71 (57.7)	0
Diarrhea	52 (42.3)	2 (1.6)
Fatigue	45 (36.6)	4 (3.3)
Decreased appetite	41 (33.3)	1 (0.8)
Pyrexia	37 (30.1)	5 (4.1)
Injection site reaction	33 (26.8)	0
Nausea	33 (26.8)	0
Hypokalemia	32 (26.0)	13 (10.6)
Cough	31 (25.2)	0
Headache	29 (23.6)	0

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Lesokhin AM et al. *Nat Med*. 2023;29:2259-2267.

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The following is TRUE about G protein-coupled receptor class 5 member D (GPRC5D):

a) GPRC5D is a transmembrane receptor essential for survival of normal and clonal plasma cells.

b) GPRC5D is expressed exclusively in hematologic tissues.

c) Talquetamab is approved for treatment of MM after failure of BCMA-directed therapy.

d) Talquetamab binds GPRC5D and CD3 and is associated with skin and nail toxicity.

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23

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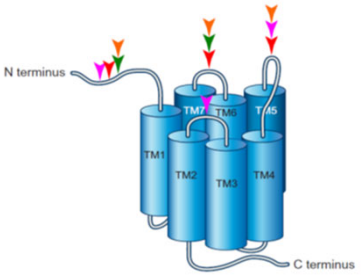
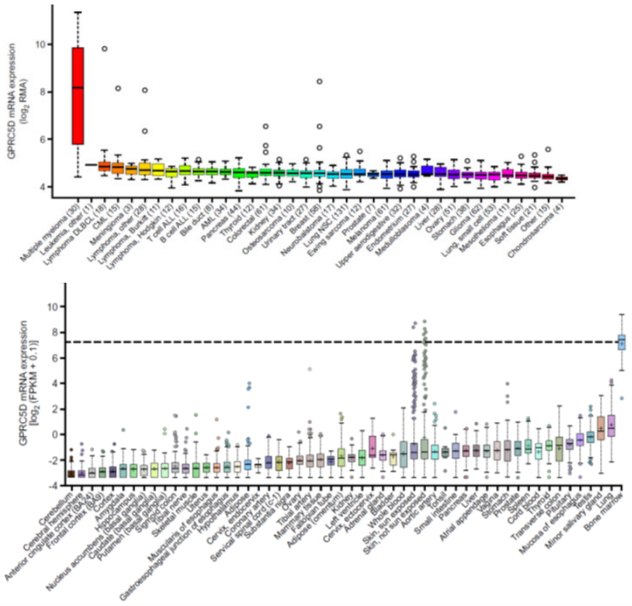
GPRC5D





Smith E.L. *Transl. Med* 11:7746, 2019.

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MonumenTAL-1: Phase 1/2 Study of Talquetamab In RRMM

N = 339

Key inclusion criteria:
- ≥ 3 prior lines, including PI, IMiD, and anti-CD38 mAb

Baseline characteristics	TCR-Naive	Prior TCR
Median age	67	61
Median prior lines	5	6
High-risk cytogenetics	~30%	41%
Penta-refractory	~26%	41%

GPRC5D × CD3

Talquetamab administration by SC injection

Treatment dose after 2 to 3 step-up doses; continued until progression

n = 143	Naive to T-cell redirection	0.4 mg/kg weekly
n = 154	Naive to T-cell redirection	0.8 mg/kg every 2 weeks
n = 78	Prior CAR T or bispecific	0.4 mg/kg weekly *or* 0.8 mg/kg every 2 weeks

Primary endpoint: ORR

Schinke CD et al. *J Clin Oncol.* 2023;41(16_suppl):8036.
Ye JC et al. *IMS* 2024.

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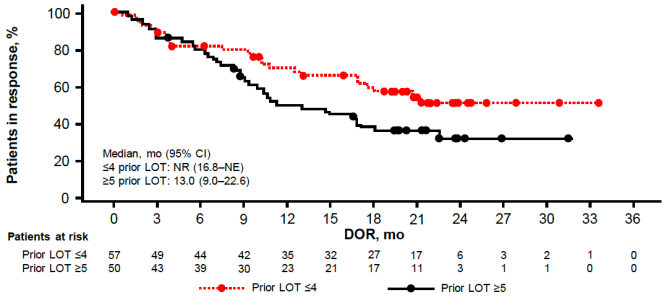
MonumenTAL-1: Phase 1/2 Study of Talquetamab in RRMM

Outcomes	TCR-Naive QW Dose n = 143	TCR-Naive Q2W Dose n = 154	Prior TCR n = 78
Median follow-up (mo)	29.8	23.4	20.5
ORR (%)	74%	70%	67%
Median PFS (mo)	7.5 (5.7-9.4)	11.2 (8.4-14.6)	7.7 (4.1-14.5)
Median DOR	9.5 mo	17.5 (12.5-NE)	N/A
24-mo OS rate (%)	60.6 (51.7-68.4)	67.1 (58.3-74.4)	57.3 (43.5-68.9)



Ye JC et al. *IMS* 2024.

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MonumenTAL-1: Phase 1/2 Study of Talquetamab in RRMM

- Most common AEs included CRS, infection, dysgeusia, and skin/nail toxicity
- 5 patients discontinued due to skin-related AEs and dysgeusia

Most Common AEs, N (%)	TCR-Naive, QW Dose n = 143		TCR-Naive, Q2W Dose n = 145		Prior TCR n = 51	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hematologic						
Anemia	66 (44.8)	45 (31.5)	66 (45.5)	40 (27.6)	25 (49.0)	14 (27.5)
Neutropenia	50 (53.0)	44 (30.8)	41 (28.3)	32 (22.1)	28 (54.9)	27 (52.9)
Thrombocytopenia	39 (27.3)	29 (20.3)	43 (29.7)	27 (18.6)	19 (37.3)	15 (29.4)
Nonhematologic						
CRS	113 (79.0)	3 (2.1)	108 (74.5)	1 (0.7)	39 (76.5)	1 (2.0)
Infection	84 (58.7)	28 (19.6)	96 (66.2)	21 (14.5)	37 (72.5)	14 (27.5)
Dysgeusia	103 (72.0)	-	103 (71.0)	-	39 (76.5)	-
Skin related	80 (55.9)	0	106 (73.1)	1 (0.7)	35 (68.6)	0
Nail related	78 (54.5)	0	78 (53.8)	0	32 (62.7)	0
Rash related	57 (39.9)	2 (1.4)	43 (29.7)	8 (5.5)	18 (35.3)	2 (3.9)
Weight decrease	59 (41.3)	3 (2.1)	60 (41.4)	8 (5.5)	15 (29.4)	0

On-target, off-tumor effects

Schinke CD et al. *J Clin Oncol*. 2023;41(16_suppl):8036.

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RedirecTT-1: Teclistamab + Talquetamab in RRMM

Characteristic	RP2R (n=44)	All doses (N=94)
Median age, years (range)	63.0 (41–80)	64.5 (39–81)
Male, n (%)	23 (52.3)	49 (52.1)
Race, n (%)		
White	32 (72.7)	75 (79.8)
Black/African American	0 (0)	1 (1.1)
Asian	12 (27.3)	17 (18.1)
Unknown	0 (0)	1 (1.1)
Extramedullary plasmacytomas ≥1,[a] n (%)	18 (40.9)	34 (36.2)
High-risk cytogenetics,[b] n (%)	8 (42.1)	21 (41.2)
ISS stage,[c] n (%)		
I	19 (46.3)	38 (44.7)
II	14 (34.1)	26 (30.6)
III	8 (19.5)	21 (24.7)
Years since diagnosis, median (range)	5.5 (0.3–12.9)	6.1 (0.3–14.6)

Characteristic	RP2R (n=44)	All doses (N=94)
Median prior LOT, n (range)	4.0 (2–10)	4.0 (1–11)
Exposure status, n (%)		
Belantamab mafodotin	5 (11.4)	18 (19.1)
CAR-T therapy[d]	2 (4.5)	4 (4.3)
Bispecific antibody[e]	2 (4.5)	7 (7.4)
Any BCMA-directed therapy	9 (20.5)	27 (28.7)
Triple-class	44 (100.0)	94 (100.0)
Penta-drug	28 (63.6)	61 (64.9)
Refractory status, n (%)		
Proteasome inhibitor	41 (93.2)	85 (90.4)
Immunomodulatory drug	41 (93.2)	91 (96.8)
Anti-CD38	43 (97.7)	93 (98.9)
Triple-class	37 (84.1)	81 (86.2)
Penta-drug	13 (29.5)	31 (33.0)
To last line of therapy	39 (88.6)	87 (92.6)

Triple-class exposed population, 36% with extramedullary plasmacytomas

Cohen YC et al. *IMS* 2024.
Cohen YC et al. *N Engl J Med* 2025.

