Bispecific T-Cell Engagers: One BITE with Lots to Swallow

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Disclosures

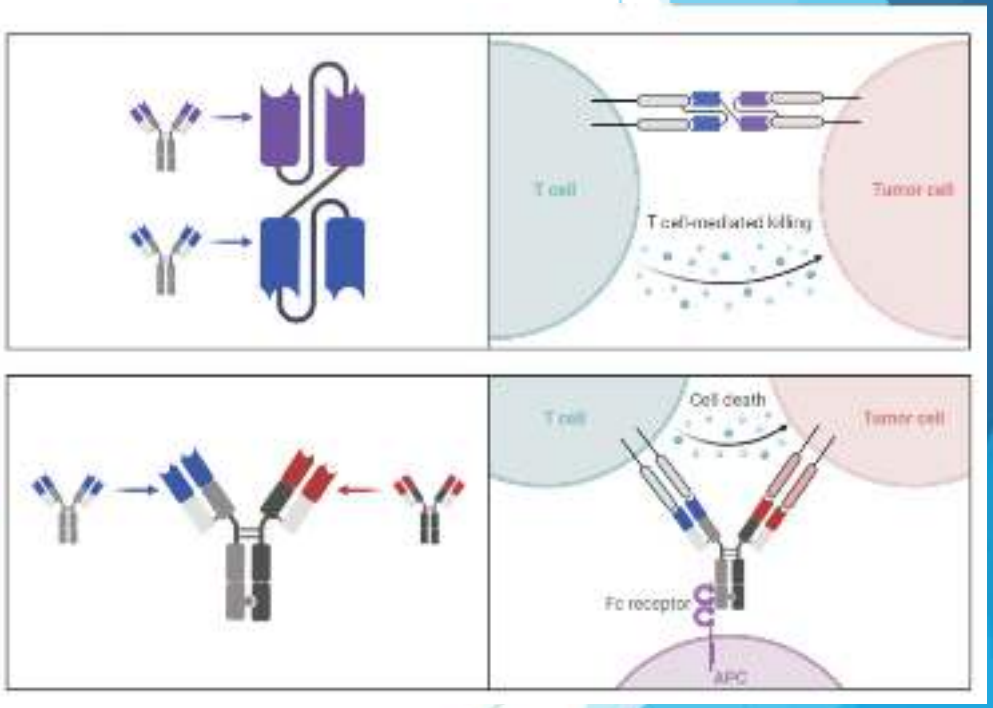
The presenters have no relevant financial relationships with commercial interests to disclose.

Objectives

- Review pharmacology, clinical data, and place in therapy for FDA-approved bispecific T-cell engager therapies
- Evaluate safety data and adverse event management for each agent
- Discuss key operational and administration logistics with each agent
- Assess factors for a safe and effective implementation into clinical practice

What are bispecific T-cell engagers?

- Bispecific antibodies or fragments designed with 2 antigen-binding domains
  - Two different tumor-associated antigens
  - Two immune-related molecules
  - **One tumor-associated antigen and one immune-related molecule**
- Readily available compared to CAR-T
- Side effect profiles include cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS)



Shanshal M, et al. Cancers (Basel). 2023;15(10):2824.

