Bispecific Therapy

FROM CLINICAL TRIALS TO REAL-WORLD EXPERIENCE - THERAPEUTIC CONSIDERATIONS AND LOGISTICAL STRATEGIES

Faculty

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Acknowledgments/credits: Baptist/MCI PharmD Group

Learning Objectives

1. Discuss the pharmacology and pharmacokinetics of current T-cell engaging bispecific antibodies (BsAbs).

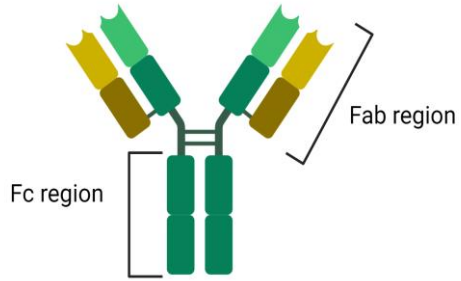
2. Review data supporting the use of current T-cell engaging bispecific antibodies (BsAbs) in hematological malignancies.

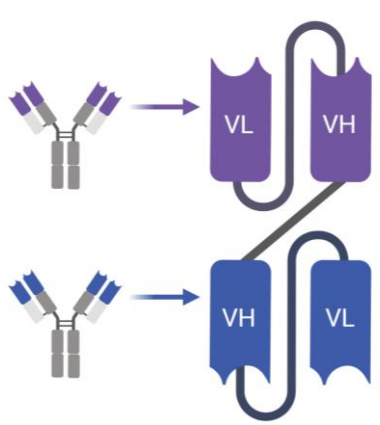
3. Describe common side effects associated with T-cell engaging bispecific antibodies (BsAbs) including cytokine release syndrome.

4. Outline logistical challenges that can occur with the administration of T-cell engaging bispecific antibodies (BsAbs) and summarize therapeutic strategies that can be utilized.

Introduction

- Bispecific antibodies represent a novel treatment approach for the treatment of hematologic malignancies
- Contain 2 different antigen-binding sites in 1 molecule
- Activate peripheral and intratumoral endogenous immune cells
- Redirects cytotoxic T lymphocytes by targeting CD3 and cell surface antigens on cancer cells





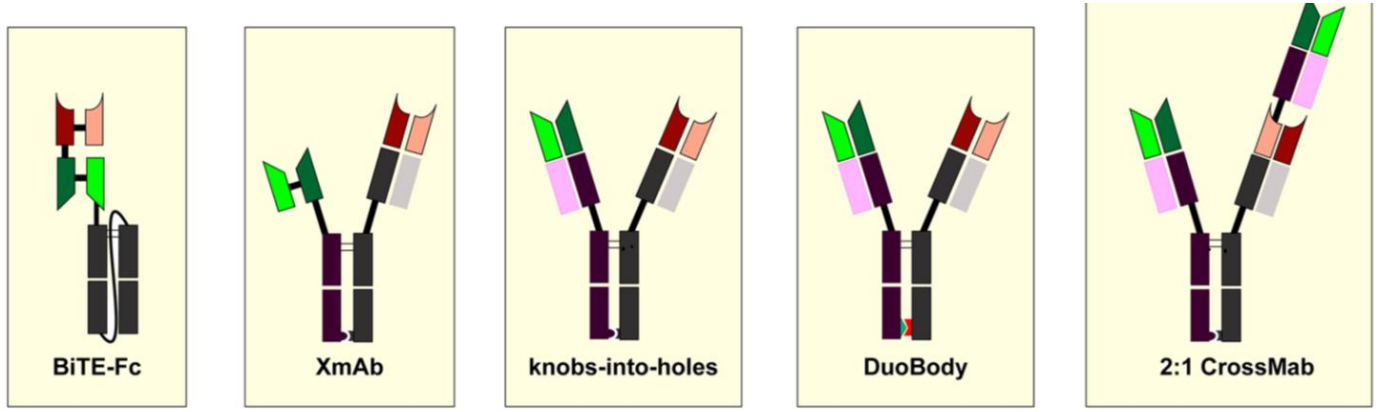
Made in biorender.com

SedykhSingh, A., et al. Br J Cancer 124, 1037–1048 (2021) ; Falchi L, et al. Blood. 2023;141(5):467-480. ; SE, et al. Drug Des Devel Ther. 2018;12:195-208 ; Zhou et al. Biomarker Research. 2021; 9:38

Bispecific Antibodies (BsAbs)

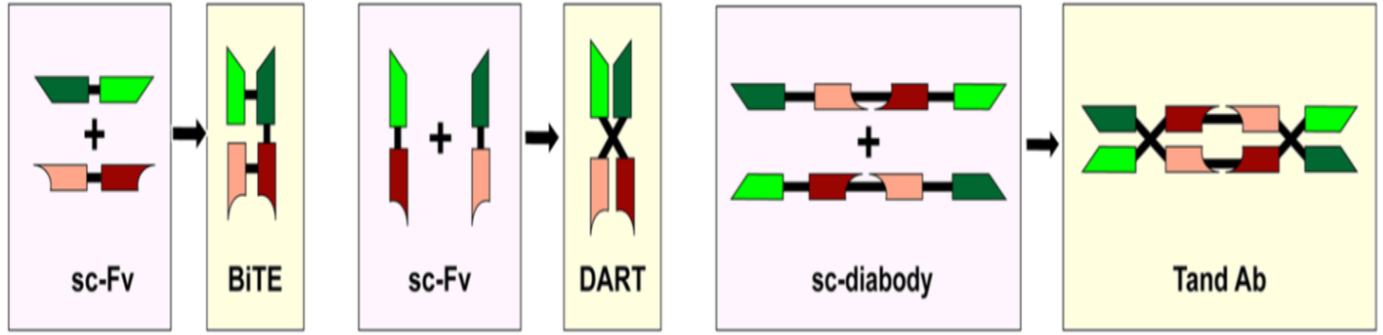
IgG-based (Fc format)

- Large molecular weight
- Fc-mediated effector function
- Increased solubility and stability
- Increased serum half-life and affinity



Non-IgG based (Fv format)

- Lack of Fc fragments
- Easy to produce
- Low immunogenicity
- Increased permeability to tumor tissues



Tian et al. Bispecific T cell engagers. J Hematol Oncol 2021 14:75; Fan G, Wang Z, Hao M, Li J. J Hematol Oncol 2015 8:130.; Zhou S, Liu M, Ren F, Meng X, Yu J. Biomark Res. 2021 May 26;9(1):38.

B-cell Lymphoma Bispecific FDA Approval Timeline

2022 **2023**

December 2022:

Mosunetuzumab-axgb
- Indication: R/R FL ≥2 L
- Study: GO29781

June 2023:

Glofitamab-gxbm
- Indication: R/R DLBCL NOS or LBCL arising from FL after ≥2 L
- Study: NP30179

May 2023:

Epcoritamab-bysp
- Indication: R/R DLBCL NOS (DLBCL from indolent lymphoma, HGBCL) after ≥2 L
- Study: EPCORE™ NHL-1

Mosunetuzumab – axgb

Indication: relapsed or refractory follicular lymphoma, after two or more lines of systemic therapy

Mechanism of action: targets CD3 on T-cells and CD20 expressed on the surface of B-cells

Approval Date: December 2022

Lunsunio (Mosunetuzumab) [prescribing information]. December 2022

Mosunetuzumab – axgb

Clinical Trial Data

Inclusion Criteria

- Grade 1-3a follicular lymphoma
- Relapsed/refractory to ≥ 2 lines of therapy
  - Anti-CD20
  - Alkylating agent
- Adults (≥ 18 years)
- ECOG 0-1
- Hepatic and renal function WNL

Dosing schedule

Cycle 1
- Day 1: 1mg
- Day 8: 2mg
- Day 15: 60mg

Cycle 2-12
- Day 1 60mg

Cycle 3 and beyond
- Day 1 30mg

- Premedication (required for C1/2)
  - Acetaminophen
  - Anti-histamine
  - Steroid
- Duration of treatment
  - 8 cycles (21 day)
    - CR – discontinue
    - PR/SD – continue for 9 more cycles

Endpoints

- Primary endpoint: CR
- Secondary Endpoints: ORR, DOR, PFS, OS, Safety

Lancet Oncol 2022,23:1055-1065

CR: complete response PR: partial response SD: stable disease ORR = Overall Response Rate, CR = Complete Response, PFS = Progressive Free Survival. OS = Overall Survival

Mosunetuzumab – axgb

Baseline Characteristics

	N=90
Age	60 (53-67)
FLIPI risk score 1-4	86 (96%)
Bulky disease (>6cm)	31 (34%)
Median previous lines of therapy	3 (2-4)
2 previous lines of therapy	34 (38%)
3 previous lines of therapy	28 (31%)
> 3 previous lines of therapy	28 (31%)
Double refractory (both anti-CD20 AND alkylator therapy)	48 (53%)
PI3K inhibitors	17 (19%)
Immunomodulatory agents	13 (14%)
Chimeric antigen receptor T-cell therapy	3 (3%)
Prior autologous stem cell transplant	19 (21%)
POD24 (progression of disease within 24 months)	47 (52%)

Budde LE et al Lancet Oncol July 2022,23:1055-1065

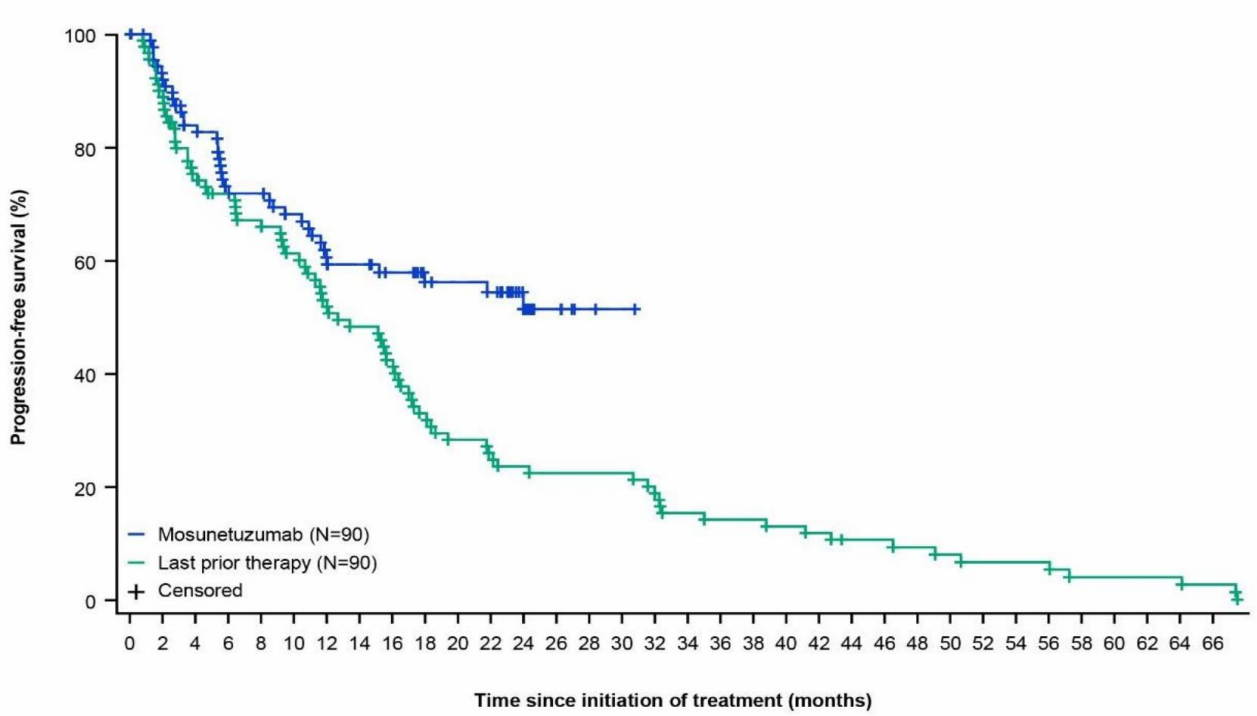
Mosunetuzumab – axgb

Results

CR: **60%** (95% CI 49.1-70.2) vs 36%

ORR: **80%** (95% CI 70.3-87.7) vs 56%

24month PFS: **51.4%** vs 23.5%



Budde LE et al Lancet Oncol July 2022,23:1055-1065; Bartlett NL, Sehn LH, Matasar MJ, et al. 2022 ASH Annual Meeting; December 10-13, 2022; New Orleans, LA. Abstract 610.

ORR= Objective Response Rate; CR: Complete response; PFS: Progression-free survival

Mosunetuzumab – axgb

Results

	Grade 1-2 (%)	Grade 3-4 (%)
Fatigue	37	0
Headache	30	1
Pruritis	21	0
ICANS	3	0

	Grade 1-2 (%)	Grade 3-4 (%)
Neutropenia Median time of onset = 70 days (31 – 106) Median duration= 8 days No incidence of FN GCSF support (69%)	2	26

	All Grade (n)	Grade 3-4 (n)
Infections UTI (n=3) Epstein-Barr viremia (n=2) Pneumonia (n=2) Septic shock (n=2) Covid and other (n=9)	18	13

Budde LE et al Lancet Oncol July 2022,23:1055-1065

Mosunetuzumab – axgb
Safety – CRS data

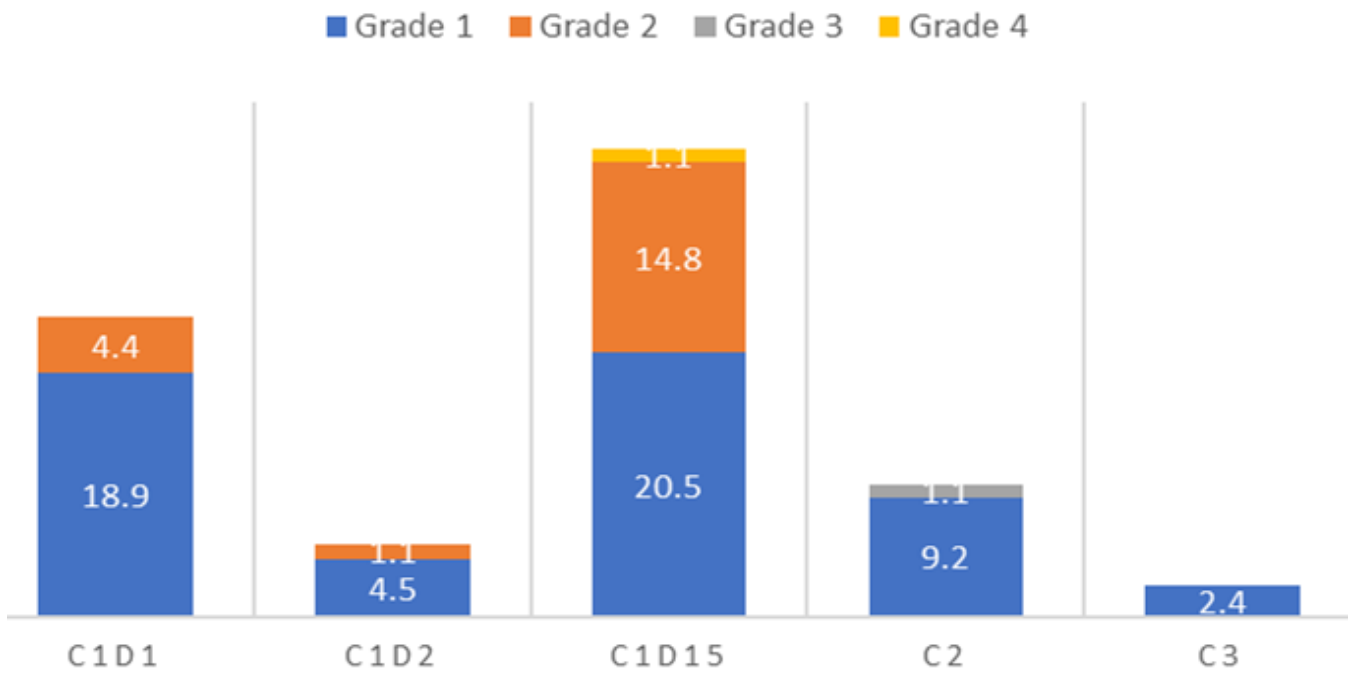
CRS: 40 patients (44%)