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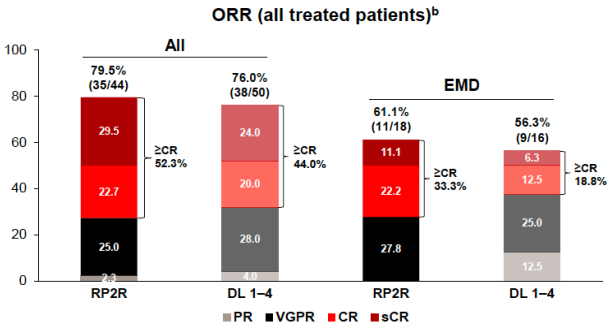
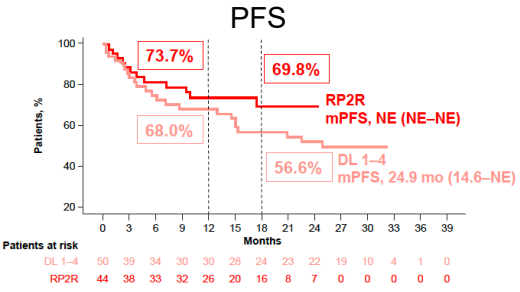
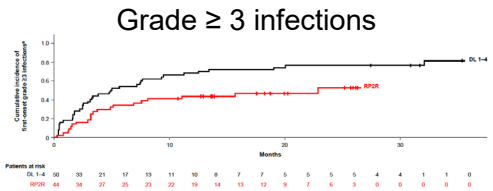
RedirecTT-1: Teclistamab + Talquetamab in RRMM







Cohen YC et al. *IMS* 2024.
Cohen YC et al. *N Engl J Med* 2025.

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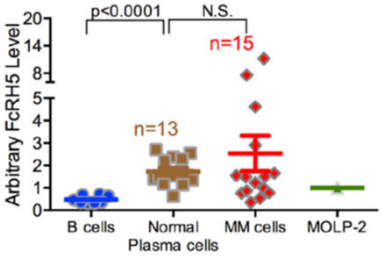
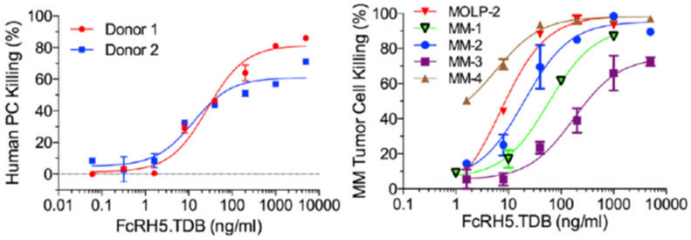
Cevostamab - *FcRH5 × CD3 BsAb*





- Fc Receptor Homologue 5
- Gene in Ch 1q
- Expressed in B cells, including PC

Ongoing Phase 1 dose/schedule finding

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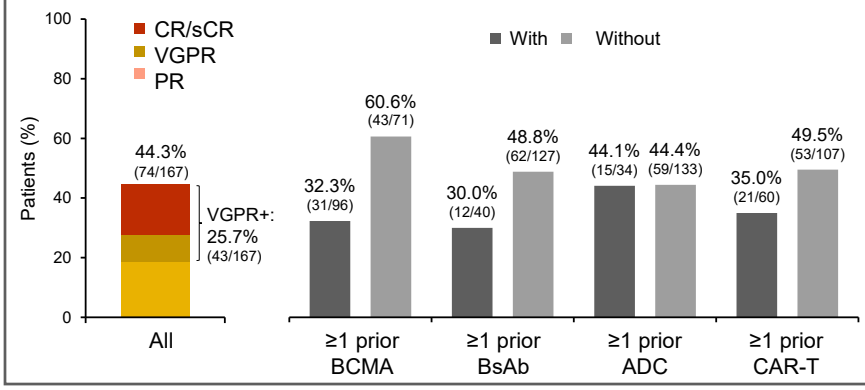
Li J. *Cancer Cell* 31:7746, 2017.

31

Response at the 160mg TD level (n=167)

- **Responses occur early**
  - Median time to first response (PR+): 1.4 months (range: 0.5–4.6)
- **Responses deepen over time**
  - Median time to best response: 2.6 months (range: 0.5–13.4)
- **MRD negativity* achieved in 11/18 patients evaluated†**

ORR at the 160mg TD level in all patients and in patient subgroups‡



Cevostamab provides clinically meaningful activity at the 160mg TD level in a heavily pretreated and highly refractory population, including >50% with prior BCMA

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Richter et al, *ASH* 2024.

32

What is TRUE about the toxicity of bispecific T-cell engagers in use in MM?

a) Bispecific T-cell engagers binding GPRC5D are more toxic than those binding BCMA.

b) Infection is the most relevant toxicity of BCMA-directed bispecifics.

c) Only bispecific antibodies binding BCMA have been associated with severe CRS.

d) Talquetamab is associated with allergy, manifesting predominantly as diffuse rash. After rash, patients can only be rechallenged in the inpatient setting.

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33

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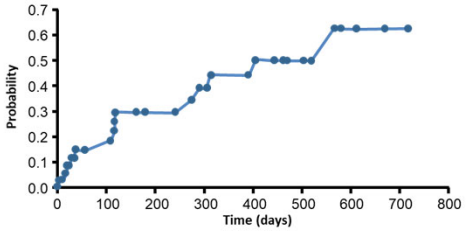
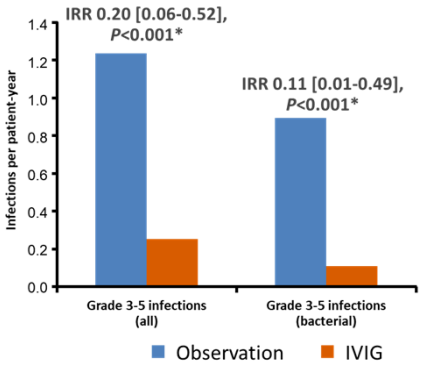
IVIG Use in Patients on BCMA-Targeted BsAbs

Probability of Grade 3-5 Infection



Grade 3-5 Infection Rate With or Without IVIG



Important Clinical Strategies
- **Antiviral prophylaxis**
- **Antibiotic prophylaxis**
- **IVIG if IgG < 400**

IRR, infusion-related reaction.
Lacman et al, *Blood Cancer Disc* 4:440, 2023.

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Infection Prevention and Management Strategies

Antimicrobial Prophylaxis

All patients
- HSV and VZV prophylaxis
- PJP prophylaxis
- VZV vaccination
- Influenza vaccination
- SARS-COV-2 vaccination per CDC/local guidelines

Antibacterial/antifungal indications
- Prolonged or G-CSF-resistant neutropenia
- High risk or history of recurrent infection
- History of prolonged high-dose steroid use (antifungal)

Management

Hypogammaglobulinemia

IVIG therapy monthly for
- IgG <400 mg/dL
- ≥ 2 severe recurrent infections by encapsulated bacteria
- Life-threatening infection
- Treatment-resistant bacterial infection

Neutropenia
- G-CSF for grade ≥3 neutropenia
- Avoid G-CSF during periods of CRS risk

Active Infection
- Treat with available therapy depending on infectious agent
- Antibiotic should be targeted when possible

Bispecific Antibody Dosing

Maintain dosing
- During prophylaxis
- During IVIG treatment

Temporarily withhold
- ANC < 0.5 × 10^9/L or febrile neutropenia
- Active infection, including COVID-19

Discontinue
- HBV reactivation

ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor; HBV, hepatitis B virus; IVIG, intravenous immunoglobulin; VZV, varicella zoster virus.
Raje N et al. *Blood Cancer J.* 2023;13:116.