Bispecific T-Cell Engagers in Multiple Myeloma

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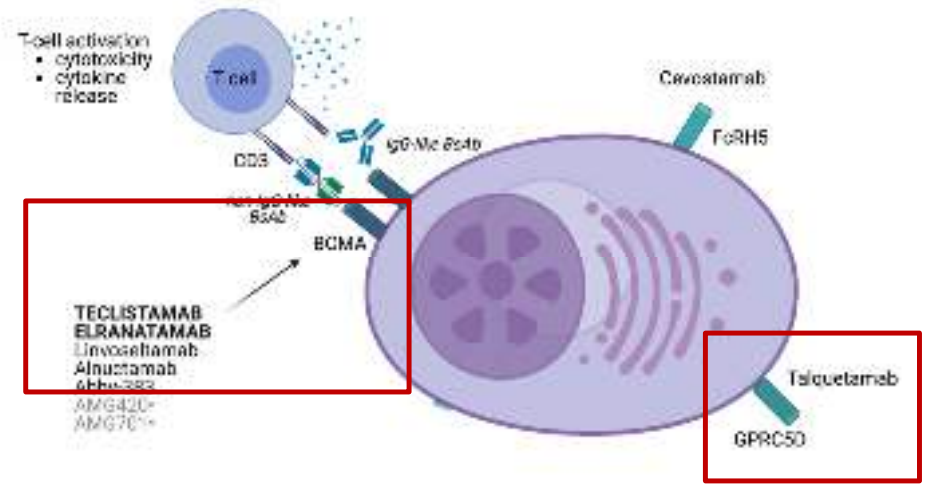
Overview of bispecifics in myeloma

	Teclistamab (Tec)	Elranatamab (Elra)	Talquetamab (Tal)
Approval Date	10/2022	8/2023	8/2023
Target	BCMA/CD3	BCMA/CD3	GPRC5D/CD3
Indication	4 or more prior lines including proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody		

BCMA: b-cell maturation antigen



Swan D, et al. Cancers (Basel). 2023;15(6):1819.

Key trial characteristics

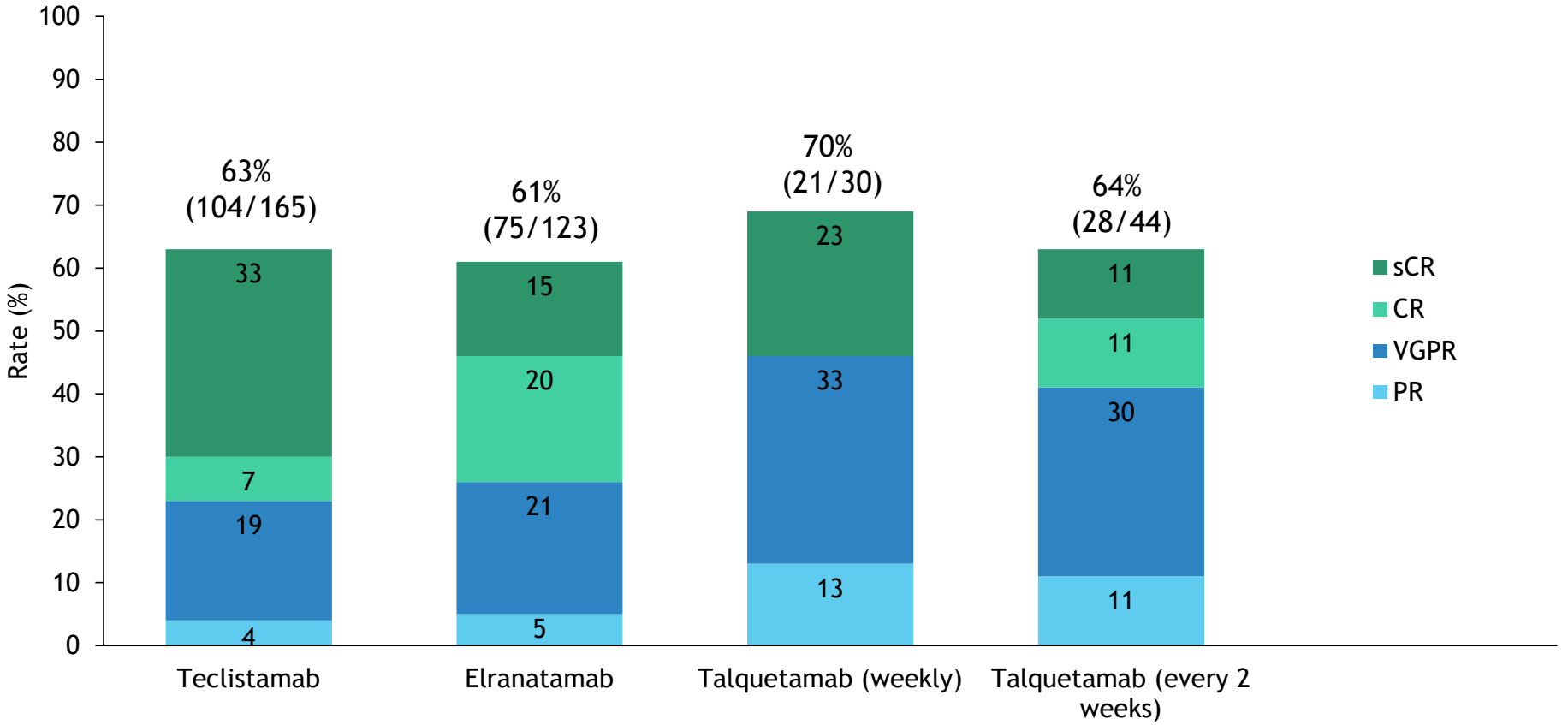
- Single-arm phase 1-2 studies
- Differences in design and population limits cross trial comparisons