Onset of CRS:

- 5 hours (C1D1)
- 27 hours (C1D15)

Duration of CRS

- 3 days



Budde LE et al Lancet Oncol July 2022,23:1055-1065

CRS: Cytokine Release Syndrome

Mosunetuzumab – axgb
Pharmacotherapy Considerations

Administration:

- Intravenous Infusion
- Hospitalization is not required (23% hospitalized in the trial)

Pre-medications:

- Corticosteroid: Dexamethasone 20 mg IV or methyprednisolone 80mg IV atleast 1 hour prior
- Antihistamine: Diphenhydramine 50mg IV/PO atleast 30 mins prior to infusion
- Antipyretic: Acetaminophen 500 to 1,000 mg IV/PO atleast 30 mins prior to infusion
  - Recommended for cycle 1 and 2

Consider prophylactic medications

- Consider G-CSF as applicable
- Consider Pneumocystis jirovecii pneumonia (PJP) and herpes virus prophylaxis

Epcoritamab – bysp

Indication: relapsed or refractory diffuse large B-cell Lymphoma NOS (DLBCL from indolent lymphoma, HGBCL) after ≥2 L after two or more lines of systemic therapy

Mechanism of action: targets CD3 on T-cells and CD20 expressed on the surface of B-cells

Approval Date: May 2023

Epkinly (Epcoritamab) [prescribing information]. May 2023

Epcoritamab – bysp

Clinical Trial Data

Inclusion Criteria

- Relapsed or refractory CD20+ large B-cell lymphoma (LBCL) after two or more lines of systemic therapy
- Adult patients
- ECOG 0-2

→

Dosing schedule

Cycle 1:,
- Day 1: 0.16mg
- Day 8: 0.8mg
- Day 15: 48 mg
- Day 22: 48mg

Cycle 2-3
- Day 1,8,15,22: 48mg

Cycle 4-9:
- Day 1,15: 48 mg

Cycle 10 and beyond:
- Day 1: 48 mg

- Premedication (required for C1)
  - Acetaminophen
  - Anti-histamine
  - Steroid (Day 1-4, 8-11, 15-18, 22-25)

→

Endpoints

- Primary endpoint: ORR
- Secondary Endpoints: CR, DOR, PFS, OS, Safety

J Clin Oncol. 2023 Apr 20;41(12):2238-2247.

ORR = Overall Response Rate, CR = Complete Response, DOR = Duration of response, PFS = Progressive Free Survival. OS = Overall Survival

Epcoritamab – bysp
Baseline Characteristics

	N=157
Age	64 (20-83)
Median previous lines of therapy	3 (2-11)
2 previous lines of therapy	46 (29%)
3 previous lines of therapy	50 (32%)
> 3 previous lines of therapy	61 (39%)
Double hit/triple-hit lymphoma	13/99 (13.1%)
Refractory to >/= 2 lines of therapy	119 (76%)
Prior CAR T-cell therapy	61 (39%)
Progressed within 6 months of CAR Tcell therapy	46/61 (75%)

J Clin Oncol. 2023 Apr 20;41(12):2238-2247.

Epcoritamab – bysp
Results

ORR: **63.1%** (95% CI 55-70.6)

CR: **38.9%** (95% CI 31.2-46.9)

Duration of Response: 12 months (6.6 –NR)

PFS months: 4.4 (3-7.9)

OS months: not reached (11.3- NR)

Time to response: 1.4 months (1-8.4)

J Clin Oncol. 2023 Apr 20;41(12):2238-2247.

ORR= Objective Response Rate; CR: Complete response; PFS: Progression-free survival; NR: not reached

Epcoritamab – bysp
Results

	Any Grade(%)	Grade > 3 (%)
Pyrexia	23.6	0
Fatigue	22.9	1.9
Pruritis	21	0
ICANS	6.4	0.6

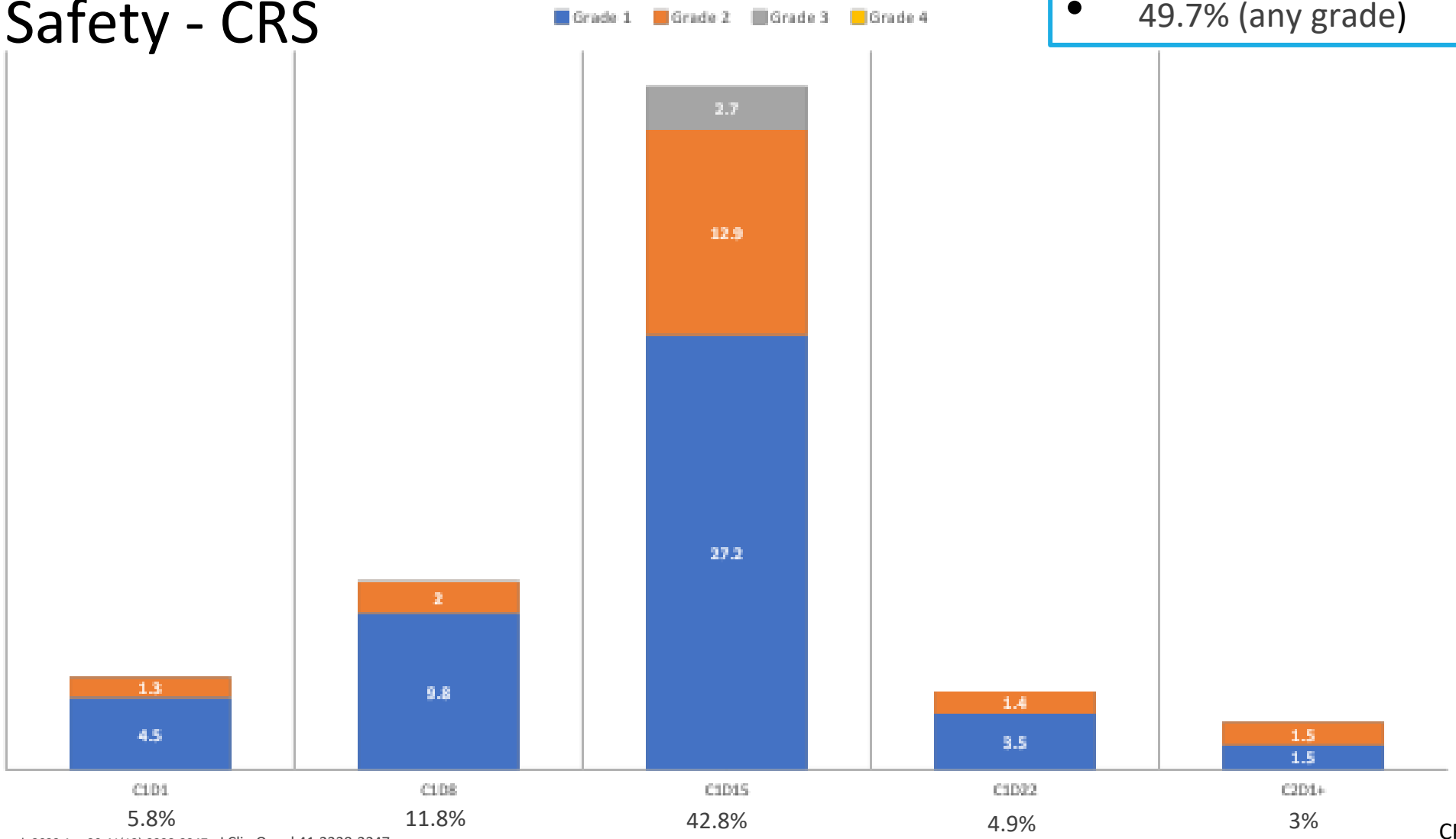
	Any Grade(%)	Grade > 3 (%)
Neutropenia Febrile Neutropenia (2.5%) GCSF support (10%)	21.7	14.6

J Clin Oncol. 2023 Apr 20;41(12):2238-2247.

Epcoritamab – bysp

Safety - CRS

- Onset of CRS: **20 hrs** (C1D1) **27 hours** (C1D15)
- Duration of CRS: **3 days**
- 49.7% (any grade)



J Clin Oncol. 2023 Apr 20;41(12):2238-2247.; J Clin Oncol 41:2238-2247

CRS: Cytokine Release Syndrome

Epcoritamab – bysp
Pharmacotherapy Considerations

Administration:

- Subcutaneous administration
- Hospitalization required for Day 15 (24 hours)

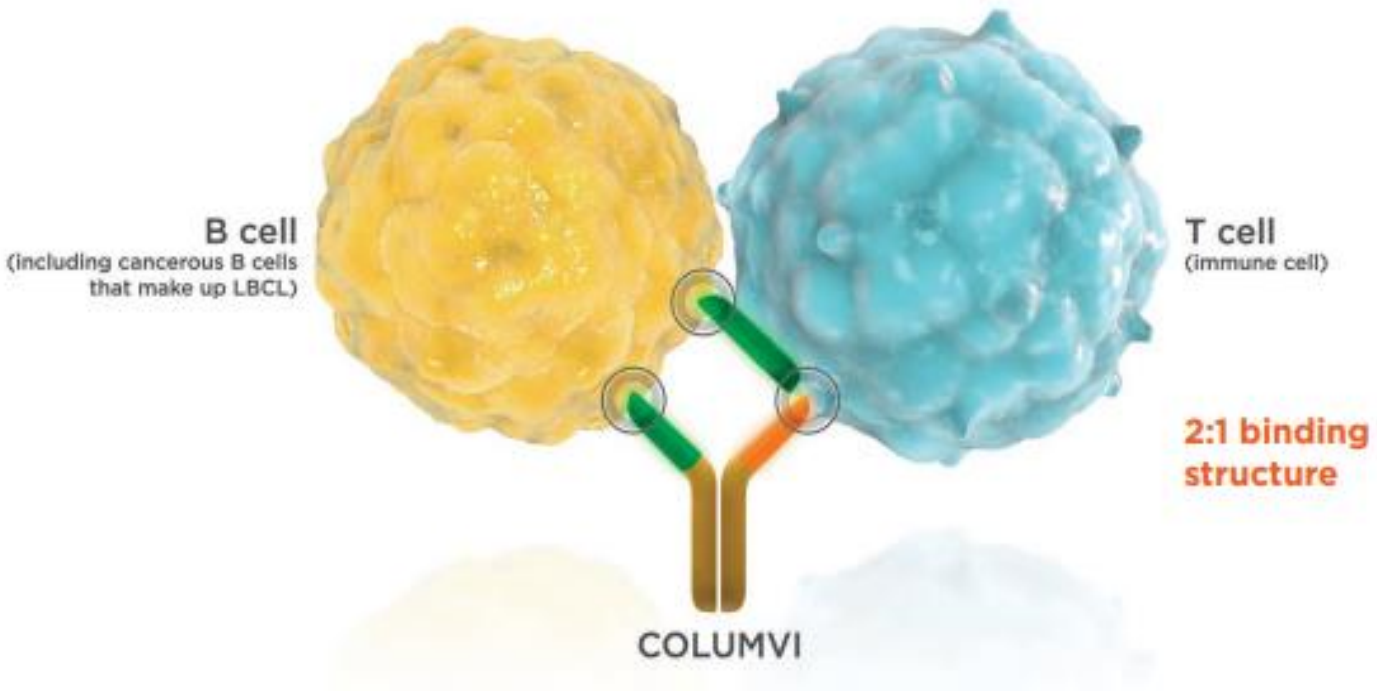
Pre-medications:

- Corticosteroid: Dexamethasone 15 mg or prednisone 100mg (and for 3 consecutive days after)
- Antihistamine: Diphenhydramine 50mg
- Antipyretic: Acetaminophen 500 to 1,000 mg
- Recommended for cycle 1; steroids can be continued for C2 if previous CRS

Consider prophylactic medications

- Consider G-CSF as applicable
- Recommend Pneumocystis jirovecii pneumonia (PJP) and consider herpes virus prophylaxis

Glofitamab-gxbm



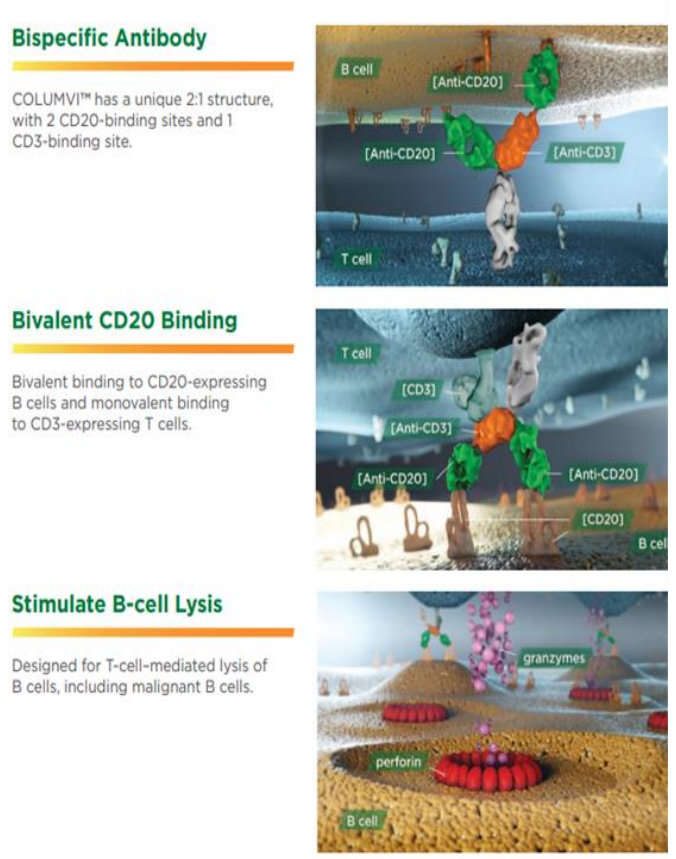
Glofitamab-gxbm
Clinical Pharmacology

Indication

Glofitamab-gxbm is approved by the Food and Drug Administration for relapsed or refractory DLBCL, NOS or LBCL arising from follicular lymphoma, after two or more lines of systemic therapy