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Summary – Bispecific T-cell Engagers

- Available, highly active therapy for advanced MM
- BCMA and GPRC5D options – we are still learning best sequence
- Nuisance of step-up dosing
- Very short term: CRS
- Long term: Infections, on-target-off-tumor toxicities
- Combinations coming up

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Bispecific Antibodies in Lymphoma

Peter Martin, MD
Professor of Medicine
Chief of the Lymphoma Program
Weill Cornell Medicine
New York, NY

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Which of the following is TRUE regarding bispecific antibodies approved for treatment of follicular lymphoma?

a) Currently approved bispecific antibodies for FL include mosunetuzumab, epcoritamab but not glofitamab or odronextamab.

b) All patients receiving bispecific antibodies for lymphoma require admission to hospital for monitoring during step up dosing.

c) Neutropenia does not occur with anti-CD20/CD3-directed bispecific antibodies.

d) T-cell depletion is common with anti-CD20/CD3-directed bispecific antibodies.

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39

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Which of the following is TRUE regarding bispecific antibodies approved for treatment of diffuse large B-cell lymphoma?

a) Patients in PR experience a similar PFS compared to patients in CR as long as they continue to receive treatment.

b) Patients receiving an anti-CD20/CD3 bispecific antibody should NOT receive pre-treatment with an anti-CD20 antibody because it blocks all the CD20.

c) Bispecific antibodies do not work after CAR T cells because of immune exhaustion.

d) Glofitamab has two anti-CD20 binding regions.

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41

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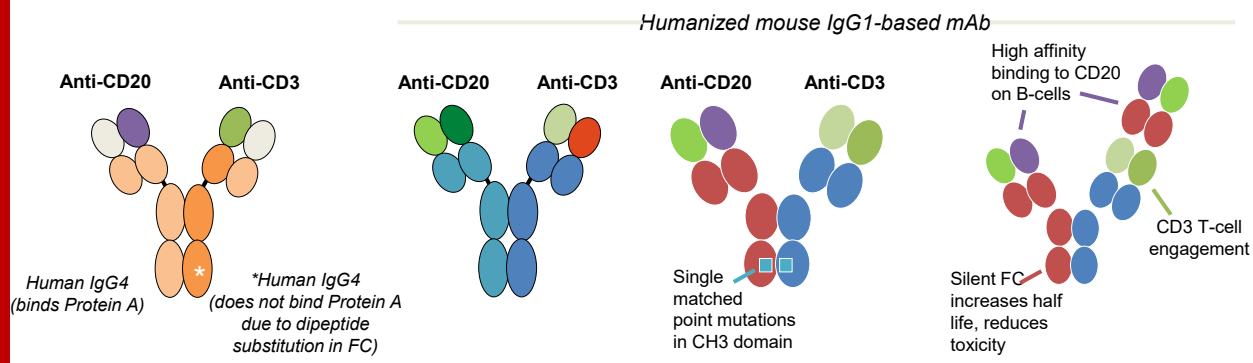
CD20/CD3 Bispecific Antibodies in B-Cell Lymphomas



Odronextamab (IV)	Mosunetuzumab (IV*)	Epcoritamab (SC)	Glofitamab (IV)
Under FDA Review for 3L+ R/R FL and DLBCL	FDA approved: 3L+ R/R FL	FDA approved: 3L+ R/R FL, 3L+ DLBCL	3L+ R/R DLBCL

Castaneda-Puglianni. *Drugs Context*. 2021;10:2021. Bannerji. *ASH* 2020. Abstr 42. Budde. *ASH* 2018. Abstr 399. Hutchings. *Lancet*. 2021;398:1157. Engelberts. *eBioMedicine*. 2020;52:102625. Hutchings. *JCO*. 2021;39:1959. Mosunetuzumab PI. Epcoritamab PI. Glofitamab PI.

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Phase II Study of Mosunetuzumab Monotherapy in R/R FL

Single-arm, pivotal phase II expansion study[1,2]

- Primary endpoint met: 60% CR vs 14% historical control (*P* <.0001) at 10-mo follow-up[2]

Adults with R/R FL (grades 1-3a) after ≥2 prior systemic tx including ≥1 anti-CD20 mAb and ≥1 alkylating agent; ECOG PS ≤1 (N = 90)

Cycle 1*: Step-up Dosing†‡	Cycle 2*‡	Cycles 3-8*‡
Mosunetuzumab IV D1: 1 mg > D8: 2 mg > D15: 60 mg	**Mosunetuzumab** IV D1: 60 mg	**Mosunetuzumab** IV D1: 30 mg

Discontinue if CR by cycle 8 §; if PR or SD, continue at 30 mg for 17 cycles (unless PD or unacceptable toxicity)

*21-day cycles. †Cycle 1 step-up dosing for CRS mitigation. ‡Premedication before each mosunetuzumab dose in cycles 1 and 2, optional from cycle 3+: IV corticosteroid given 1 hr before, IV antihistamine and oral antipyretic given 30 min before. §Retreatment allowed at relapse for those achieving CR.

No mandatory hospitalization for treatment administration.

- **Primary endpoint:** CR (best response) rate by IRF, assessed vs 14% historical control CR rate
- **Secondary endpoints:** ORR, DoR, PFS, safety, and tolerability

1. Bartlett. *ASH* 2022. Abstr 610. 2. Budde. *Lancet Oncol*. 2022;23:1055. NCT02500407.

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Mosunetuzumab Phase II Study: Baseline Characteristics

Characteristic	Mosunetuzumab (N = 90)
Median age, yr (range)	60 (53-67)
Male, n (%)	55 (61)
ECOG PS 0/1, n (%)	53/37 (59/41)
Ann Arbor stage, n (%) ▪ I-II ▪ III-IV	 21 (23) 69 (77)
Median prior lines, n (range)	3 (2-4)
Refractory to last prior therapy, %	62 (69)
Refractory to any prior anti-CD20 therapy, %	71 (79)
PD within 24 mo from start of first-line therapy (POD24), %	47 (52)
Double refractory to prior anti-CD20 therapy and alkylator, %	48 (53)
Prior ASCT, %	19 (21)

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Bartlett. *ASH* 2022. Abstr 610. Budde. *Lancet Oncol*. 2022;23:1055.

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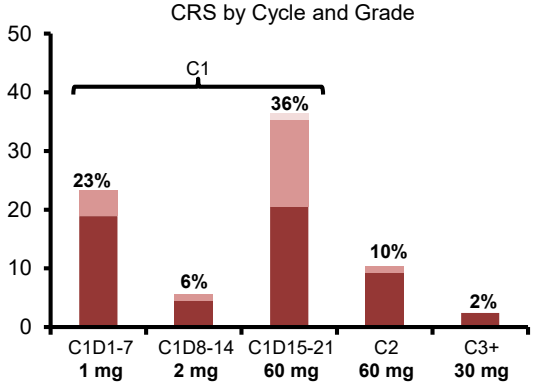
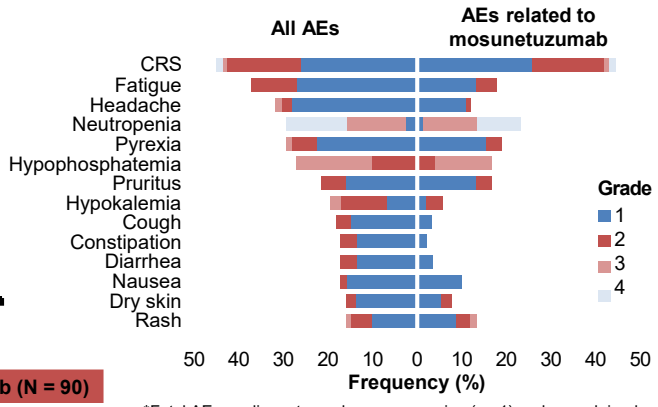
Mosunetuzumab Phase II Study: Safety

CRS by Cycle and Grade



CRS per ASTCT Criteria	Mosunetuzumab (N = 90)
Median duration, days (range)	3 (1-29)
Patients who received tx for CRS (n = 40) ▪ Corticosteroids only ▪ Tocilizumab only ▪ Both	 6 (15%) 3 (8%) 4 (10%)

AEs in ≥15% of Patients by Grade



*Fatal AEs: malignant neoplasm progression (n =1) and unexplained (n = 1). †D/c: mosunetuzumab related, CRS (n = 2); unrelated to mosunetuzumab, EBV viremia (n = 1), Hodgkin disease (n = 1).