	Tec (n=165)	Elra (n=123)	Tal (n=130)
Age, years, median (range)	64 (33-84)	68 (36-89)	64 (39-84)
Extramedullary disease	28%	39%	42%
High risk cytogenetics	26%	26%	16%
Required prior therapies	At least 3 lines, triple-class exposed	Triple-class refractory	Refractory/intolerant to established therapies including PI and IMID
Prior lines, n, median (range)	5 (2-14)	5 (2-22)	6 (2-17)
Penta-drug refractory	30%	42%	25%

PI: proteosome inhibitor | IMID: immunomodulatory drug | triple-class: IMID, PI, anti-CD38 monoclonal antibody | penta-drug: 2 IMIDs, 2 PIs, anti-CD38 monoclonal antibody | EMD: extramedullary disease

Moreau P, et al. N Engl J Med. 2022;387(6):495-505. | Chari A, et al. N Engl J Med. 2022;387(24):2232-2244.
Lesokhin AM, et al. Nat Med. 2023;29(9):2259-2267.

Response rates were promising (and comparable)



sCR: stringent complete response | CR: complete response | VGPR: very good partial response | PR: partial response

Moreau P, et al. N Engl J Med. 2022;387(6):495-505. | Chari A, et al. N Engl J Med. 2022;387(24):2232-2244. | Lesokhin AM, et al. Nat Med. 2023;29(9):2259-2267.

Additional outcomes

	Tec (n=165) 22 m follow-up	Elra (n=123) 16 m follow-up	Tal-w (n=30) 12 m follow-up	Tal-2w (n=44) 12 m follow-up
Response rate (all)	63%	61%	70%	64%
EMD	36%	39%	45%	40%
>50-60% BMPC	44%	~45-50%	n/a	n/a
High risk cytogenetics	60%	~50-55%	67%	56%
Prior BCMA	Excluded	45%	50-75%	50-75%
Penta-drug exposed	60% (refractory)	46% (refractory)	83% (exposed)	78% (exposed)
Onset of response	1.2 m (Best: 3.8 m)	1.2 m (CR+: 6.1 m)	0.9 m (CR+: 9.3 m)	1.2 m (CR+: 2.3 m)
Progression-free survival	12.5 m	15-m: 50.2%	7.5 m	12 m
Duration of response	18.4 m	15-m: 71%	10.2 m	7.8 m
Overall survival	22 m	15-m: 56%	1-y: 76%	1-y: 77%

BMPC: bone marrow plasma cells | m: months | y: year

Touzeau C, et al. Hemasphere. 2023;7(Suppl):e5955094. | Jakubowiak AJ, et al. Blood 2023; 142 (Supplement 1): 3377. | Carolina D et al. JCO 41, 8036-8036(2023). | Ajay K. Nooka et al. JCO 41, 8008-8008(2023). | Tomasson M, et al. Blood 2023; 142 (Supplement 1): 3385.