Mechanism of action

Glofitamab-gxbm is a bispecific T-cell engaging antibody that targets CD3 and CD20 in a novel 2:1 tumor–T-cell binding configuration , resulting in T-cell activation and proliferation, cytokine secretion, and lysis of CD20-expressing B cells



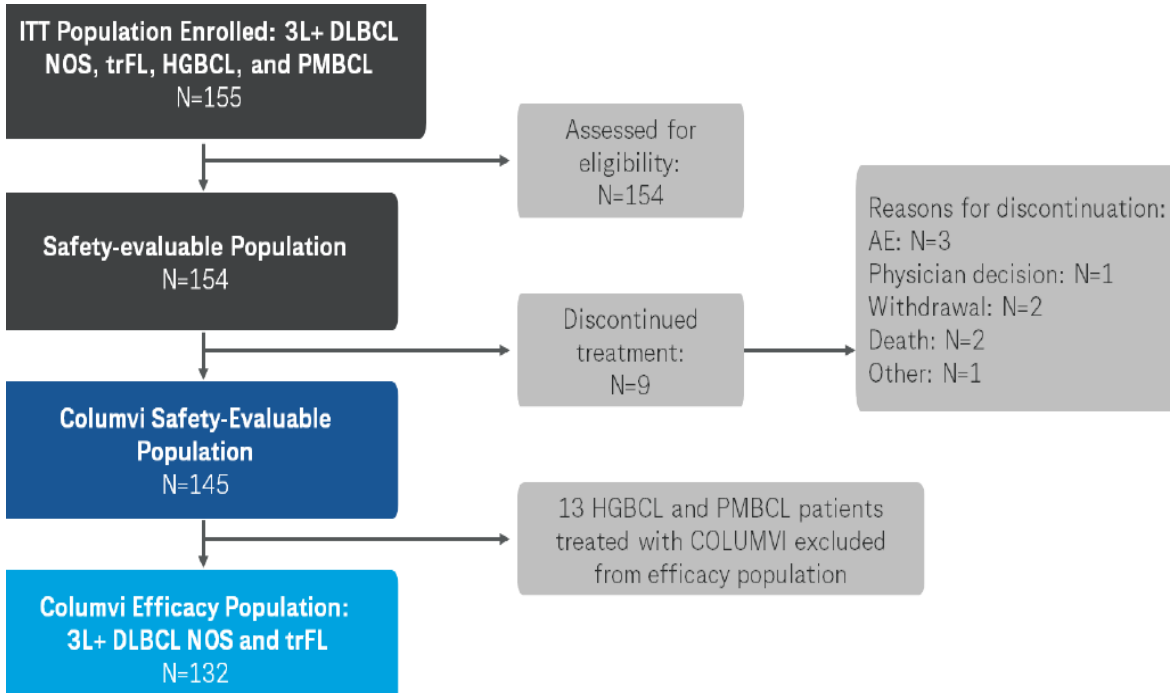
Columvi (Glofitamab) [prescribing information]. June 2023

DLBCL, NOS = Diffuse large B-cell lymphoma, not otherwise specified;
LBCL= Large B-cell lymphoma

Glofitamab-gxbm
Clinical Trial

Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

An open-label, multicenter, multicohort, single-arm clinical trial



- Median age 67 years (range: 21-90)
- Diagnosis of DLBCL, NOS in 80% of patients, 20% had transformed follicular lymphoma
- Median number of prior therapies was 3 (range 2-7), 55% of patients had primary refractory disease, 83% with refractory to last previous therapy, 19% with prior autologous stem cell transplant, and 30% with prior CAR T-cell therapy

Dickinson MJ, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231; Columvi (Glofitamab) [Formulary Dossier] Genentech Inc; 2023

DLBCL, NOS =Diffuse large B-cell lymphoma, not otherwise specified; CAR-T= Chimeric antigen receptor

Glofitamab-gxbm
Clinical Trial
Pivotal Phase II – Design

Inclusion Criteria

- DLBCL, NOS or LBCL arising from FL
- ECOG PS 0-1
- ≥2 prior therapies including:
  - anti-CD20 antibody
  - anthracycline agent

→

Dosing schedule

Cycle 1
- Pretreatment with Obinutuzumab 1000 mg (Day 1)
- Glofitamab-gxbm step-up dosing:
  - 2.5 mg (Day 8)
  - 10 mg (Day 15)

Cycle 2-12
- Glofitamab-gxbm 30 mg on Day 1 every 3 weeks for 11 cycles

→

Endpoints

- Primary endpoint:
  - CR rate by IRC
- Secondary endpoints:
  - ORR
  - DOCR
  - DOR

Day 8: Hospitalize all patients during and for 24 hours post-infusion
Day 15: Hospitalize patients who experienced CRS during step-up dose 1 for 24 hours
Cycles 2-12: Hospitalize **patients who experienced CRS with previous infusion for 24 hours**

Dickinson MJ, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231; Columvi (Glofitamab) [durable remissions achieved with a unique T-cell engaging bispecific antibody brochure]. M-US-00017615 (v1.0), Printed in USA. CA: Genentech Inc; June 2023; Columvi (Glofitamab) [Formulary Dossier] Genentech Inc; 2023

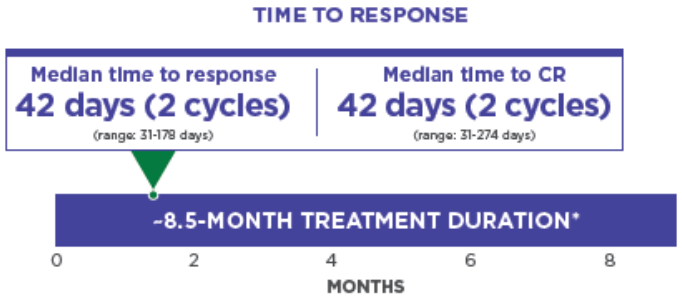
DLBCL, NOS =Diffuse large B-cell lymphoma, not otherwise specified; LBCL= Large B-cell lymphoma; FL=Follicular lymphoma; CR=Complete response; IRC=Independent review committee; ORR=Overall response rate; DOCR=Duration of complete response; DOR=Duration of response

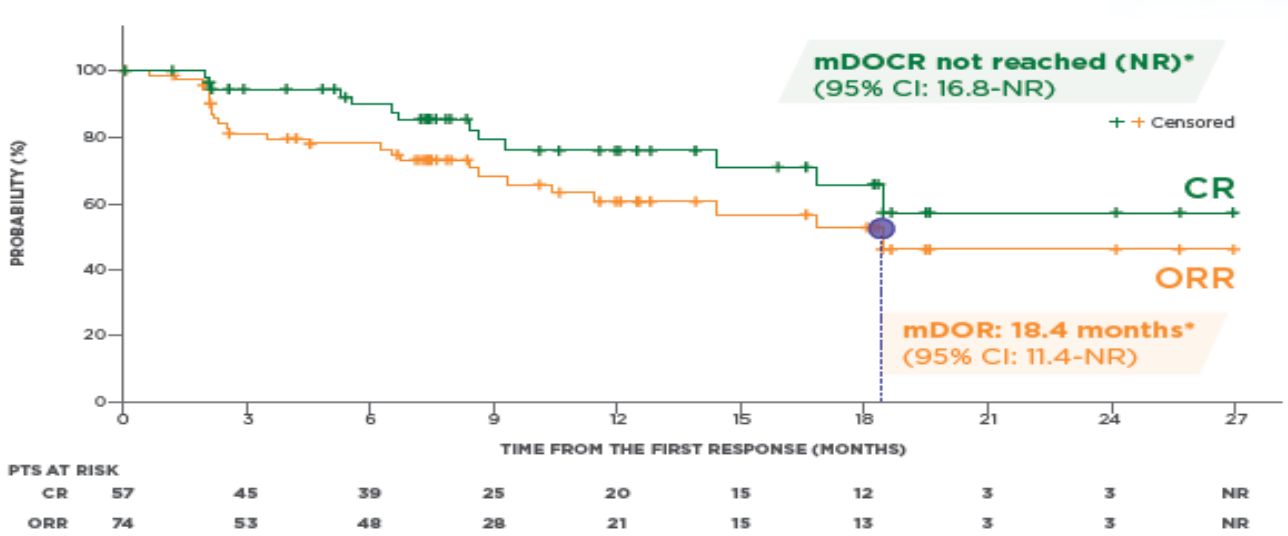
Glofitamab-gxbm
Clinical Trial
Pivotal Phase II – Efficacy Results

Overall Response Rate
(n=74/132; 95% CI: 47%-65%)

- 13% of patients experienced partial response (n=17/132; 95% CI: 8%-20%)

Complete Response
(n=57/132; 95% CI: 35%-52%)





mDOR was 18.4 months (95% CI: 11.4-NR) and mDOCR was not reached (95% CI: 16.8-NR)

Among responders, the estimated median follow-up for DOR was 11.6 months.

*From date of first response (PR or CR) until disease progression or death due to any cause.

Dickinson MJ, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231; Columvi (Glofitamab) [durable remissions achieved with a unique T-cell engaging bispecific antibody brochure]. M-US-00017615 (v1.0), Printed in USA. CA: Genentech Inc; June 2023; Columvi (Glofitamab) [Formulary Dossier] Genentech Inc; 2023

mDOCR= Median duration of complete response; mDOR=Median duration of response

Glofitamab-gxbm
Clinical Trial
Pivotal Phase II – Safety Results

Adverse Reactions	COLUMVI N=145	
	All Grades (%)	Grade 3 to 4 (%)
Immune system disorders		
Cytokine release syndrome	70	4.1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	21	2.1
General disorders		
Fatigue†	20	1.4
Pyrexia	16	0
Edema‡	10	0
Skin and subcutaneous tissue disorders		
Rash§	20	1.4
Gastrointestinal disorders		
Constipation	14	0
Diarrhea	14	0
Nausea	10	0
Abdominal pain‖	10	0
Neoplasms		
Tumor flare	12	2.8
Neurologic Disorders		
Headache	10	0

- Serious adverse reactions occurred in 48% to which in ≥2% of patients included CRS, COVID-19 infection, sepsis, and tumor flare
- Fatal adverse reactions occurred in 5% of patients from COVID-19 infection (3.4%), sepsis (1.4%), and delirium (0.6%)
- ARs led to dose interruptions in 19% of patients, most frequently (≥2%) from neutropenia and thrombocytopenia
- ARs leading to treatment discontinuation were reported in 7% of patients

  –Included infection, delirium, neutropenia, CRS
- ICANS reactions were also observed
  - All Grade: 7 (4.8%); Grade ≥3: 2 (2.1%)

Dickinson MJ, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231; Columvi (Glofitamab) [durable remissions achieved with a unique T-cell engaging bispecific antibody brochure]. M-US-00017615 (v1.0), Printed in USA. CA: Genentech Inc; June 2023; Columvi (Glofitamab) [Formulary Dossier] Genentech Inc; 2023

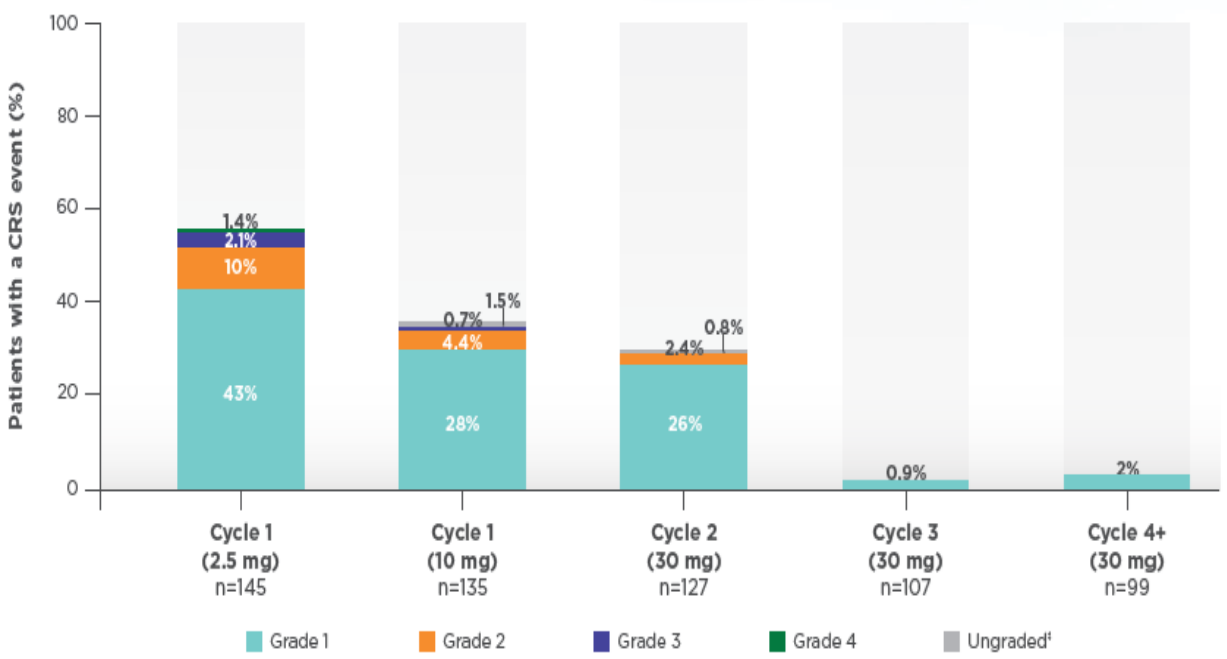
ARs=Adverse Reactions; CRS= Cytokine Release Syndrome; ICANS=Immune effector cell-associated neurotoxicity syndrome