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1. Bartlett. *ASH* 2022. Abstr 610. 2. Budde. *Lancet Oncol*. 2022;23:1055.

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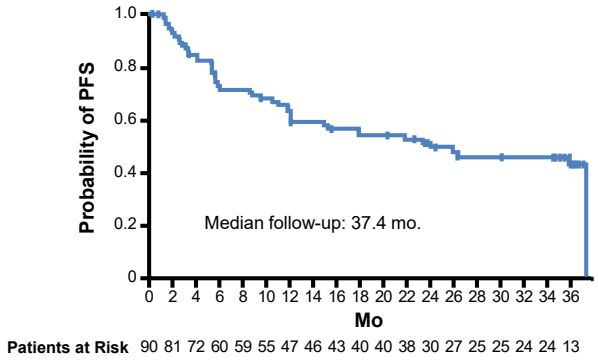
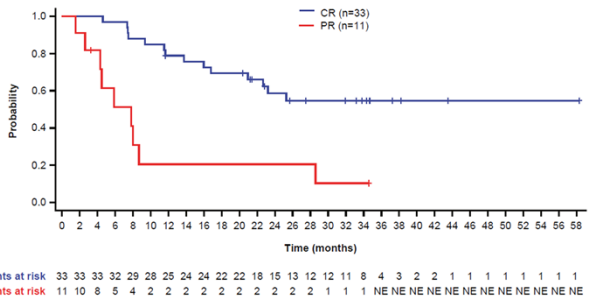
Mosunetuzumab Phase II Study: Efficacy

PFS by Investigator on Registrational Arm[1]



DoR by response type[2]



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1. Schuster. *ASH* 2023. Abstr 603. 2. Budde. *JCO.* 2024;42:2250.

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EPCORE NHL-1: Epcoritamab in R/R B-Cell NHL

Phase I/II open-label, dose escalation/expansion study

Patients with R/R CD20+ B-cell NHL after ≥2 previous lines of tx and ≥1 anti-CD20 mAb; ECOG PS 0-2; FDG PET-avid; measurable disease by CT/MRI; previous CAR T-cell therapy allowed (planned N = 700)

Cycle 1 Step-Up Dosing*

Epcoritamab SC
D1: 0.16 mg
D8: 0.8 mg
D15: 48 mg
D22: 48 mg

→ **Epcoritamab** 48 mg SC in 28-day cycles QW cycles 2-3, Q2W cycles 4-9, Q4W cycles 10+ → *Until PD or unacceptable toxicity*

*With corticosteroid prophylaxis. To mitigate CRS.

Primary endpoint: ORR by IRC

Secondary endpoints: DoR, TTR, PFS, OS, CR rate, safety

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Linton. *ASH* 2023. Abstr 1655. NCT03625037.

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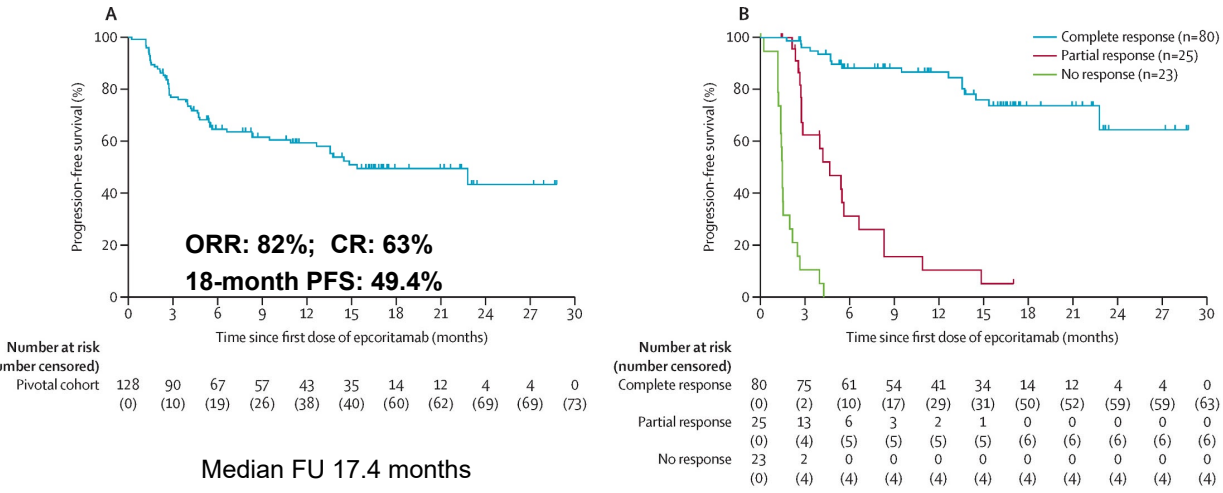
EPCORE NHL-1: Efficacy of Epcoritamab in FL



Median FU 17.4 months

LEUKEMIA & LYMPHOMA SOCIETY®

Linton. *Lancet Haematol* 2024;11:E593.

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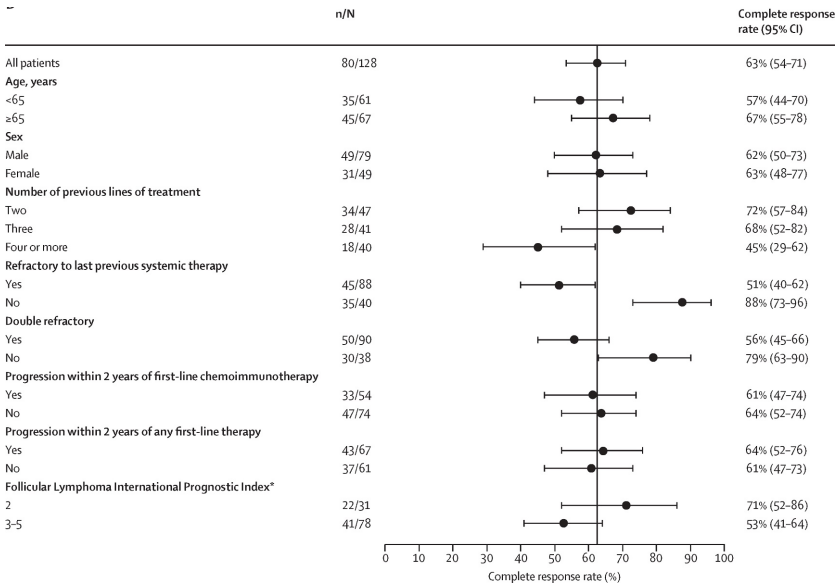
EPCORE NHL-1: Complete Response in FL



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Linton. *Lancet Haematol* 2024;11:E593.

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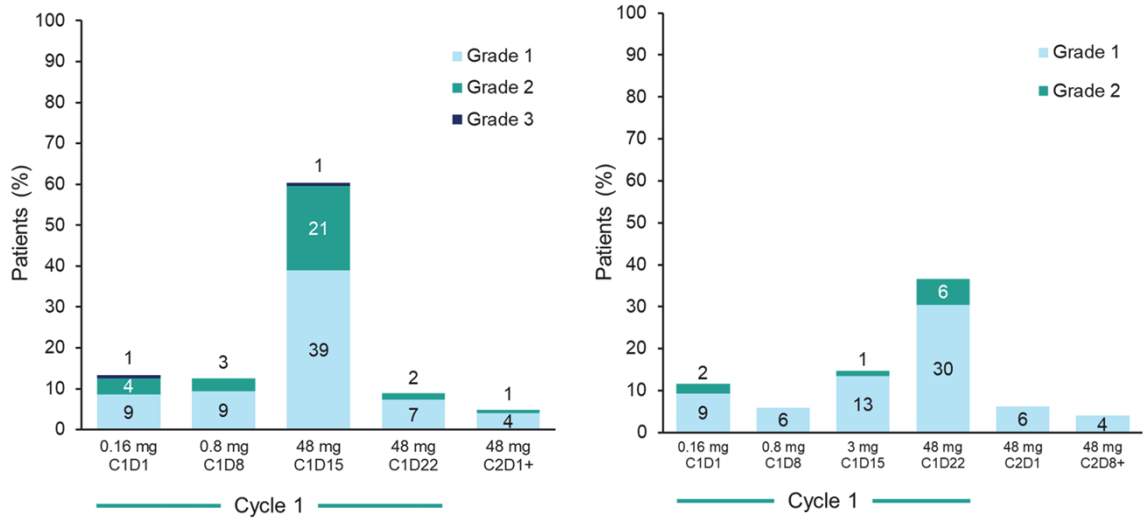
EPCORE NHL-1: CRs in Pivotal vs Optimization Cohort in FL



Linton. *Lancet Haematol* 2024;11:E593.