True or False

Talquetamab is a bispecific T-cell engager that targets CD3 and BCMA.

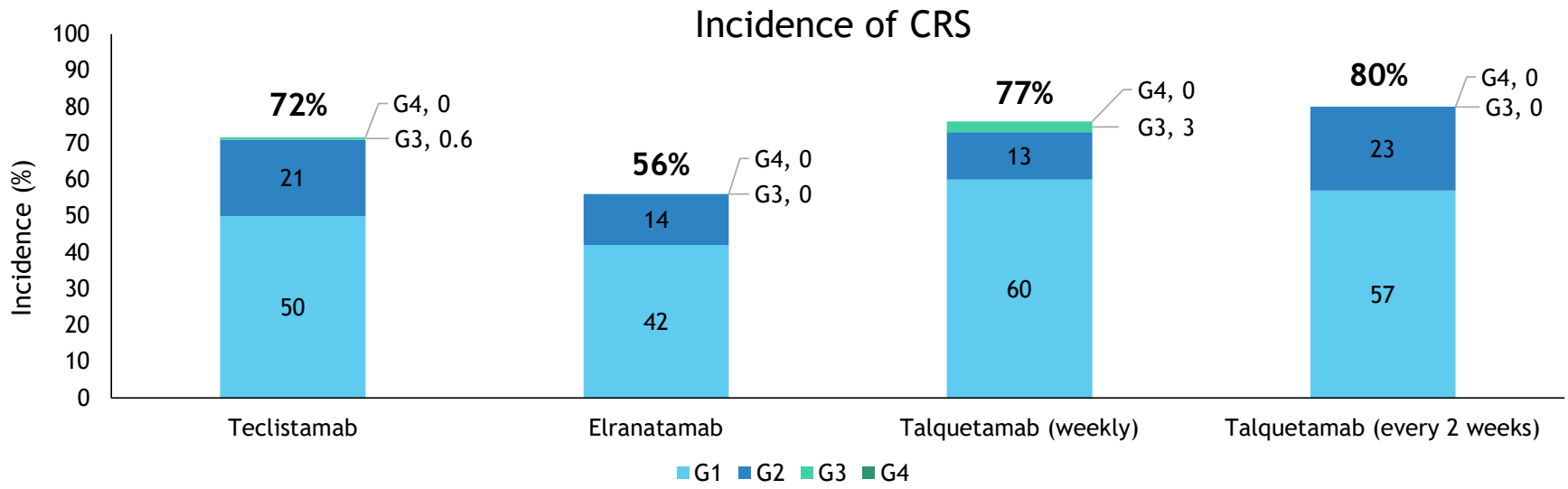
Adverse events: CRS grading/management

	Fever	Hypotension	Hypoxia	Management
Grade 1	>38 C	None	None	Supportive care. Assess for infection. Consider tocilizumab. Consider dexamethasone. Hold further doses until resolution
Grade 2	>38 C	Not requiring vasopressors	Low-flow nasal canula or blow-by	Supportive care. Assess for infection. Give tocilizumab. Consider dexamethasone. If no improvement, consider methylprednisolone, siltuximab, anakinra, etc. Hold further doses until resolution
Grade 3	>38 C	Single vasopressor (Excluding vasopressin)	High-flow nasal cannula, facemask, nonrebreather, Venturi	
Grade 4	>38 C	Multiple vasopressors (Excluding vasopressin)	Positive pressure (CPAP, BiPAP, intubation, ventilation)	

Lee DW, et al. Biol Blood Marrow Transplant. 2019;25(4):625-638. | Teclistamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2022 | Elranatamab [prescribing information]. Pfizer Inc. New York, NY. 2023 | Talquetamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2023