Glofitamab-gxbm

Clinical Trial

Pivotal Phase II – CRS

CRS Incidence by grade and cycle



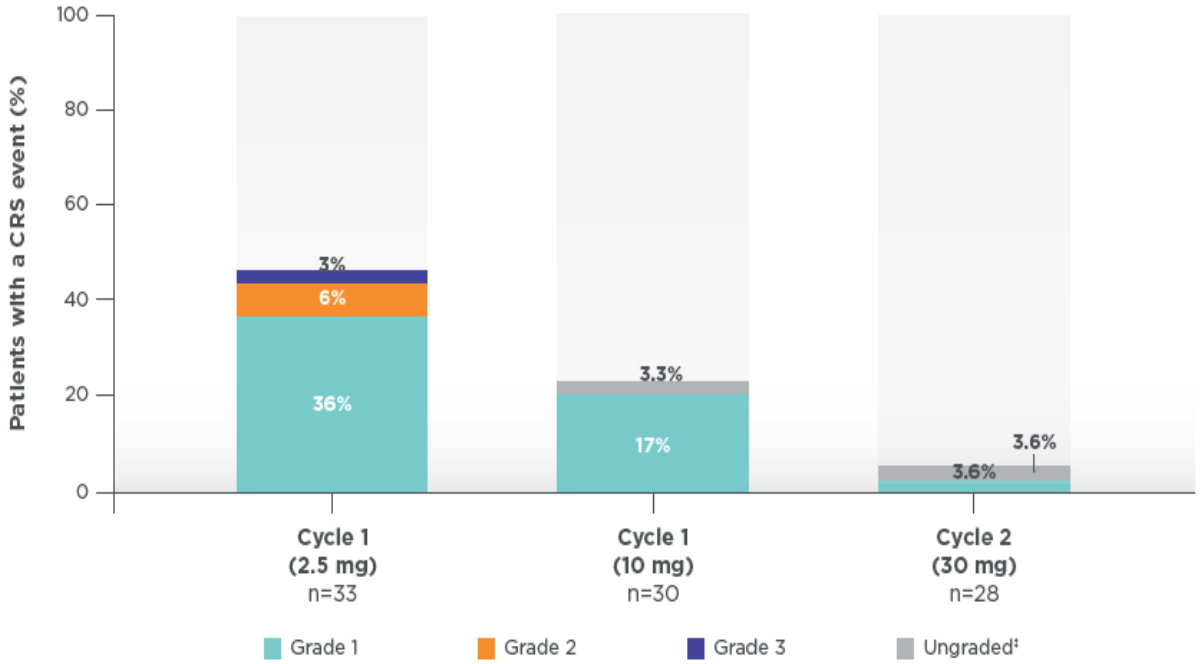
- CRS of any grade occurred in 70% of patients
  - CRS Grade 1 occurred in 52% of patients, 14% Grade 2, 2.8% Grade 3, and 1.4% Grade 4
  - Grade 1-2 CRS event was observed in 94.1% of patients
  - Grade 3 or 4 CRS was only observed during Cycle 1
  - Recurrent CRS occurred in 34% of all patients
- The median time to onset of CRS
  - C1D8: 14hrs (5-74hrs), C1D15: 29hrs (7-125hrs), C2D1: 28hrs (2-62hrs)
- CRS after any dose resolved in 98% of cases, with a median duration of 2 days (range: 1-14 days)

Dickinson MJ, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231; Columvi (Glofitamab) [durable remissions achieved with a unique T-cell engaging bispecific antibody brochure]. M-US-00017615 (v1.0), Printed in USA. CA: Genentech Inc; June 2023; Columvi (Glofitamab) [Formulary Dossier] Genentech Inc; 2023

CRS: Cytokine Release Syndrome

Glofitamab-gxbm
Clinical Trial
Pivotal Phase II – CRS

Observed CRS with dexamethasone premedication



Mandatory dexamethasone premedication led to a lower incidence of any grade CRS than treatment with any glucocorticoid

Dickinson MJ, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231; Columvi (Glofitamab) [durable remissions achieved with a unique T-cell engaging bispecific antibody brochure]. M-US-00017615 (v1.0), Printed in USA. CA: Genentech Inc; June 2023; Columvi (Glofitamab) [Formulary Dossier] Genentech Inc; 2023

CRS: Cytokine Release Syndrome

Glofitamab-gxbm
Pharmacotherapy Considerations

Administration:

- Administer only as an intravenous infusion through a dedicated infusion line that includes a sterile 0.2-micron in-line filter
  - Cycles 1-2: over 4 hours
  - Cycles 3-12: over 2 hours
    - Patients experiencing cytokine release syndrome (CRS): Cycles 1-2: over 8 hours; Cycles 3-12: over 4 hours
- Patients should be hospitalized during and for 24 hours after completion of infusion of step-up dose 1 (2.5 mg on Cycle 1 Day 8)

Pre-medications:

- Corticosteroid: Dexamethasone 20 mg IV at least 1 hour prior to infusion
- Antihistamine: Diphenhydramine 50 IV/PO at least 30 minutes prior to infusion
- Antipyretic: Acetaminophen 500 to 1,000 mg orally at least 30 minutes prior to infusion
  - Dexamethasone required for Cycles 1-3; may be administered in Cycles 4-12 if any CRS experienced with the previous dose

Consider prophylactic medications

- Antiviral agent to prevent herpes simplex virus reactivation
- Anti-PJP agent to present pneumocystis jiroveci pneumonia infection
- Anti-CMV agent to present cytomegalovirus infection

Contraindications, Warnings and Precautions

- US Boxed Warning: Cytokine release syndrome
- Warnings and Precautions: Neurologic toxicity, serious infections, tumor flare, embryo-fetal toxicity
- Contraindications: None

Multiple Myeloma Bispecific Antibody FDA Approval Timeline

2022 **2023**

October 2022:

Teclistamab-cqyv
Indication: Relapsed/Refractory Multiple Myeloma after at least 4 prior lines of therapy
- Study: MajesTEC-1

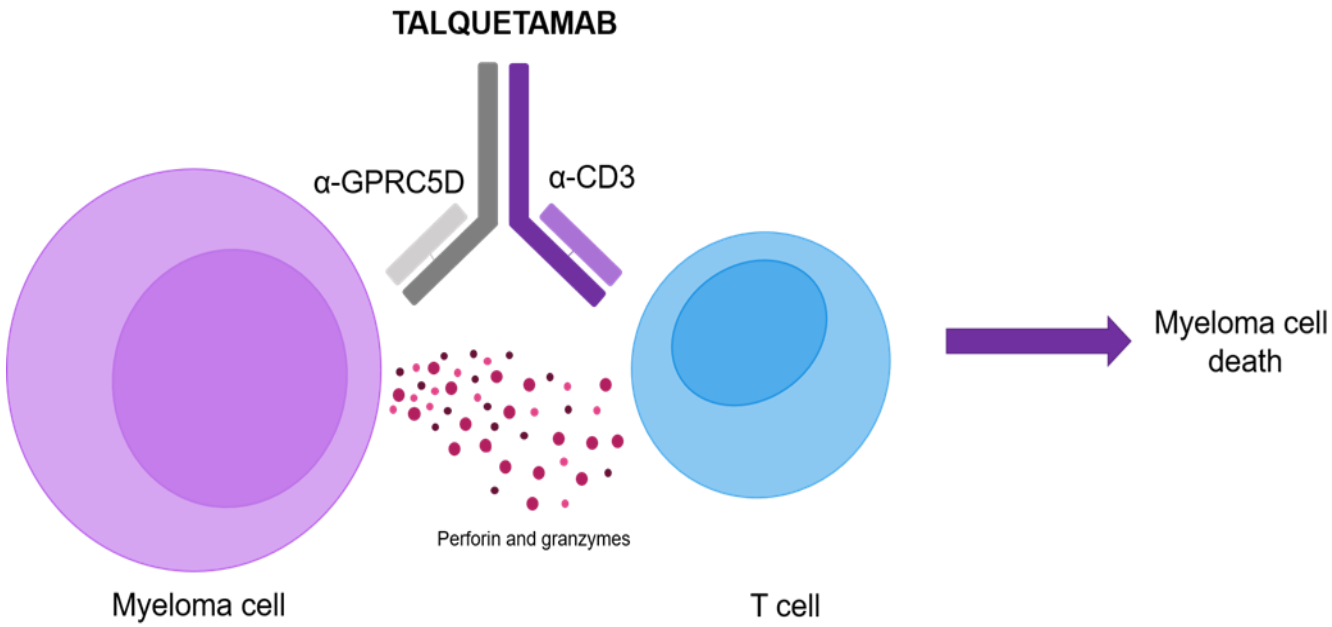
August 2023:

Talquetamab-tgvs
Indication: Relapsed/Refractory Multiple Myeloma after at least 4 prior lines of therapy
- Study: MMY1001 (MonumenTAL-1) Trial

August 2023:

Elranatamab-bcmm
Indication: Relapsed/Refractory Multiple Myeloma after at least 4 prior lines of therapy
- Study: MagnetisMM-3 trial

Talquetamab-tgvs



Talquetamab-tgvs
Clinical Pharmacology

Indication

Talquetamab-tgvs is approved by the Food and Drug Administration for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agents, and an anti-CD38 monoclonal antibody

Mechanism of action

Talquetamab-tgvs is a bispecific T-cell engaging antibody that targets CD3 and G protein-coupled receptor class C group 5 member D (GPRC5D), resulting in the lysis of malignant plasma cells that occurs via T-cell recruitment and activation

Talvey (talquetamab) [prescribing information]. August 2023

Talquetamab-tgvs
Clinical Trial

MonumenTAL-1: Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma

Prospective, open-label, multicenter, phase I/2 clinical trial

232 patients met study criteria and received talquetamab-tgvs subcutaneous (n=130) or IV (n=102)

- Subcutaneous doses had a more favorable pharmacokinetics, safety, and efficacy profile and was selected for phase 2 of the study
  - N=30 - 405 µg/kg weekly
  - N=44 - 800 µg/kg every 2 weeks

	Talquetamab 405 µg/kg QW (n = 30)	Talquetamab 800 µg/kg Q2W (n = 44)
Median age – years (range)	62 (46–80)	64 (47–84)
Median time since diagnosis – years (range)	5.6 (1.7-19.6)	6.4 (0.8-21.3)
Median lines of previous therapy – no. (range)	6 (2-14)	5 (2-17)
Previous stem-cell transplantation – no. (%)	27 (90)	33 (75)
Previous therapy exposure – no. (%)		
Triple-class exposure	30 (100)	43 (98)
Penta-drug exposure	24 (80)	30 (68)
Refractory status – no. (%)		
Immunomodulatory drug	28 (93)	42 (95)
Proteasome inhibitor	25 (83)	36 (82)
Anti-CD38 monoclonal antibody	30 (100)	39 (89)
Triple-class refractory	23 (77)	33 (75)
Penta-drug refractory	6 (20)	9 (20)
Refractory to last line of therapy	26 (87)	39 (89)

Chari A et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med*. 2022;387(24):2232-2244.

Talquetamab-tgvs
Clinical Trial
Phase II – Design

Inclusion Criteria

- Relapse/refractory with proteasome inhibitor, anti-CD38, immunomodulator as prior therapy
- ECOG PS 0-1

→

Dosing schedule

Weekly step-up dosing schedule	Weekly dosing schedule
Day 1 (step-up dose 1): 10 µg/kg Day 4 (step-up dose 2): 60 µg/kg Day 7 (first treatment dose): 405 µg/kg	405 µg/kg once weekly Starting 1 week after the first treatment dose and weekly thereafter
Biweekly (every 2 weeks) step-up dosing schedule	**Biweekly (every 2 weeks) dosing schedule**
Day 1 (step-up dose 1): 10 µg/kg Day 4 (step-up dose 2): 60 µg/kg Day 7 (step-up dose 3): 300 µg/kg Day 10 (first treatment dose): 800 µg/kg	800 µg/kg every 2 weeks Starting 2 weeks after the first treatment dose and every 2 weeks thereafter

Patients should be hospitalized for 48 hours after administration of all doses within the step-up dosing schedule
Subcutaneous injection into abdomen (preferred) or thigh

→

Endpoints

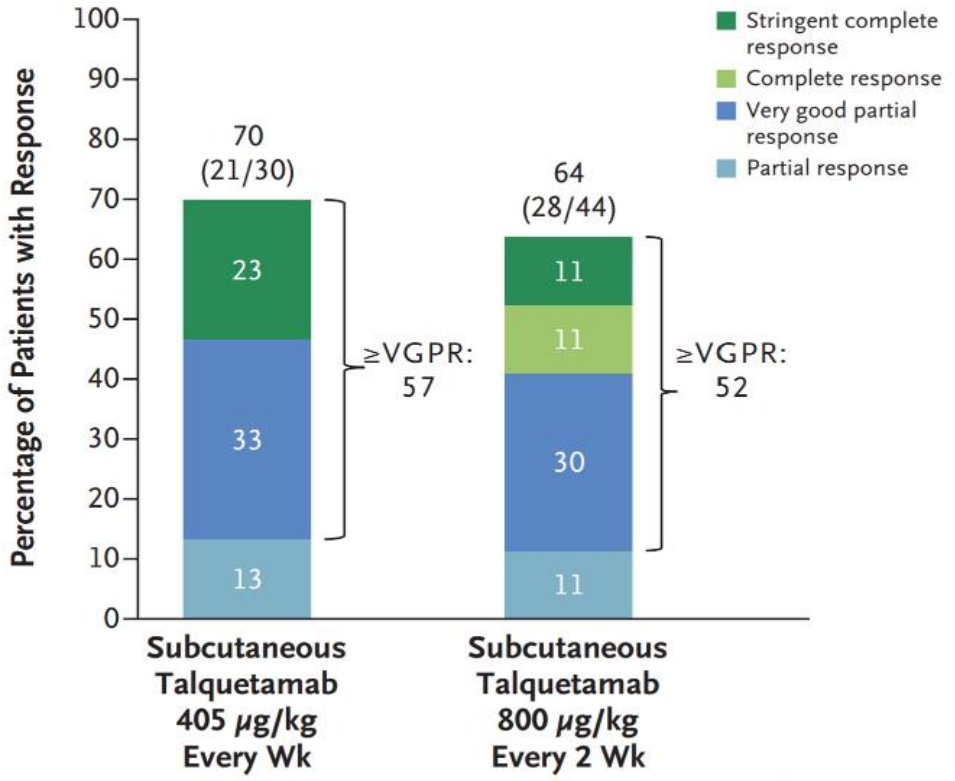
- Primary endpoint:
  - Frequency and severity of ARs
- Secondary endpoints:
  - ORR
  - DOR
  - TTR
  - PFS

Chari A et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med*. 2022;387(24):2232-2244.

ARs=Adverse reactions; ORR=Overall response rate; DOR=Duration of response; TTR=Time to respond; PFS=Progression free survival

Talquetamab-tgvs
Clinical Trial
Phase II – Efficacy Results

	Talquetamab 405 µg/kg QW (n = 30)	Talquetamab 800 µg/kg Q2W (n = 44)
Overall Response – no. (%)	21 (70.0)	28 (63.6)
Best Response – no. (%)		
S-CR	7 (23.3)	5 (11.4)
CR	0	5 (11.4)
VGPR	10 (33.3)	13 (29.5)
PR	4 (13.3)	5 (11.4)
SD	9 (30.0)	13 (29.5)
PD	0	3 (6.8)
Median time to response – months (range)	0.9 (0.2-3.8)	1.2 (0.3-6.8)
Median time to CR – months (range)	9.3 (1.7-17.1)	2.3 (2.1-6.8)
Median response duration – months (95% CI)	10.2 (3.0-NR)	7.8 (4.6-NR)
Progression-free survival (patients)	10/21	19/28



S-CR=Stringent complete response; CR=Complete response; VGPR=Very good partial response; PR=Partial response; SD=Stable disease; PD=Progressive disease

Chari A et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med*. 2022;387(24):2232-2244.