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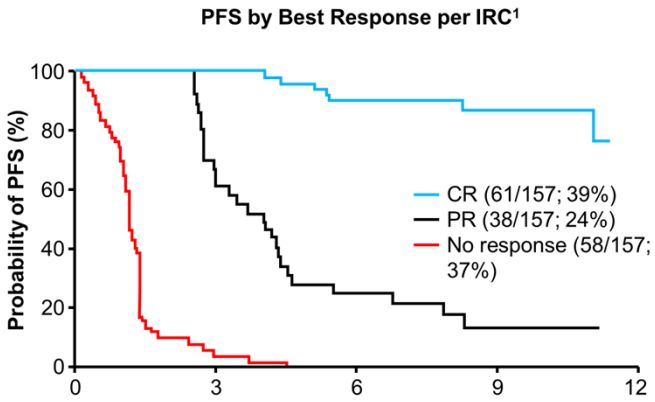
EPCORE NHL-1: Epcoritamab Efficacy in DLBCL



Best response rates[2]
- CR: 39.0%
- ORR: 63.0%

Subgroup CR rate[2]
- After CAR T cell: 34%
- Refractory: 30%

Survival
- Median PFS: 4.4 mo[2]
- OS: 57% at 12 mo[1]
- Median DOR: 12 mo[2]
- Median DOR of CR: NR[2]

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1. Thieblemont C et al. *EHA* 2022. Abstract LB2364; 2. Thieblemont C et al. *J Clin Oncol.* 2023;41(12):2238-2247.

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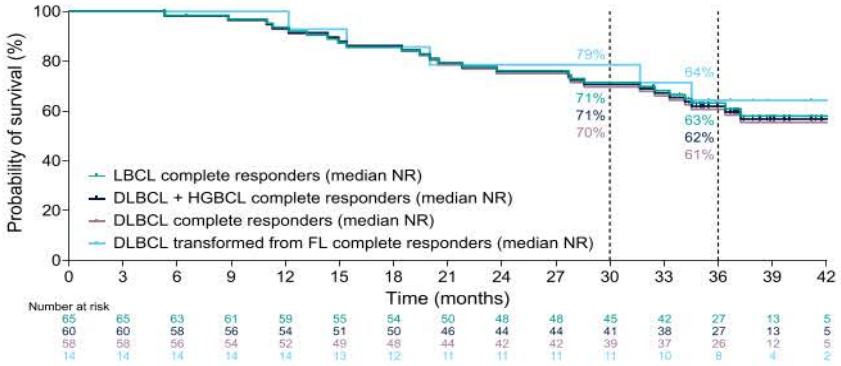
3-Year Update

Long-Term PFS and OS Benefits With Complete Response

- Median PFS for the overall population (N=157) was 4.2 mo (95% CI, 2.8–5.5)
- Among complete responders (n=65), median PFS was 37.3 mo (95% CI, 26.0–NR)
  - 36-mo PFS estimate was 53%
- **Median OS for the overall population (N=157) was 18.5 mo (95% CI, 11.7–27.7); among complete responders, it was NR**
- At 36 mo, an estimated 75% of complete responders had not initiated a new antilymphoma therapy



Vose J et al. *ASH 2024* Abstract 4480.

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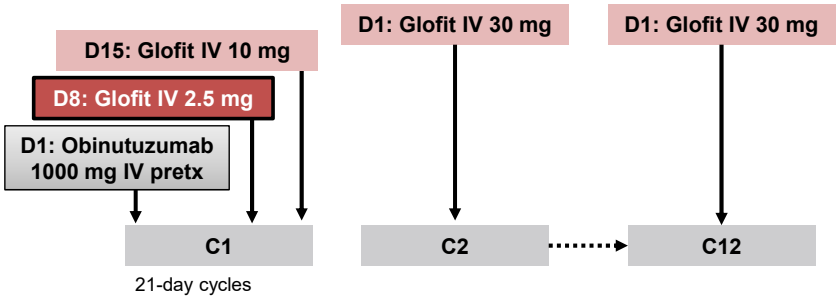
Phase II Expansion Study: Glofitamab After 2 Prior Lines of Therapy in DLBCL

Single-arm phase II expansion trial

Patients with DLBCL-NOS, HGBCL, transformed FL, or PMBCL; ECOG PS 0-1 and ≥2 prior therapies, including anti-CD20 and anthracycline (N = 155)



Primary endpoint: CR rate by IRC

Key secondary endpoints: ORR rate, DoR, DoCR, PFS, and OS

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Dickinson MJ et al. *N Engl J Med.* 2022;387(24):2220-2231.

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Phase II Expansion Study of Glofitamab: Baseline Characteristics

Characteristic	Glofitamab (N = 154)
Median age, yr (range)	66.0 (21-90)
Male, n (%)	100 (64.9)
Ann Arbor stage, n (%)	
▪ I	10 (6.5)
▪ II	25 (16.2)
▪ III	31 (20.1)
▪ IV	85 (55.2)
NHL subtype, n (%)	
▪ DLBCL	110 (71.4)
▪ Transformed from FL	27 (17.5)
▪ HGBCL	11 (7.1)
▪ PMBCL	6 (3.9)
Bulky disease, n (%)	
▪ >6 cm	64 (41.6)
▪ >10 cm	18 (11.7)

Characteristic	Glofitamab (N = 154)
Prior lines of therapy, median (range)	3 (2-7)
▪ 2 prior lines, n (%)	62 (40.3)
▪ ≥3 prior lines, n (%)	92 (59.7)
Prior therapy received, n (%)	
▪ Anti-CD20 antibody	154 (100)
▪ Anthracycline	149 (96.8)
▪ CAR T-cell therapy	51 (33.1)
▪ ASCT	28 (18.2)
Refractory disease, n (%)	
▪ To any prior therapy	139 (90.3)
▪ To last prior therapy	132 (85.7)
▪ Primary refractory	90 (58.4)
▪ To prior CAR T-cell therapy	46 (29.9)
▪ To any prior anti-CD20 antibody	128 (83.1)

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Dickinson MJ et al. *N Engl J Med.* 2022;387(24):2220-2231.

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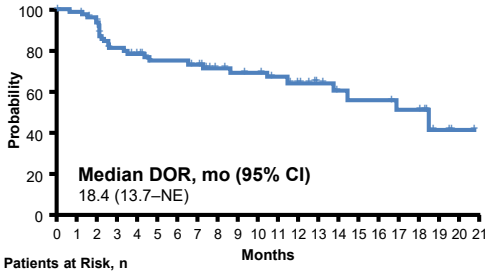
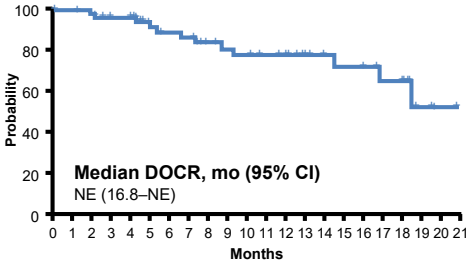
Phase II Expansion Study of Glofitamab: Efficacy

Median follow-up: 12.6 mo

Duration of overall response by IRC



Duration of complete response by IRC



Response, %	N = 155
Best response	
▪ ORR	51.6
▪ CR	39.4
Subgroup CR rate	
▪ After CAR T-cell therapy	35
▪ Relapsed	70
▪ Refractory	34
Survival, Mo	**N = 155**
Median PFS	4.9
Median OS	11.5

	N = 80
Median DOR follow-up, mo (range)	10.6 (0–21)
12-mo DOR, % (95% CI)	63.6 (51.1–76.2)
Ongoing response at CCOD, n (%)	53 (66.3)

	n = 61
Median DOCR follow-up, mo (range)	10.6 (0–21)
12-mo DOCR, % (95% CI)	77.6 (64.3–90.8)
CRs ongoing at CCOD, n (%)	49 (80.3)

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Dickinson MJ et al. EHA 2022. Abstract S220; Dickinson MJ et al. *N Engl J Med.* 2022;387(24):2220-2231.