Adverse events: CRS

- Mostly are low grade and occur within step-up phase



	Tec (n=165)	Elra (n=123)	Tal-w (n=30)	Tal-2w (n=44)
Onset	2 days (1-6)	2 days (1-9)	2 days (1-22)	2 days (1-5)
Duration	2 days (1-9)	2 days (1-19)	2 days (1-3)	2 days (1-5)

Moreau P, et al. N Engl J Med. 2022;387(6):495-505. | Chari A, et al. N Engl J Med. 2022;387(24):2232-2244. | Lesokhin AM, et al. Nat Med. 2023;29(9):2259-2267.

Adverse events: ICANS grading/management

	ICE	Consciousness	Seizure	Motor	ICP elevation or cerebral edema	Management
Grade 1	7-9	Awakens spontaneously	None	None	None	Neuro workup. Supportive care. Consider dexamethasone. Consider seizure prophylaxis
Grade 2	3-6	Awakens to voice	None	None	None	Neuro workup. Supportive care. Give dexamethasone. Consider methylprednisolone
Grade 3	0-2	Awakens to tactile stimulation	Clinical seizure or on EEG that resolve with intervention	None	Focal/local edema	
Grade 4	0	Unarousable or requires vigorous stimulation	Life-threatening, prolonged, or recurrent seizure	Deep focal weakness such as hemiparesis or paraparesis	Diffuse cerebral edema, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad	

ICE: Immune effector cell associated encephalopathy score | ICP: intracranial pressure | EEG: electroencephalogram

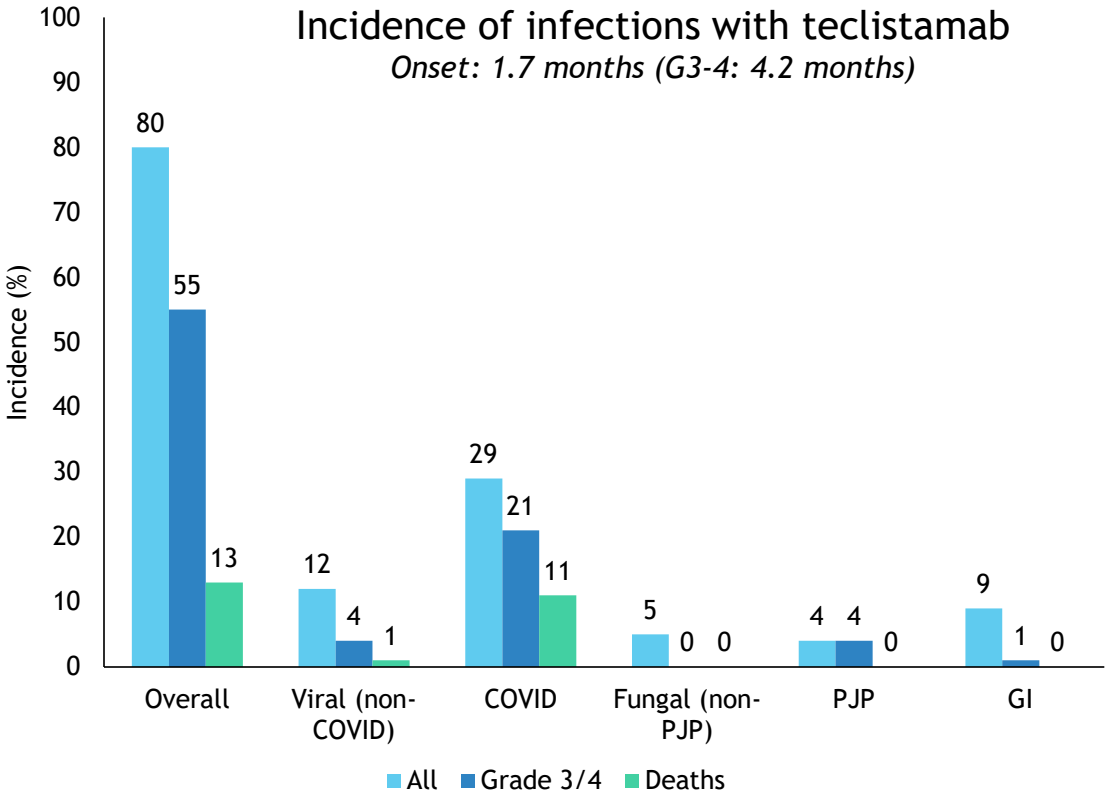
Lee DW, et al. Biol Blood Marrow Transplant. 2019;25(4):625-638. | Teclistamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2022 | Elranatamab. [prescribing information]. Pfizer Inc. New York, NY. 2023 | Teclistamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2023