Talquetamab-tgvs
Clinical Trial
Phase II – Safety Results

	Talquetamab 405 µg/kg QW		Talquetamab 800 µg/kg Q2W	
Event – no. (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Any adverse event	30 (100)	26 (87)	44 (100)	38 (86)
Hematologic – no. (%)				
Anemia	18 (60)	9 (30)	19 (43)	10 (23)
Neutropenia	20 (67)	18 (60)	16 (36)	14 (32)
Lymphopenia	12 (40)	12 (40)	17 (39)	17 (39)
Thrombocytopenia	11 (37)	7 (23)	10 (23)	5 (11)
Leukopenia	12 (40)	9 (30)	8 (18)	6 (14)

	Talquetamab 405 µg/kg QW	Talquetamab 800 µg/kg Q2W
CRS grade – no. (%)	23 (76.7)	35 (79.5)
Grade 1	18 (60.0)	25 (56.8)
Grade 2	4 (13.3)	10 (22.7)
Grade 3	1 (3.3)	0
Median time to CRS – days (range)	2 (1-22)	2 (1-5)
Median CRS duration – days (range)	2 (1-3)	2 (1-5)

	Talquetamab 405 µg/kg QW		Talquetamab 800 µg/kg Q2W	
Event – no. (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Non-Hematologic				
Headache	6 (20)	0	11 (25)	0
Arthralgia	7 (23)	0	4 (9)	0
Dry mouth	9 (30)	0	25 (57)	0
Dysgeusia	19 (64)	N/A	25 (57)	N/A
Dysphagia	11 (37)	0	12 (27)	0
Nausea	9 (30)	0	7 (16)	0
Diarrhea	9 (30)	0	7 (16)	0
Decreased weight	9 (30)	0	14 (32)	1 (2)
Skin-related event	20 (67)	0	31 (70)	1 (2)
Nail-related event	17 (57)	0	12 (27)	1 (2)
Rash-related event	14 (47)	0	13 (30)	7 (16)
Pyrexia	10 (33)	0	8 (18)	0
Increased AST	3 (10)	0	15 (34)	3 (7)
Increased ALT	6 (20)	1 (3)	13 (30)	3 (7)
Hypophosphatemia	8 (27)	5 (17)	8 (18)	3 (7)
Increased GGT	6 (20)	1 (3)	10 (23)	3 (7)

Chari A et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med*. 2022;387(24):2232-2244.

CRS= Cytokine Release Syndrome

Talquetamab-tgvs
Clinical Trial
Phase II – Safety Results

	Talquetamab 405 µg/kg QW	Talquetamab 800 µg/kg Q2W
≥ 1 neurotoxic event – no. (%)	3 (10.0)	2 (4.5)
Anosmia	0	1 (2.3)
Aphasia	1 (3.3)	0
Encephalopathy	1 (3.3)	0
Confusional state	1 (3.3)	1 (2.3)

	Talquetamab 405 µg/kg QW	Talquetamab 800 µg/kg Q2W
≥ 1 infection – no. (%)	14/30 (47%)	15/44 (34)
Grade 3-4	2/30 (7%)	3/44 (7)
Opportunistic infection	2/30 (7%)	2/44 (5)

Chari A et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med*. 2022;387(24):2232-2244.

Talquetamab-tgvs
Pharmacotherapy Considerations

Administration:

- Subcutaneous injection
- Patients should be hospitalized for 48 hours after administration of each step-up dose (including first treatment dose)

Pre-medications:

- Corticosteroid: Dexamethasone 16 mg IV/PO 1-3 hours prior to infusion
- Antihistamine: Diphenhydramine 50 IV/PO 1-3 hours prior to infusion
- Antipyretic: Acetaminophen 650 to 1,000 mg IV/PO 1-3 hours prior to infusion
  - Recommended 1-3 prior to each step-up dose and repeated step-up doses or cytokine release syndrome

Consider prophylactic medications

- Antiviral agent to prevent herpes simplex virus reactivation
- Anti-PJP agent to present pneumocystis jiroveci pneumonia infection

Contraindications, Warnings and Precautions

- US Boxed Warning: Cytokine release syndrome, neurologic toxicity
- Warnings and Precautions: Oral toxicity and weight loss, infections, cytopenias, skin toxicity, hepatotoxicity, embryo-fetal toxicity
- Contraindications: None

REMS

Prescribers, pharmacies, and healthcare settings must be enrolled to dispense to patients

Talquetamab-tgvs
Recommended Management

Oral and Mucosal Changes: Can affect weight loss over time

- Symptomatic management with mouth rinses, pain management, nutrition consult

Skin and Nail related adverse events

- Skin management: oral and topical glucocorticoid. If refractory, consult dermatology
- Nail management : Nail soaks, topical moisturizers, and topical steroids

Talquetamab [Clinical protocol]. Janssen Biotech, Inc. 2022.;

Teclistamab-cqyv
Clinical Pharmacology

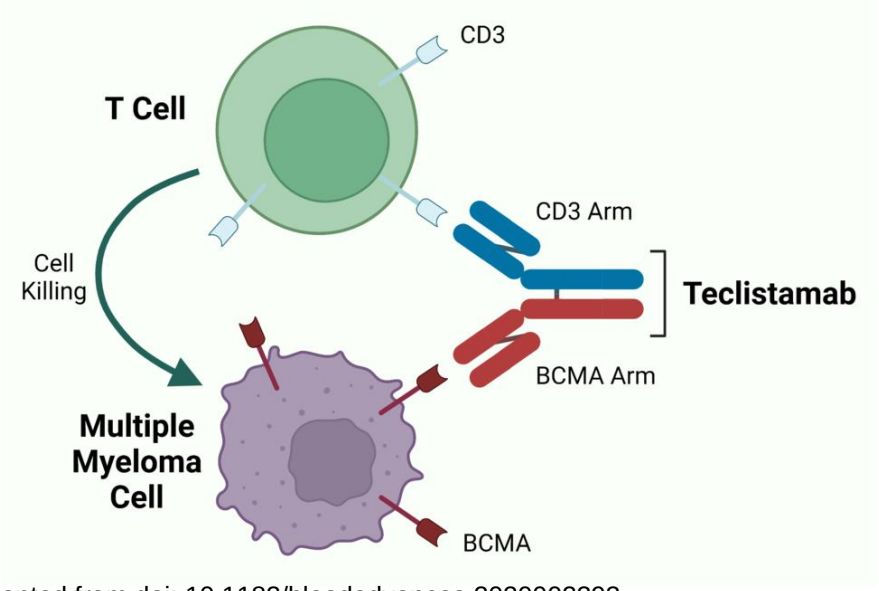
Indication

Adult patients with RRMM after at least 4 prior lines of therapy including iMiD, PI, and anti-CD38 antibody

Mechanism of action

bispecific T-cell engaging antibody that binds to the CD3 receptor expressed on the surface of T-cells and B-cell maturation antigen (BCMA) expressed on the surface of multiple myeloma cells and some healthy B-lineage cells

Bridge between myeloma cells and CD3 receptor on T-cells
→ T-cell activation leads to myeloma cell death



Credit: Adapted from doi: 10.1182/bloodadvances.2020002393.

RRMM: Relapsed/refractory multiple myeloma;
iMiD: immunomodulatory drug; PI: proteasome inhibitor;

Shah N, et al. *Leukemia*. 2020;34(4):985-1005
Teclistamab-cqyv. Prescribing Information; October 2022.

Teclistamab-cqyv

MajesTEC-1: Phase 1/2 single arm, open-label, multicenter trial

Inclusion Criteria

- RRMM
- Previously received ≥3 lines of prior therapy, progressive and measurable disease
- ECOG 0-1
- N = 165

Previous BCMA-targeted therapy **excluded**

Subcutaneous injection into abdomen (preferred) or thigh

Step-up dosing schedule	Weekly dosing schedule
• Day 1 (step-up dose 1): 0.06 mg/kg • Day 4 (step-up dose 2): 0.3 mg/kg • Day 7 (first treatment dose): 1.5 mg/kg	• 1.5 mg/kg once weekly • Starting 1 week after the first treatment dose and weekly thereafter

Patients should be hospitalized for 48 hours after administration of all doses within the step-up dosing schedule

Baseline Characteristics

- Median age 64 years; 58.2% male
- Median number of previous lines of therapy: 5
- High-risk cytogenetic profile: 25.7%
- Relapsed/Refractory status
  - 77.6% triple-class refractory
  - 30.3% penta-drug refractory
  - 89.7% resistance to last therapy
- Prior Cancer Therapy Regimen:
  - 81.8% prior Auto-SCT

Endpoints

- **Primary endpoint:** ORR (PR or better)
- **Secondary endpoints:** DOR, VGPR or better, CR or better, time to response, PFS, OS, MRD negativity, safety, PKs, immunogenicity

Moreau P, et al. N Engl J Med. 2022;387(6):495-505.

Teclistamab-cqyv
Safety

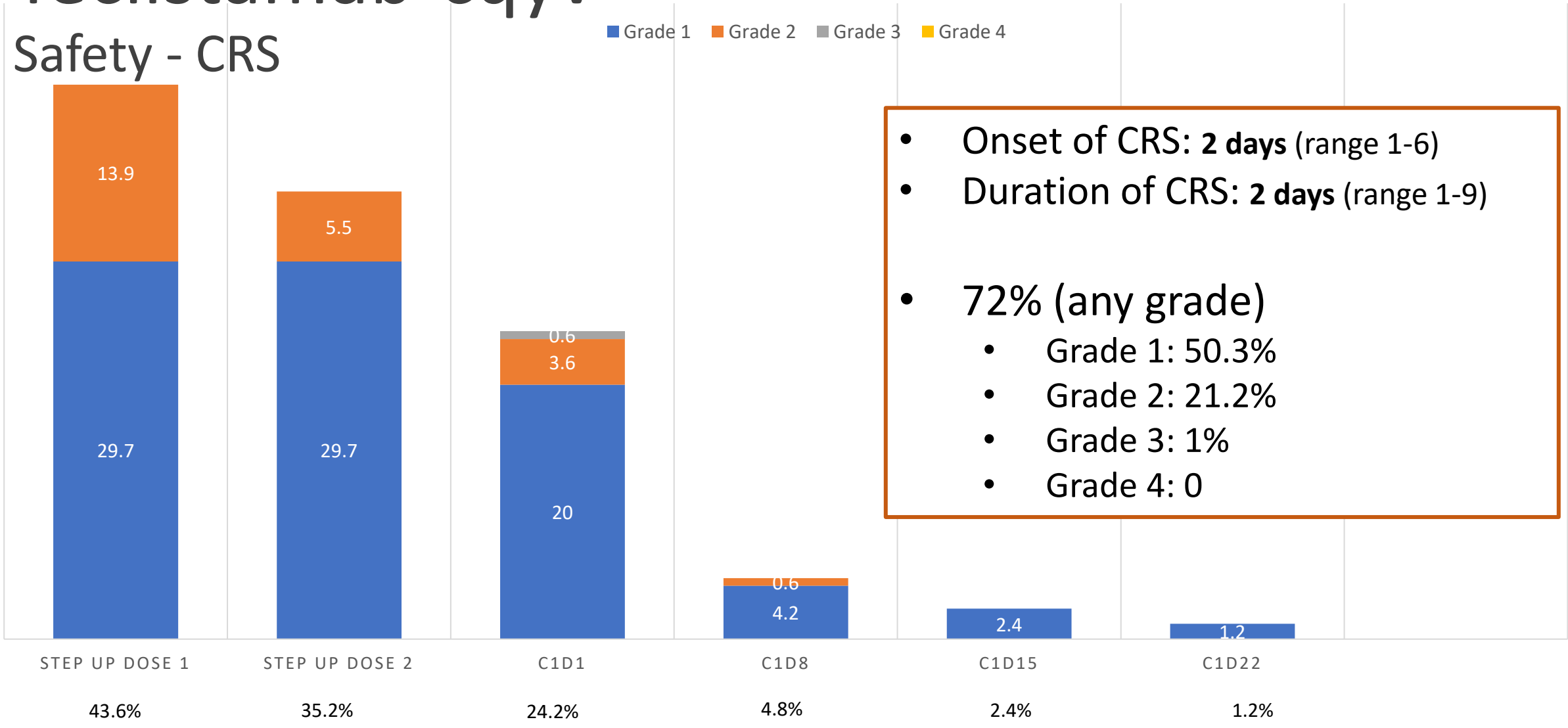
Adverse Events (N = 165)	
CRS (all grade), % Grade 1 Grade 2 Grade 3	72 50.3 21.2% 0.6%
Median time to CRS onset after most recent dose, days (range)	2 (1-6)
ICANS, %	3
Infections, %	76.4
Neutropenia, %	70.9
Anemia, %	52.1
Thrombocytopenia, %	40
Hypogammaglobulinemia, %	74.5

Other common ADRs (≥20%): pyrexia, musculoskeletal pain, injection site reaction, fatigue, nausea, headache, pneumonia, and diarrhea.

Moreau P, et al. N Engl J Med. 2022;387(6):495-505.