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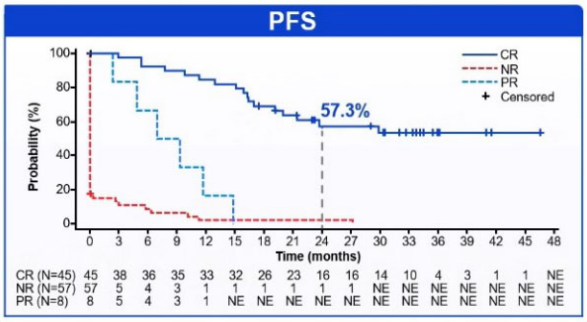
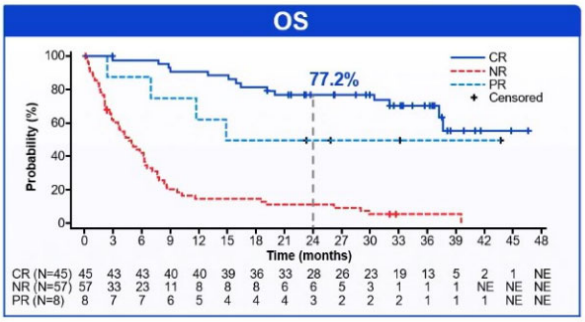
3-Year Follow Up





Landmark PFS from EOT in patients with CR at EOT*	N=45
Median PFS, months (95% CI)	NE (20.0–NE)
24-month PFS rate, % (95% CI)	57.3 (41.2–73.4)

Landmark OS from EOT in patients with CR at EOT*	N=45
Median OS, months (95% CI)	NE (37.2–NE)
24-month OS rate, % (95% CI)	77.2 (64.8–89.6)

Most patients with a CR at EOT remained progression-free and alive at 24 months after EOT

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Dickinson M et al. *ASH 2024* Abstract 865.

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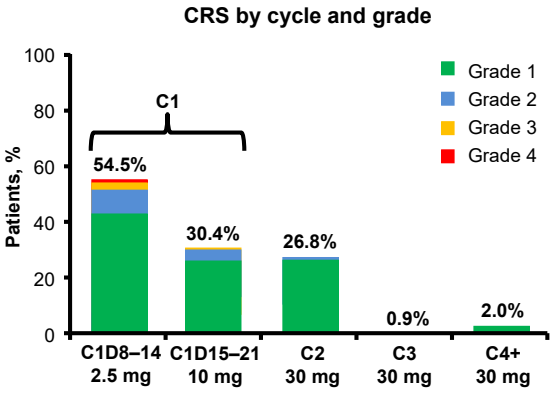
Phase II Expansion Study of Glofitamab: Safety

CRS Parameter	Glofitamab (N = 154)
Any-grade CRS, n (%) ▪ Grade 1 ▪ Grade 2 ▪ Grade 3 ▪ Grade 4	97 (63.0) 73 (47.4) 18 (11.7) 4 (2.6) 2 (1.3)
Median time to CRS onset from C1D8 dose, hr (range)	13.6 (6.2–51.8)
Corticosteroids given, n/N (%)	27/97 (27.8)
Tocilizumab given, n/N (%)	31/97 (32.0)
Any ICANS, n (%) ▪ Grade ≥3	12 (7.8) 4 (2.6)



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Dickinson MJ et al. *N Engl J Med.* 2022;387(24):2220-2231.

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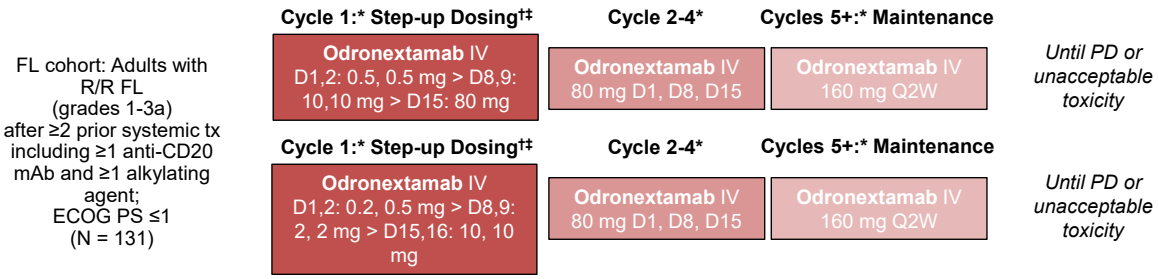
ELM-2: Odronextamab Monotherapy in R/R FL

Multicohort, open-label phase II study in R/R B-cell NHL (FL, DLBCL, MCL, MZL, others)



*21-day cycles. †Cycle 1 step-up dosing at study initiation was 1/20/80 mg but was modified to further mitigate CRS risk.
‡Each step-up dose delivered as split infusions and is accompanied with premedication to further mitigate CRS risk.

- **Primary endpoint:** ORR by ICR per Lugano criteria
- **Secondary endpoints:** ORR by investigator, CR rate, DoR, PFS, OS, safety/tolerability
- Patients were admitted for inpatient monitoring for 24 h following each infusion up to and including C2D1

Kim. *ASH* 2022. Abstr 949. NCT03888105.

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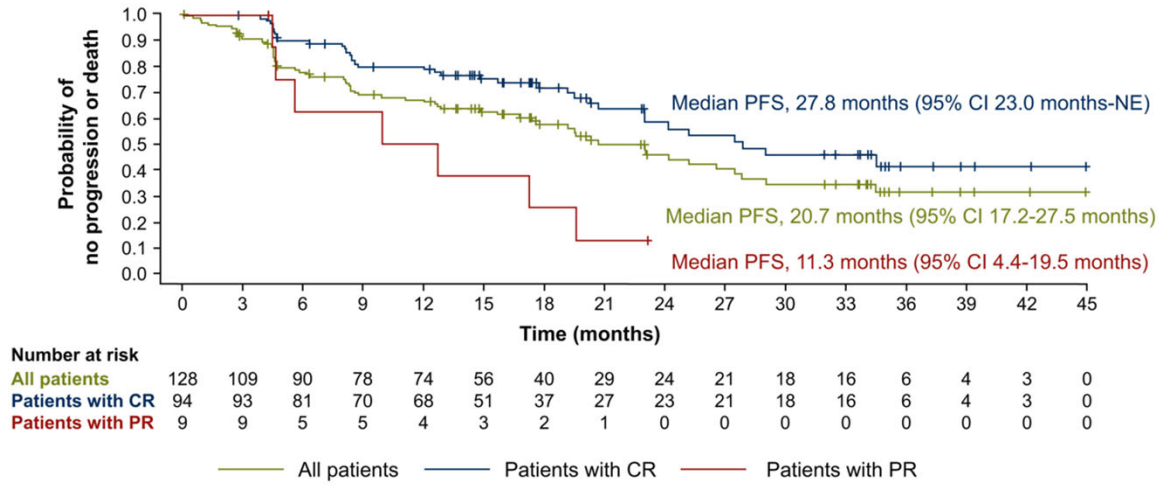
ELM-2: Survival by Response Type



Kim. *Ann Oncol.* 2024;35:1039.

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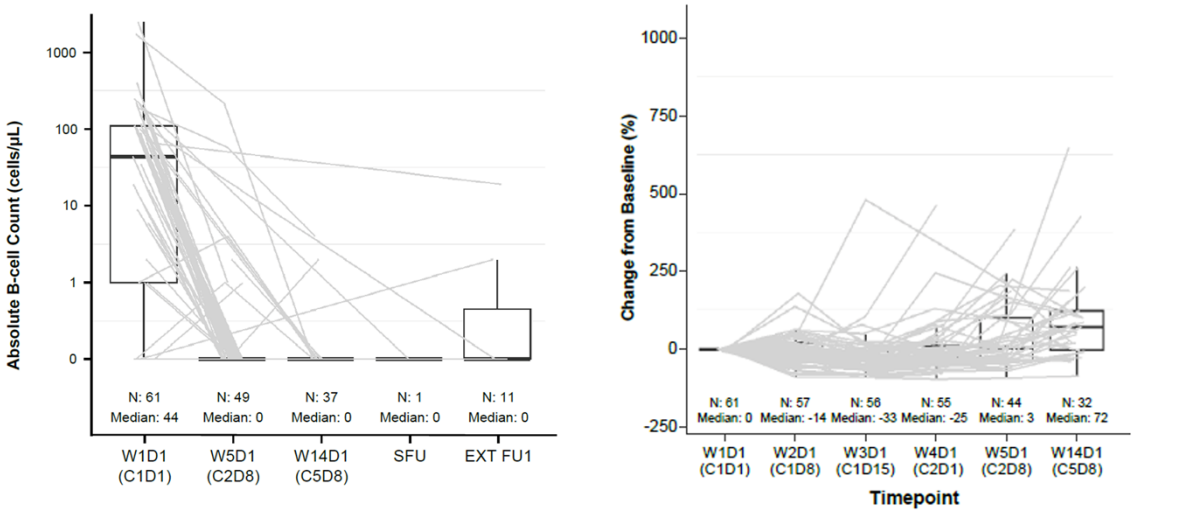
ELM-2: B-cell and T-cell Kinetics



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Kim. *Ann Oncol*. 2024;35:1039.