Teclistamab-cqyv

Safety - CRS



- Onset of CRS: **2 days** (range 1-6)
- Duration of CRS: **2 days** (range 1-9)

- 72% (any grade)
  - Grade 1: 50.3%
  - Grade 2: 21.2%
  - Grade 3: 1%
  - Grade 4: 0

Moreau et al. Engl J Med. 2022 Aug 11;387(6):495-505

CRS: Cytokine Release Syndrome

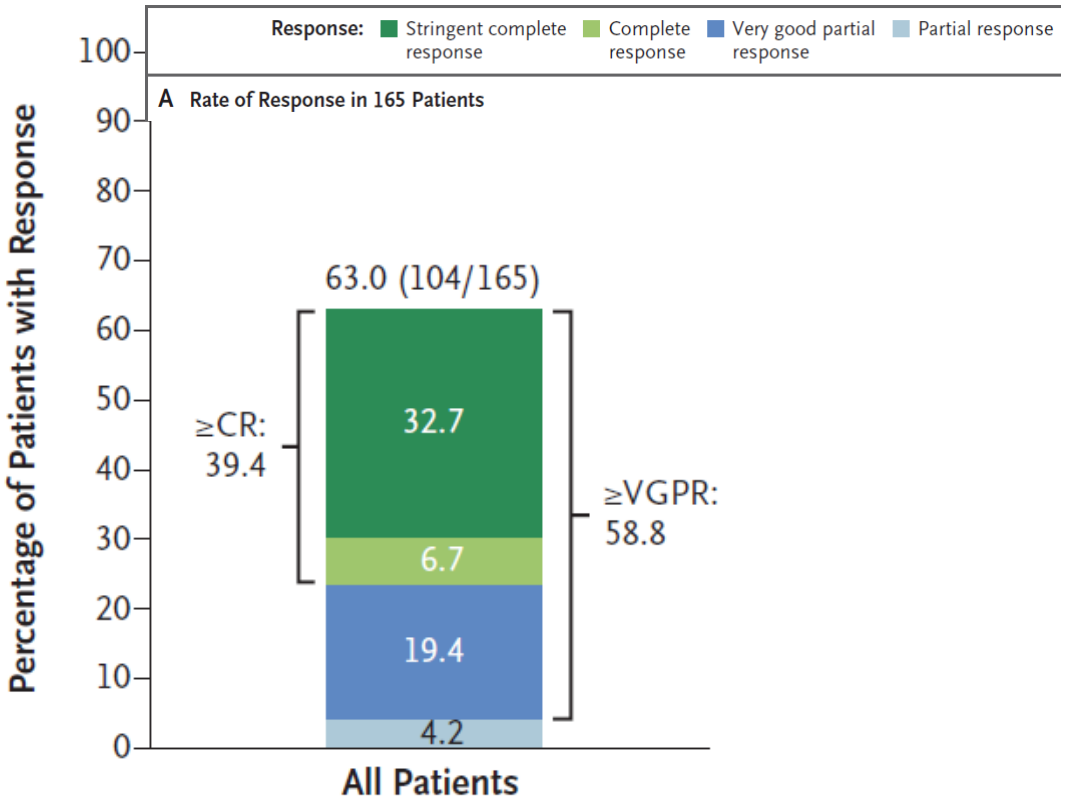
Teclistamab-cqyv

Efficacy

Median follow up: 14.1 mo

MRD negativity*:
46% (patients with CR or better)

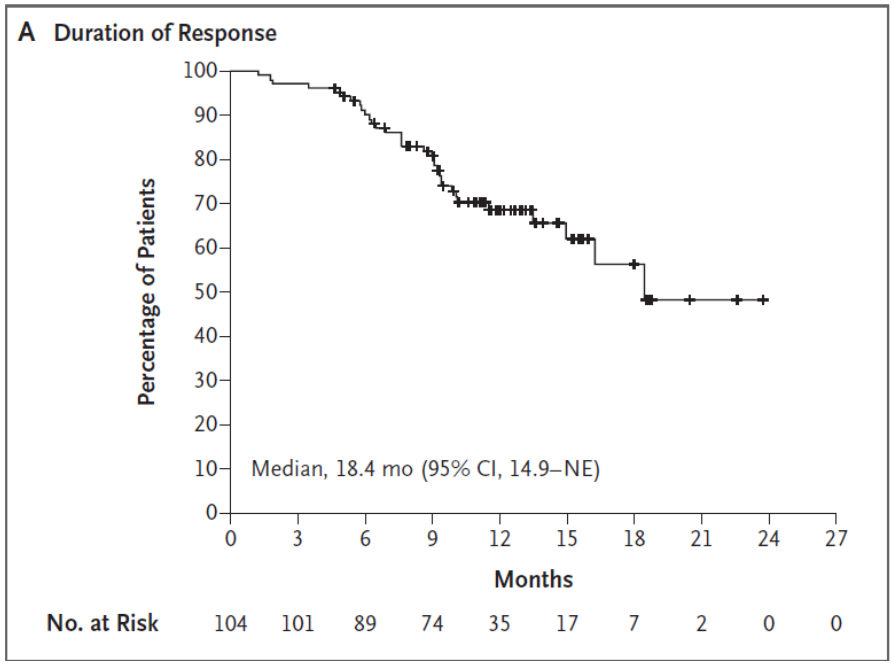
*threshold of 10^{-5}

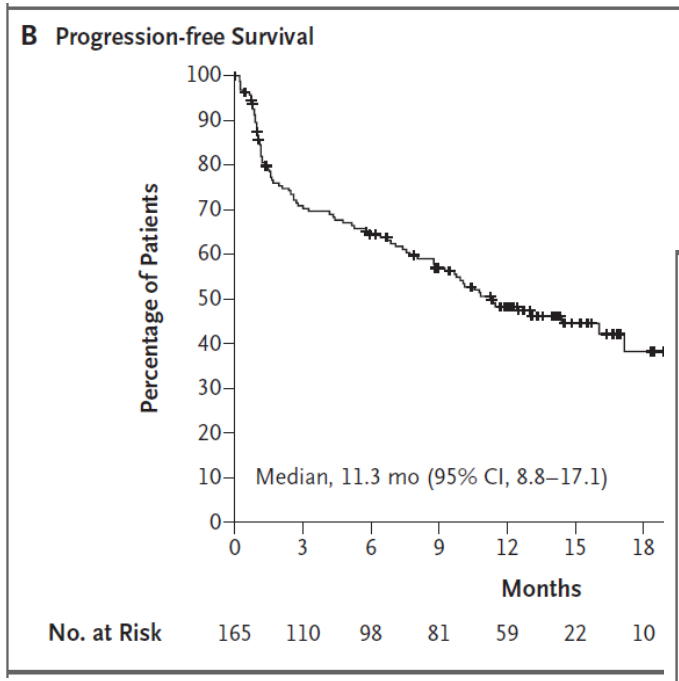


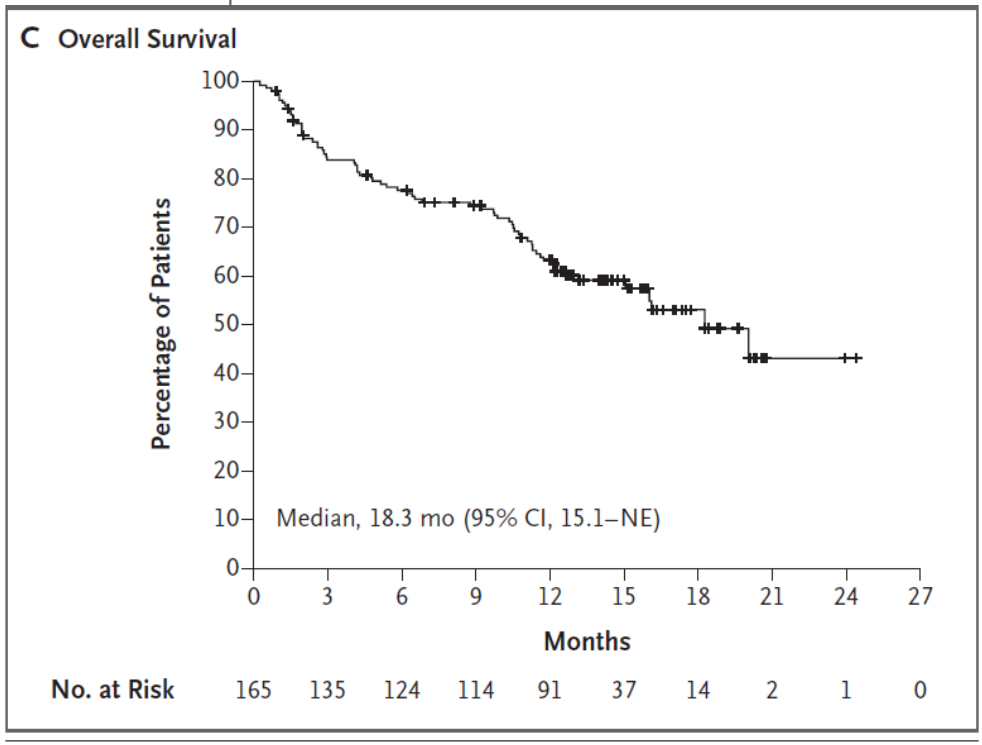
Moreau P, et al. N Engl J Med. 2022;387(6):495-505.

Teclistamab-cqyv

Efficacy







Moreau P, et al. N Engl J Med. 2022;387(6):495-505.

Teclistamab-cqyv

Administration:

- Subcutaneous injection
- Patients should be hospitalized for 48 hours after administration of each step-up dose (including first treatment dose)

Pre-medications:

- Administer the following 1-3 hours before each step-up dose (including step-up dose 1, step-up dose 2, and the first treatment dose)
  - Corticosteroid (oral or intravenous dexamethasone 16 mg)
  - H1RA (oral or IV diphenhydramine 50 mg or equivalent)
  - Antipyretics (oral or IV acetaminophen 650 mg to 1,000 mg or equivalent)

Duration of therapy:

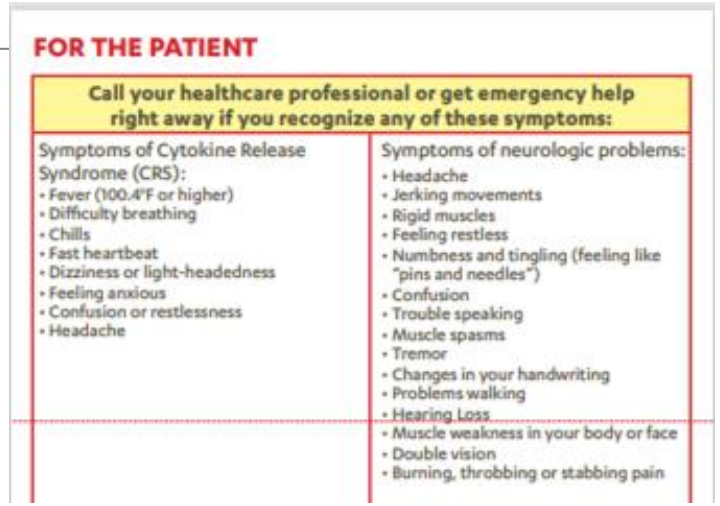
- Continue until disease progression or unacceptable toxicity

Prophylactic/supportive care therapy

- Anti-PJP agent to present pneumocystis jiroveci pneumonia infection
- Antiviral agent to prevent herpes simplex virus reactivation

REMS program

Prescribers, pharmacies and healthcare settings must be enrolled to dispense to patients



FOR THE PATIENT

Call your healthcare professional or get emergency help right away if you recognize any of these symptoms:

Symptoms of Cytokine Release Syndrome (CRS):
- Fever (100.4°F or higher)
- Difficulty breathing
- Chills
- Fast heartbeat
- Dizziness or light-headedness
- Feeling anxious
- Confusion or restlessness
- Headache

Symptoms of neurologic problems:
- Headache
- Jerking movements
- Rigid muscles
- Feeling restless
- Numbness and tingling (feeling like "pins and needles")
- Confusion
- Trouble speaking
- Muscle spasms
- Tremor
- Changes in your handwriting
- Problems walking
- Hearing Loss
- Muscle weakness in your body or face
- Double vision
- Burning, throbbing or stabbing pain

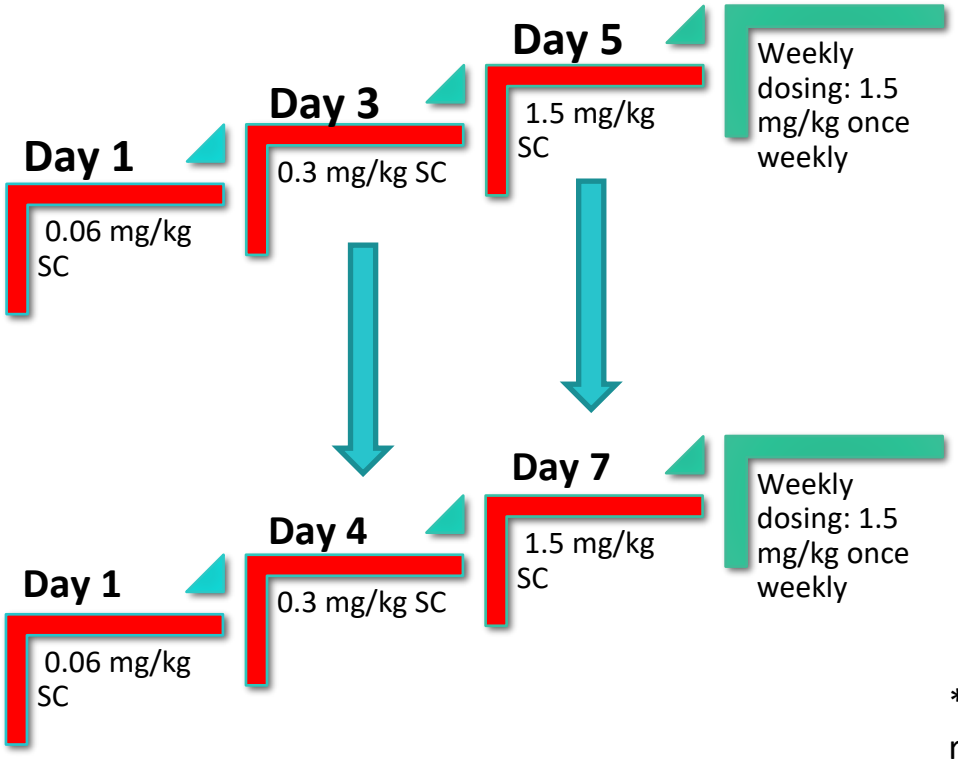
Black Box Warnings:

- ☐ CRS
- ☐ Neurologic toxicities

Teclistamab-cqyv [prescribing information]. Janssen Biotech. 8/2023

H1RA: Histamine 1 receptor antagonist

Teclistamab-cqyv
Dosing Considerations



Step-up dose #2 and the first treatment dose may be given between 2 - 4 days after the previous dose

Option to switch to Q2W (Q4W*) dosing if:

- ≥PR after ≥4 cycles (Phase 1)
- ≥CR for ≥6 months (Phase 2)

*Patients could further switch to monthly dosing if they demonstrated continued response on the Q2W schedule.

Usmani SZ, et al. ASCO 2023. Poster 8034

Teclistamab-cqyv [prescribing information]. Janssen Biotech. 8/2023

Elranatamab-bcmm
Clinical Pharmacology

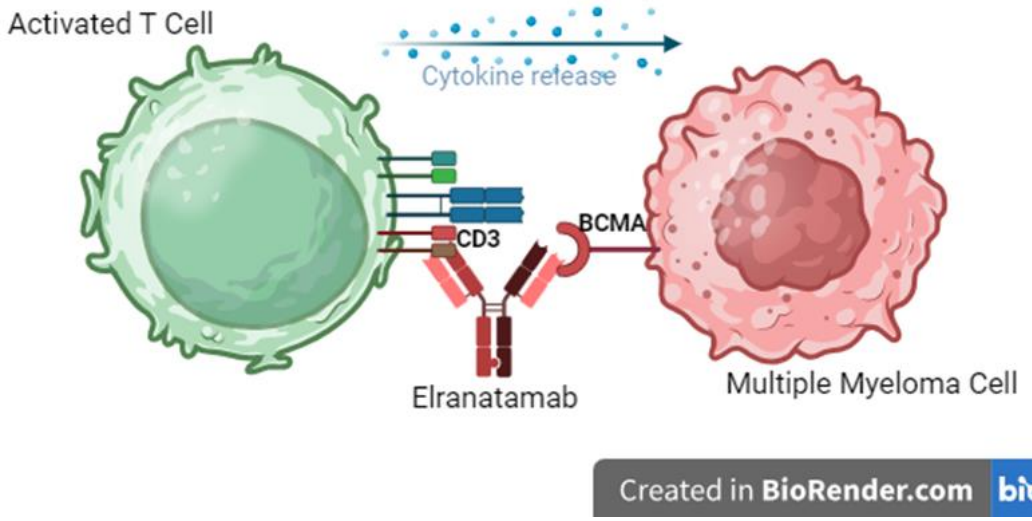
Indication

Adult patients with RRMM after at least 4 prior lines of therapy including iMiD, PI, and anti-CD38 antibody

Mechanism of action

Bispecific B-cell maturation antigen (BCMA)-directed T-cell engaging antibody that binds BCMA on plasma cells, plasmablasts, and multiple myeloma cells and CD3 on T-cells leading to cytolysis of the BCMA-expressing cells

→ Elranatamab-bcmm activated T-cells, caused proinflammatory cytokine release, and resulted in multiple myeloma cell lysis



Elranatamab-bcmm [prescribing information]. Pfizer Inc. August 2023.

Elranatamab-bcmm

MagnetisMM-3: Phase 2 single-arm, open-label, multicenter trial

Inclusion Criteria

- RRMM
- Previously received 4+ lines of prior therapy, progressive and measurable disease
- ECOG 0-2
- N = 187
  - Cohort A: No prior BCMA-directed therapy N=123
  - Cohort B: Prior BCMA-directed therapy N=64

Subcutaneous injection into abdomen (preferred) or thigh

Priming doses	Weeks 2-24	Weeks 25+
Step-up Dosing • Day 1: 12 mg • Day 4: 32 mg **First Treatment Dose** • Day 8: 76 mg	**Weekly Dosing** • 76 mg once weekly • Starting 1 week after the first treatment dose and weekly thereafter	**Responders (patients who achieve PR or better lasting at least 2 months):** Biweekly (every 2 weeks) Dosing • 76 mg every 2 weeks

Endpoints

- **Primary endpoint:** ORR (PR or better)
- **Secondary endpoints:** DOR, DOR CR or better, time to response, PFS, OS, MRD negativity, PFS, safety, PK immunogenicity

Patients should be hospitalized for 48 hours after administration of first step-up dose, and for 24 hours after second step-up dose.

Baseline Characteristics (Cohort A)

- Median age 68 years; 55% male
- Median number of previous lines of therapy: 5
- High-risk cytogenetic profile: 25%
- Relapsed/Refractory status
  - 96.7% triple-class refractory
  - 42% penta-drug refractory
- Prior Cancer Therapy Regimen:
  - 70.7% prior Auto-SCT

Lesokhin AM et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med (2023).

Elranatamab-bcmm
Safety

Safety

Adverse Events (N = 123/119*)	
CRS (all grade), % Grade 1 Grade 2 Grade 3	56.3* 42* 14.3* 0
Median time to CRS onset after most recent dose, days (range)	2 (1-9)
ICANS, %	3.4
Infections, %	42
Neutropenia, %	48.8
Anemia, %	48.8
Thrombocytopenia, %	30.9

Other common ADRs (≥20%): fatigue, injection site reaction, diarrhea, musculoskeletal pain, decreased appetite, rash, cough, nausea, pyrexia

*patients who received 2 step up doses

Lesokhin AM et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med (2023).

Elranatamab-bcmm

Safety - CRS

N=119

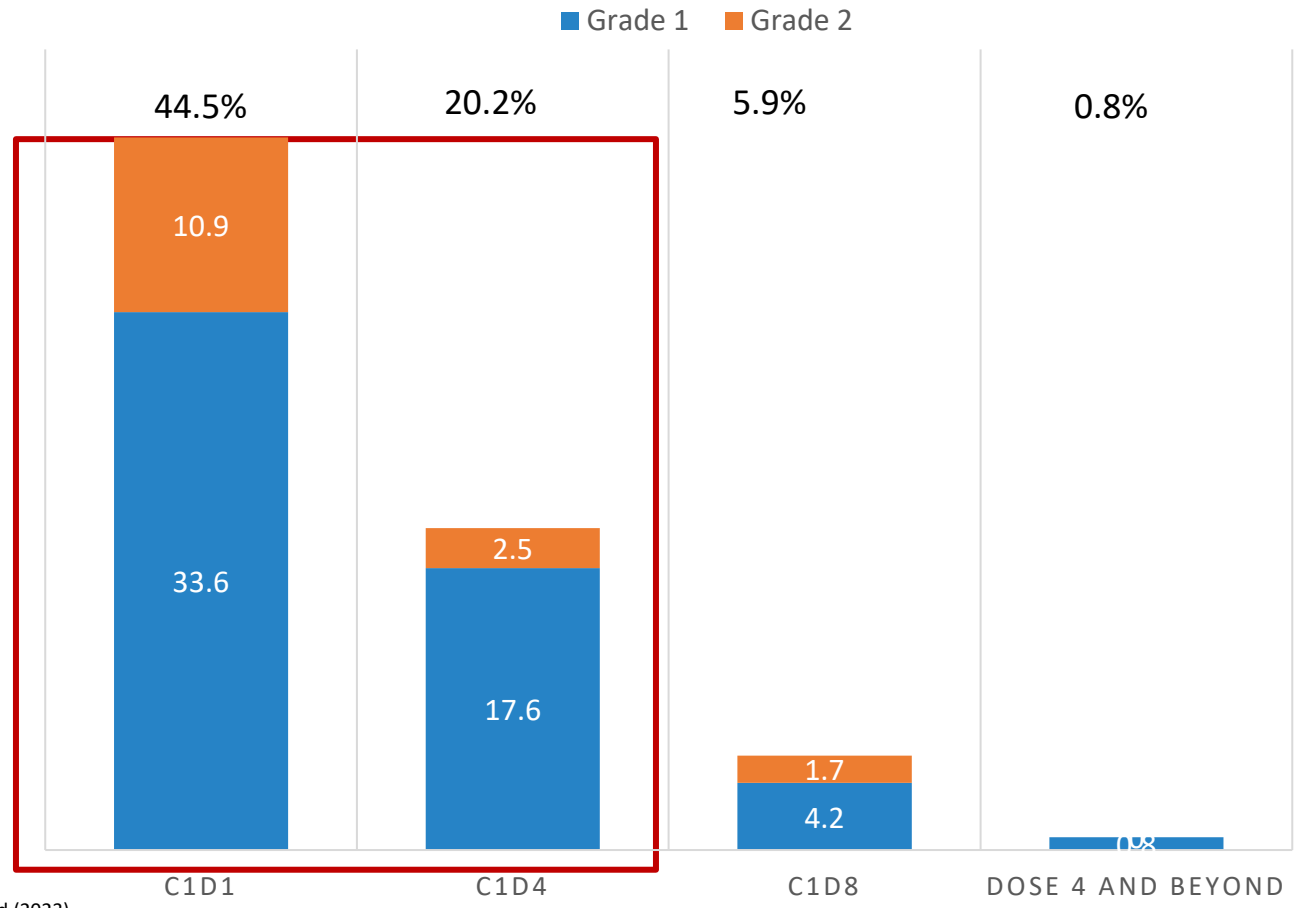
CRS: 56.3%

Median onset of CRS:

- 2 days (1-9)

Median time to resolution

- 2 days (1-19)



Lesokhin AM et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med (2023).

CRS: Cytokine Release Syndrome

Elranatamab-bcmm

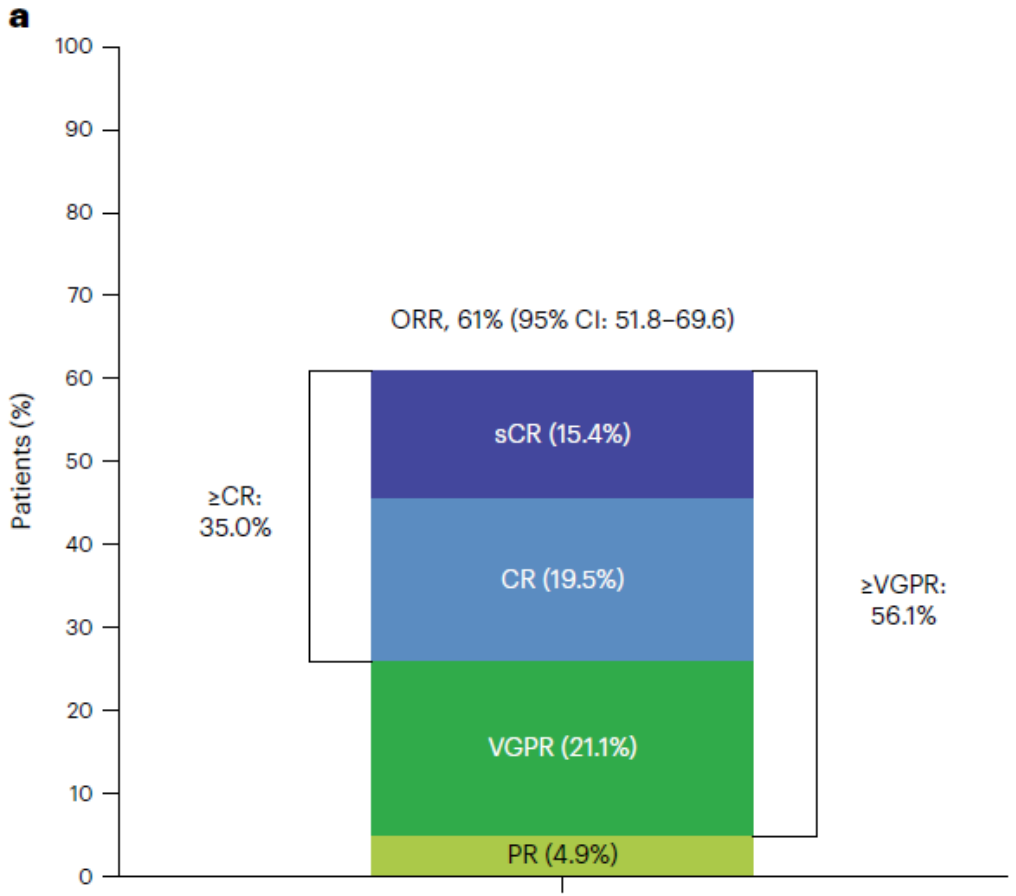
Efficacy

(Cohort A)

Median follow up: 14.7 mo

MRD negativity*: 89.7% (patients with CR or better)

*threshold of 10^{-5}

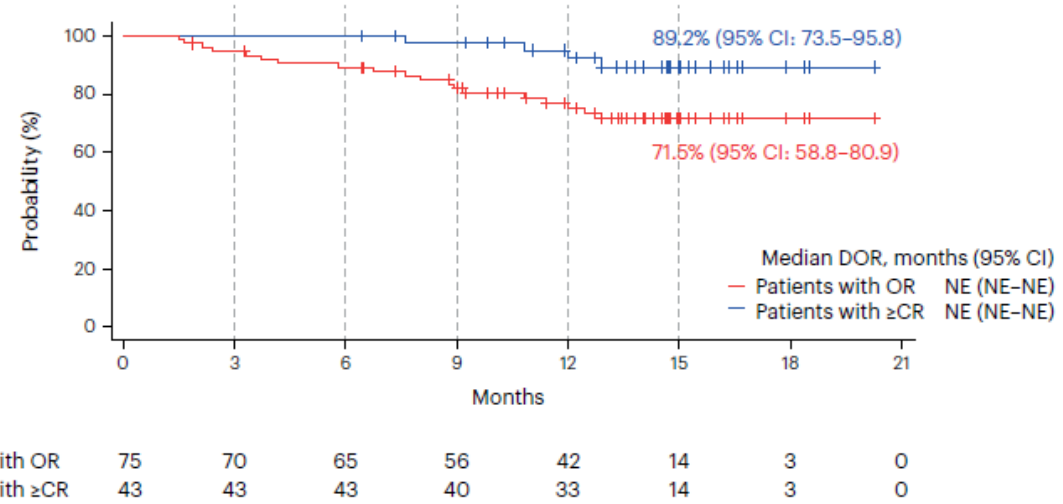


Lesokhin AM et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med (2023).

Elranatamab-bcmm

Efficacy

a



No. at risk								
Patients with OR	75	70	65	56	42	14	3	0
Patients with ≥CR	43	43	43	40	33	14	3	0

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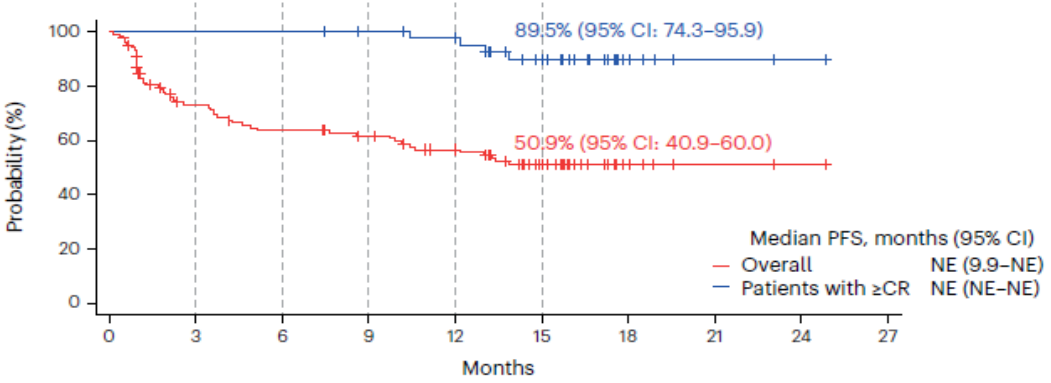
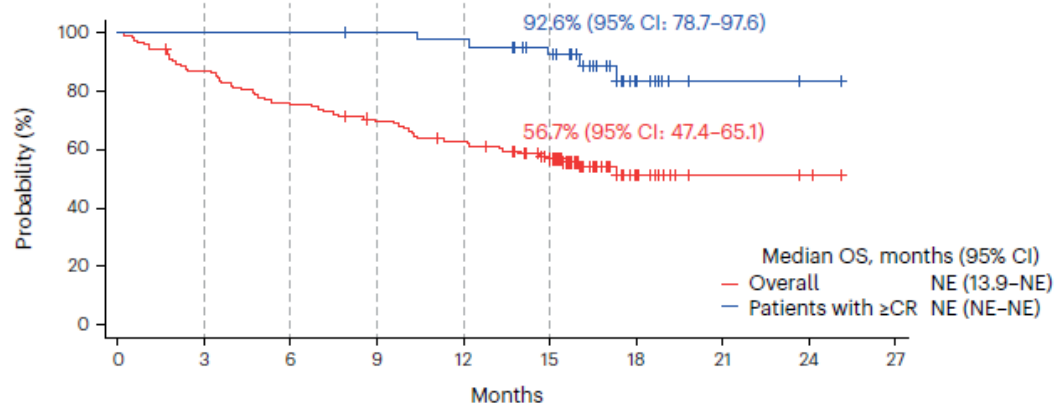


No. at risk										
Overall	123	78	67	62	52	37	6	2	1	0
Patients with ≥CR	43	43	43	41	38	29	6	2	1	0

No. at risk										
Overall	123	78	67	62	52	37	6	2	1	0
Patients with ≥CR	43	43	43	41	38	29	6	2	1	0

c



No. at risk										
Overall	123	106	92	83	74	58	12	3	2	0
Patients with ≥CR	43	43	43	42	41	35	9	2	1	0

Lesokhin AM et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med (2023).