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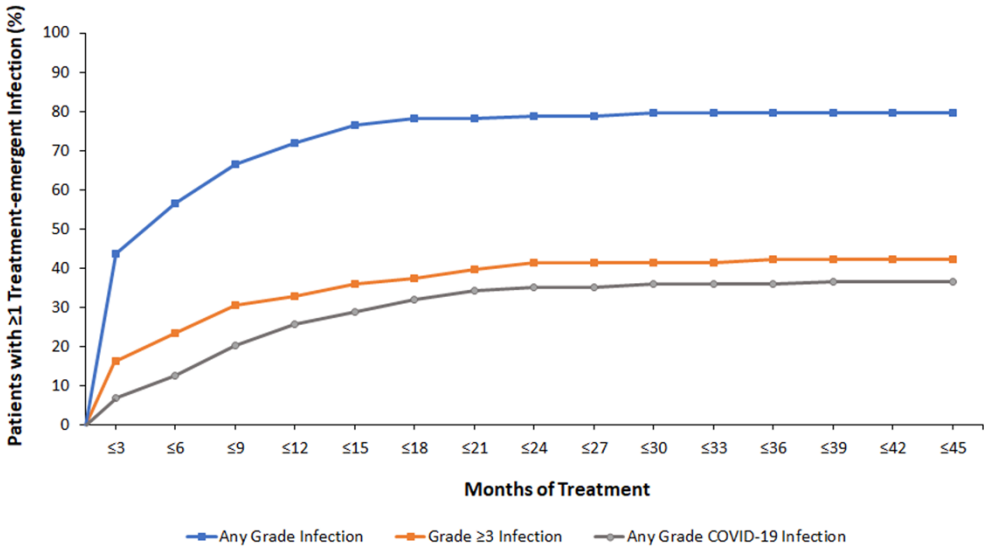
Odronextamab: Cumulative Infections



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Kim. *Ann Oncol*. 2024;35:1039.

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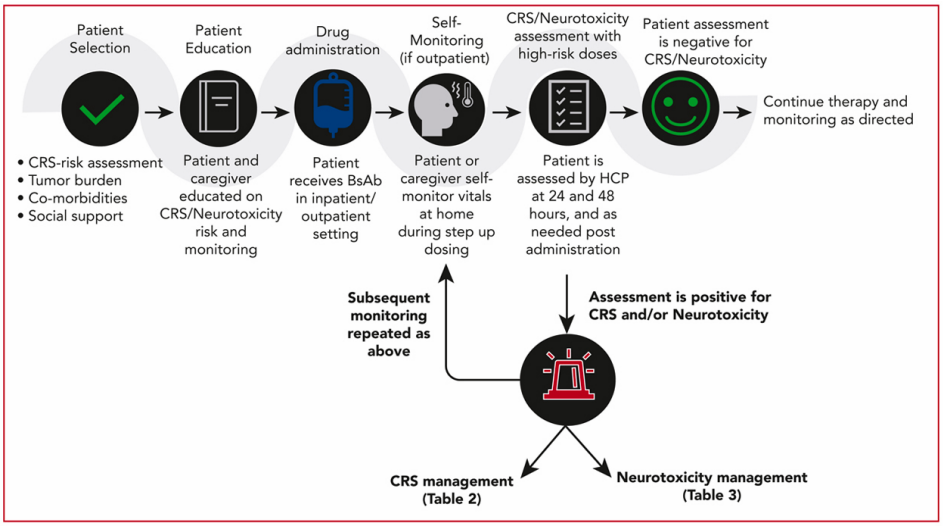
Consensus Recommendations: Management of AEs Associated With CD3×CD20 Bispecific Antibody Therapy



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Crombie et al. *Blood* 2024;143:1565.

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Key Considerations Before Initiating CD3xCD20 Bispecific Abs

Facility

- Ensure insurance authorization for BsAb and supportive care medications (including tocilizumab), if applicable
- Ensure there is a facility with tocilizumab available within close radius of patient's location with a minimum of 2 doses of tocilizumab available for immediate use
- Ensure that clinic staff including registered nurses, pharmacists, and providers are aware of tocilizumab location and how to administer
- Designated location (clinic/infusion center) for patients to be treated outpatient if concerns for grade 1 or, in unique instances, grade 2 CRS
- Institutions should have dedicated pathways for escalating care for patients with grade 2 CRS not responsive to outpatient management or for patients with more severe CRS
- Use electronic medical records, if available, to create standard order sets for CRS management or acute care plans

Personnel

- Provide education to staff involvement in administration, monitoring, and management of toxicities associated with BsAbs
- Appoint a dedicated health care team (eg, oncologist, advanced practice provider, nurse, and pharmacist) to monitor and manage complications. This can be the same team or a rotating team depending on institution capabilities.

Patient resources

- Ensure patients have access to a thermometer. This can be provided by the health care facility or purchased by the patient. Blood pressure cuff and pulse oximeter can also be helpful if available to the patient.
- Encourage patients to have educational sheet completed (Figure 1)
- Prescription for dexamethasone to use as needed for CRS. Patients should be instructed to administer only after discussing with care team.
- Ideally patients should remain near a facility that stocks tocilizumab during the treatment days with highest risk for development of CRS

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Crombie et al. *Blood* 2024;143:1565.

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Prevention of Infection

Withhold if grade 4 neutropenia or active infection

Neutropenia: consider liberal use of growth factors

***Pneumocystis jirovecii* pneumonia: prophylaxis strongly recommended**

Herpes virus: prophylaxis strongly recommended

Consider IVIG for IgG <400/chronic infection

CMV has been reported

Check CMV status? Monitor?

Fungal infections have been reported

PML has been reported

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Mosunetuzumab PI. Epcoritamab PI.

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Current and Future Landscape

FOLLICULAR LYMPHOMA

Approved in 3rd Line Therapy

- CD20 x CD3 Bispecific Antibodies
- 2 products: Mosunetuzumab and Epcoritamab

Numerous Ongoing Clinical Trials

- Combination Therapies in R/R setting
  - R2 Combo Reported and Phase III ongoing
- Frontline
  - Single Agent and Combinations
- Alternate Targets
  - CD19 BsAB

DIFFUSE LARGE B-CELL LYMPHOMA

Approved in 3rd Line Therapy

- CD20 x CD3 Bispecific Antibodies
- 2 products: Epcoritamab and Glofitamab

2nd Line + Combinations Published

- Gem-Ox Chemotherapy
- Mosunetuzuamb + Polatuzumab

Frontline Studies Ongoing

- Randomized Phase 3 Trials
- Elderly/Non-Chemo Candidates

*Not all encompassing

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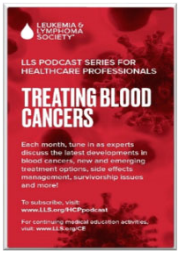
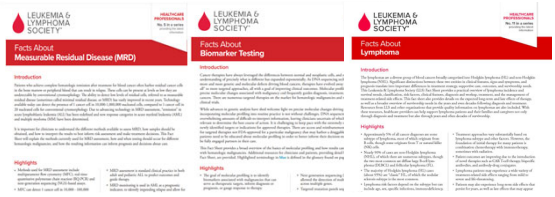
FREE LLS RESOURCES FOR HEALTHCARE PROVIDERS



- ❑ CME & 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
- ❑ LLS Research Grant Programs: www.LLS.org/Research or email researchprograms@LLS.org