Elranatamab-bcmm

Administration

- Subcutaneous injection
- Patients should be hospitalized for 48 hours after administration of first step-up dose, and for 24 hours after administration of the second step-up dose

Pre-medications

- Administer the following 1 hour before each step-up dose (including the first treatment dose)
  - Corticosteroid (oral or intravenous dexamethasone, 20 mg or equivalent)
  - Antihistamine (oral diphenhydramine 25 mg or equivalent)
  - Antipyretics (oral acetaminophen 650 mg or equivalent)

Duration of therapy

- Continue until disease progression or unacceptable toxicity

Prophylactic/supportive care therapy

- Antiviral agent to prevent herpes simplex virus reactivation
- Anti-PJP agent to present pneumocystis jiroveci pneumonia infection

REMS program

- Prescribers, pharmacies and healthcare settings must be enrolled to dispense to patients

FOR THE PATIENT

Call your healthcare provider or get emergency help right away if you have any of these symptoms:

- Fever 100.4°F (38°C) or higher
- Trouble breathing
- Chills
- Dizziness or light-headedness
- Fast heartbeat
- Headache
- Agitation, trouble staying awake, confusion or disorientation, seeing or hearing things that are not real
- Trouble speaking, thinking, remembering things, paying attention, or understanding things
- Problems walking or muscle weakness
- Shaking (tremors), loss of balance, or muscle spasms
- Numbness and tingling (feeling like "pins and needles")
- Burning, throbbing, or stabbing pain
- Changes in your handwriting

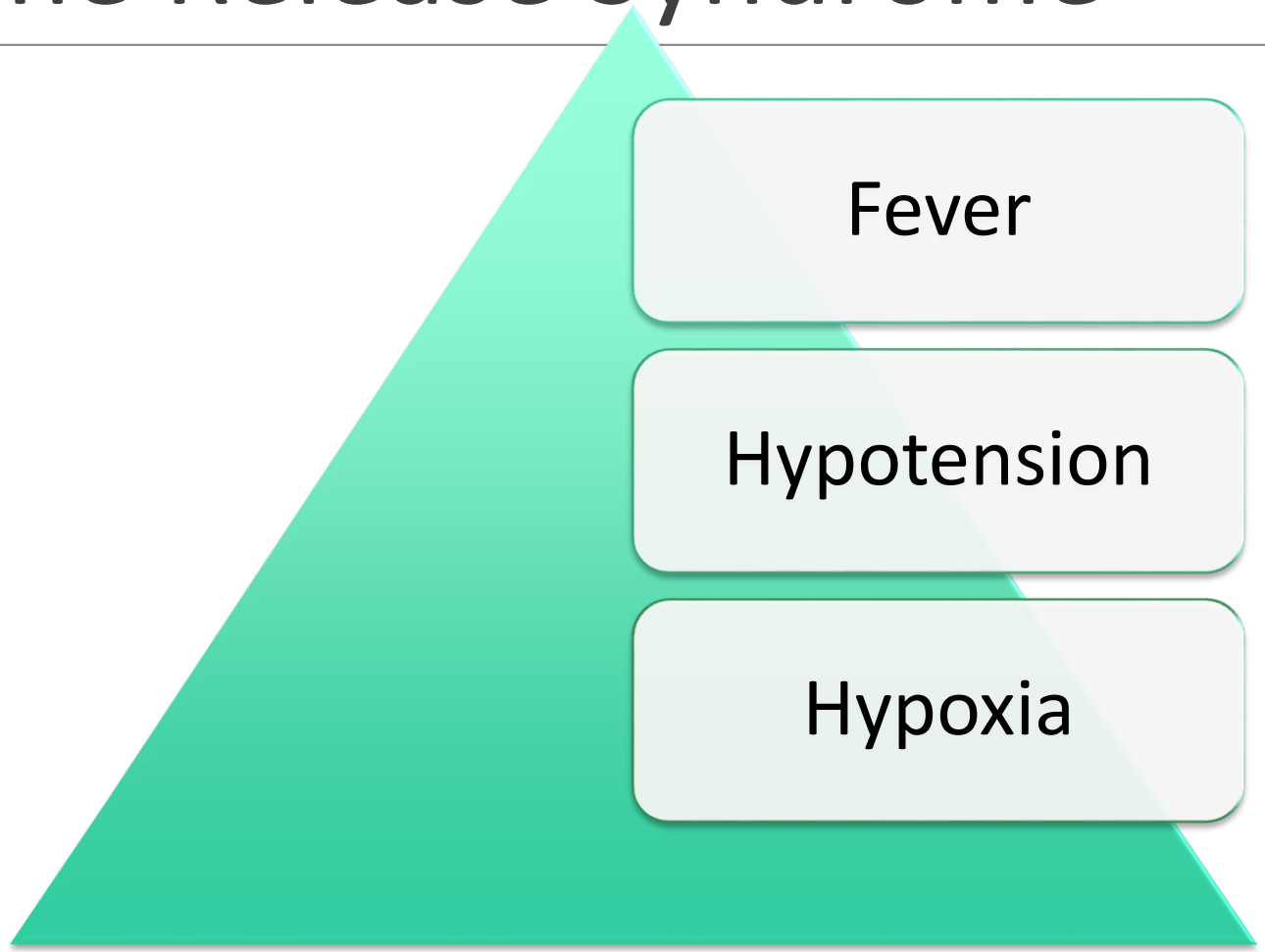
Black Box Warnings:

- ☐ CRS
- ☐ Neurologic toxicities

Elranatamab-bcmm [prescribing information]. Pfizer Inc. August 2023.

Toxicity & Management

Cytokine Release Syndrome



Lee, D.W.; Santomasso, B.D.; Locke, F.L.;et L . Biol. Blood Marrow Transplant. 2019, 25, 625–638.

Neurotoxicity

- ICE score
- Level of consciousness
- Seizure
- Motor finding
- Elevated ICP or cerebral edema
- Other Symptoms: headache, peripheral neuropathy, dizziness

Lee, D.W.; Santomasso, B.D.; Locke, F.L.;et L . Biol. Blood Marrow Transplant. 2019, 25, 625–638.

Mitigation Strategies

Premedication

- Steroids, antihistamine, acetaminophen

Step-up dosing

Bridging therapies

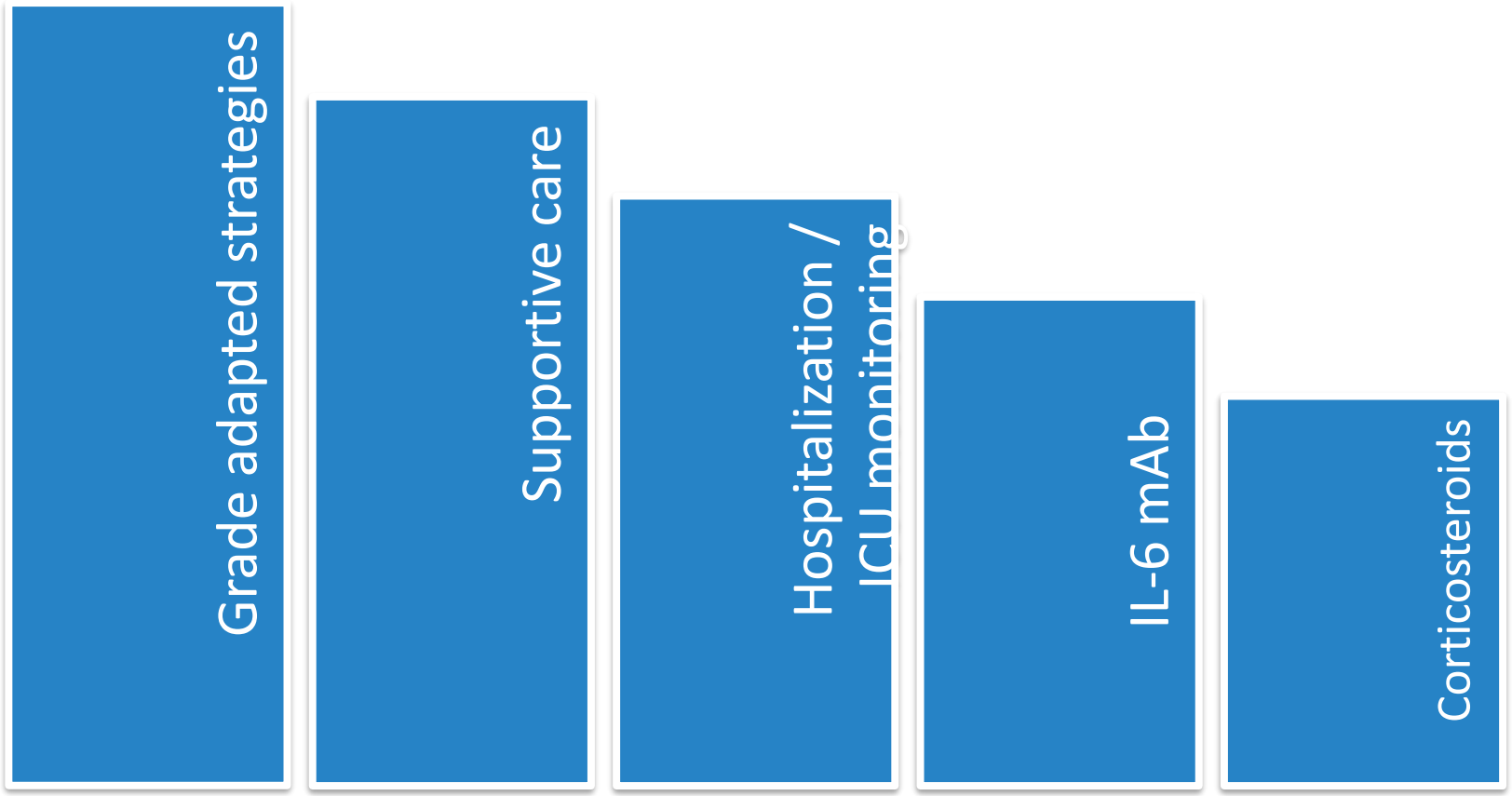
- Obinutuzumab prior to CD20 bispecifics

Alternative routes

- SQ mosunetuzumab reduced peak IL-6 levels

Topp, M.S., et al. Lancet Oncol. 2015, 16, 57–66.; Bartlett, N.L., et al. J. Clin. Oncol. 2019, 37, 7518.; Baliga, R, et al.. Blood 2019, 134, 1574.; Matasar, M.J, et al.. Blood 2020, 136, 45–46.

Management



Salvaris R, Ong J, Gregory GP.. J Pers Med. 2021 Apr 29;11(5):355; Ravi G, Costa LJ. Am J Hematol. 2022 Jun 15. doi: 10.1002/ajh.26628. Epub ahead of print.; Mocquot P, Mossazadeh Y, Lapierre L, et al. J Clin Pharm Ther. 2022 Sep;47(9):1337-1351

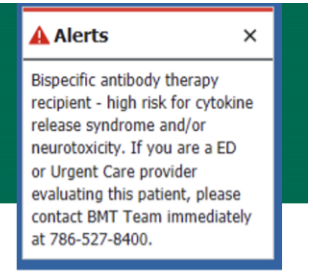
Real World Considerations

Flagging patient's charts via smart zone alert

Staff competency and training

Toxicity management guidelines for all products vs individual products management

Bispecific Smart Zone Alert



- Smart Zone Design
  - Goal is to notify ED or urgent care provider a BMT physician needs to be consulted for possible management of unique toxicities (CRS, ICANS)
  - Alert set up to fire in **ED and urgent care encounters** for **ED and urgent care providers, nursing, and support staff** upon registration and alert clears automatically after **48 hours**
  - **Any bispecific antibody** (blina, tec, talq, elrana, mosun, epcor) in **any status** (active, complete, discontinued, future) ordered within past **365 days**
  - Go live tentative 7/5

Inpatient - Logistical Strategies and Therapeutic Considerations

MCI clinic notifies the oncology unit charge nurse of any direct/unplanned admissions

- Implementation of a shared Team's worksheet for direct admissions – updates daily
  - Allows time for the allocation of bispecific T-cell antibody

Patients are hospitalized as per the package insert recommendations

- Exceptions based on specific patient case

CRS/ICANS monitoring

- CRS laboratories: LDH, ferritin, and CRP daily; vital signs multiple times per day
- Neurology checks every 4 hours and ICE assessment done every shift
- Institutional management is in progress, but managed per package insert/trial protocol

Patients without sign or symptoms of CRS/ICANS are discharge home to continue therapy outpatient

- Medication reconciliation and education is performed by transition of care pharmacist/specialist
- Clinical staff pharmacist emails outpatient team for the procurement of medication for the following cycle

CRS= Cytokine Release Syndrome; ICANS=Immune effector cell–associated neurotoxicity syndrome; ICE=Immune effector cell–associated encephalopathy; CAR-T= Chimeric antigen receptor

MCC IPOP program

- Inpatient-Outpatient program with APP assessment on days of administration for Cycle 1-2
- Close monitoring, lab follow-up, lower threshold for admission
- IPOP pharmacist dedicated for education, medication reviews

MCC

Bispecific Antibody	Scheduled Hospitalization	Outpatient Assessment
Elranatamab	C1 Day 1,3	C1 Day 8,15,22
Epcoritamab	C1 Day 15	C1 Day 1,2,8,9,22,23
Glofitamab	C1 Day 8	C1 Day 15,16 C2 Day 1,2
Mosunetuzumab	-	C1 Day 1,8,15,16

Thank You

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