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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
- ❑ **Support Resources**
  - Financial Assistance: www.LLS.org/Finances
    - Urgent Need
    - Patient Aid
    - Travel Assistance
  - 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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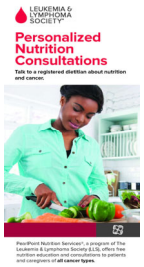
FREE LLS RESOURCES FOR PATIENTS

- **Nutrition Education Services Center (NESC)** – one-on-one **free** nutrition education and consultations to patients of all cancer types with RDs who have expertise in oncology nutrition www.LLS.org/Nutrition
- **Information Specialists** (IRC) – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges.
- **Reach out** **Monday–Friday, 9 am to 9 pm ET**
  - Phone: 800.955.4572
  - Live chat: www.LLS.org/IRC
  - Email: LLS.org/ContactUs
  - HCP Patient Referral Form: www.LLS.org/HCPreferral



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CLINICAL TRIAL SUPPORT CENTER (CTSC)

CTSC PROCESS FOR SUPPORTING PATIENTS

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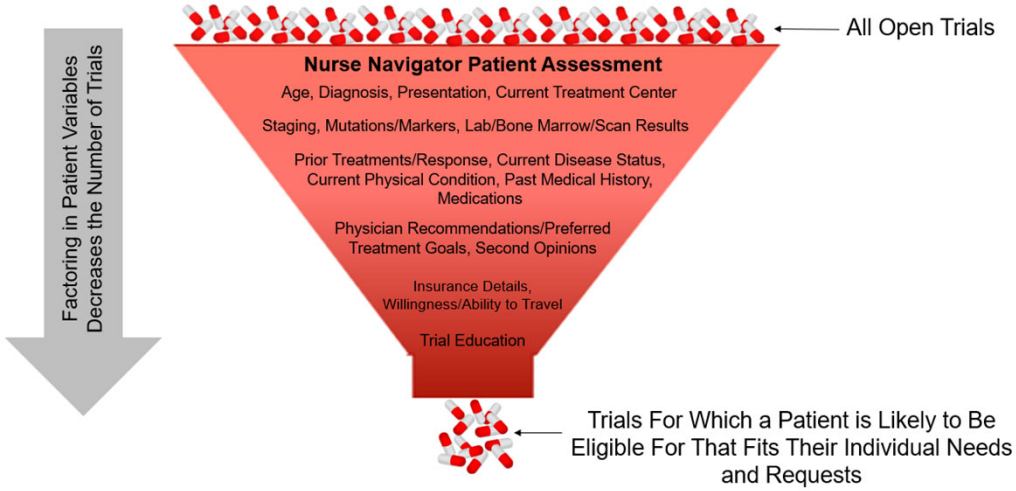
Individualized Clinical Trial Matching by the CTSC



"Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer", Mark Fleury, PH.D, April 11, 2018. Copyright year 2018.
Adapted with copyright attribution permission from Dr. Fleury: https://www.fightcancer.org/figure-10-patient-facing-clinical-trial-matching

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HOW TO ACCESS THE CLINICAL TRIAL SUPPORT CENTER (CTSC)

Information Resource Center (IRC) 1-800-955-4572

Patient or caregivers can complete an online referral form:

https://www.lls.org/navigation

Healthcare Providers can refer a patient at:

https://www.hematology.org/clinicaltrialnavigation/

Email: CTSC@lls.org

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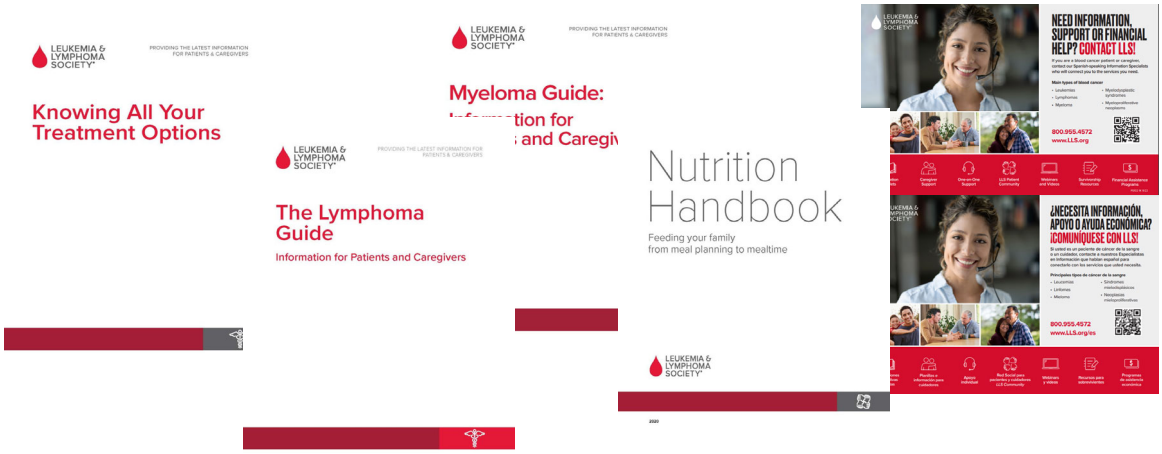
FREE LLS RESOURCES FOR YOUR PATIENTS



BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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Q & A

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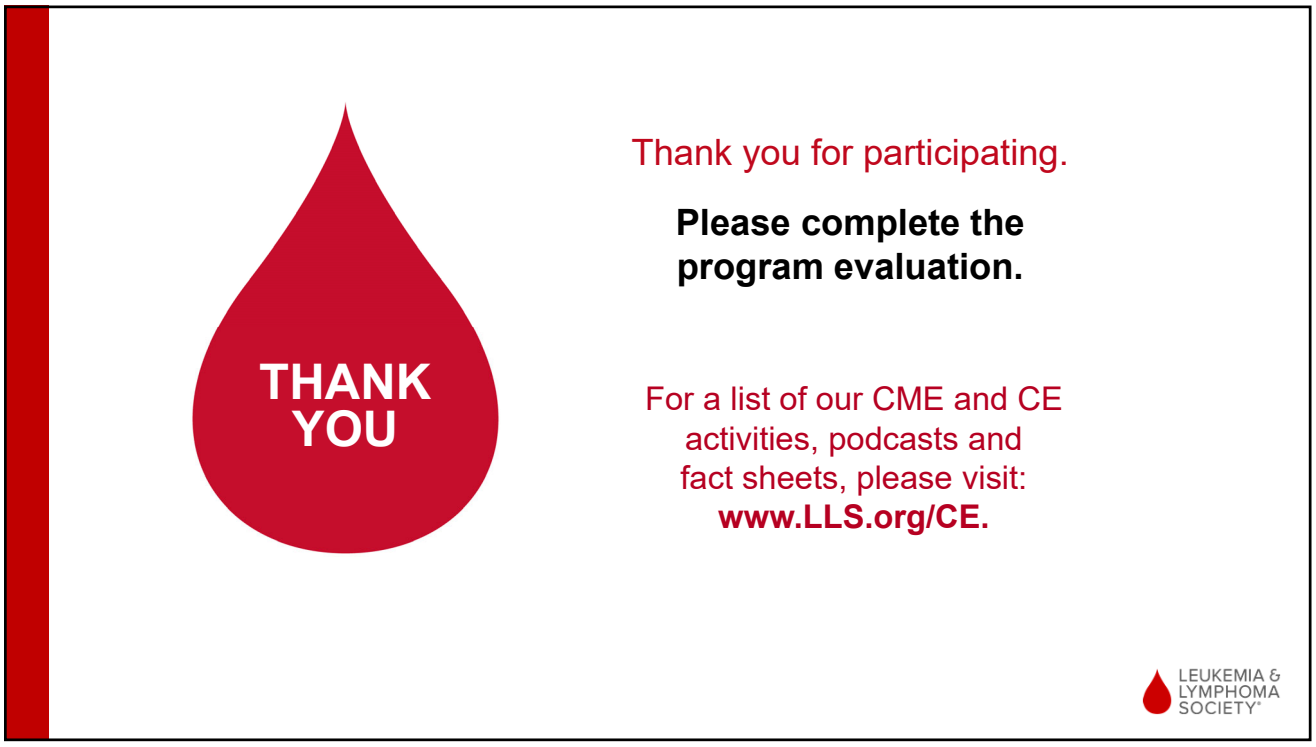
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Thank you for participating.
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