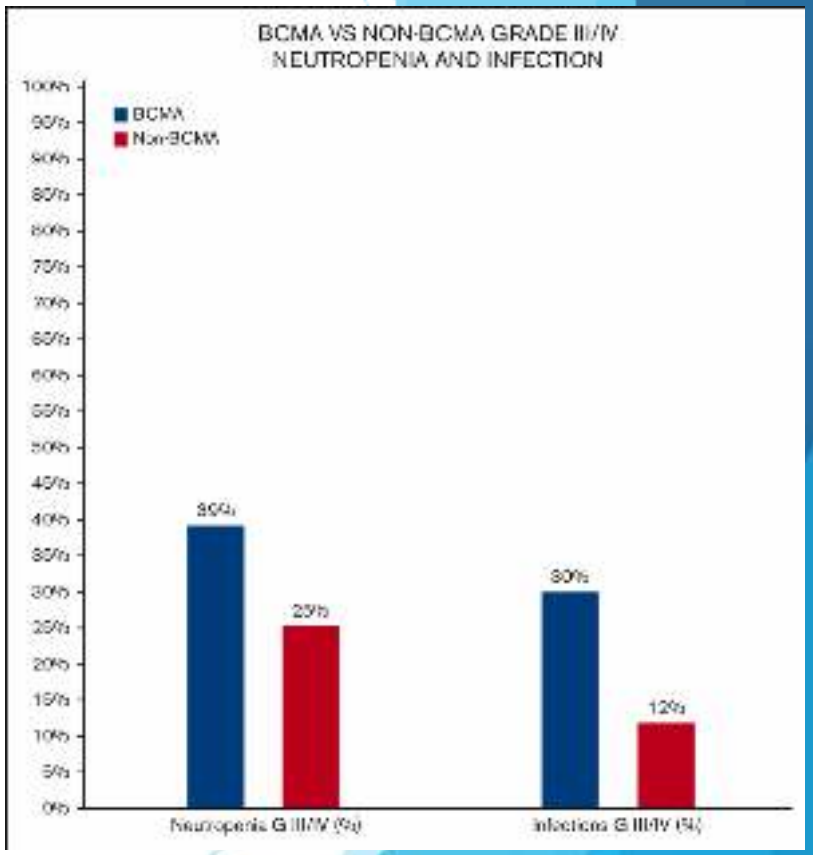
Adverse events: ICANS and others

- ICANS: 3% (except talquetamab ~10%). Grade 1-2
  - Onset: 3-4 days
  - Duration: 2-3 days
- Other neurotoxicity: headache, neuropathy
- Gastrointestinal: diarrhea, constipation, hepatotoxicity
- Arthralgia
- Injection site reaction

Moreau P, et al. N Engl J Med. 2022;387(6):495-505. | Chari A, et al. N Engl J Med. 2022;387(24):2232-2244. | Lesokhin AM, et al. Nat Med. 2023;29(9):2259-2267.

Adverse events: Infections





PJP: Pneumocystis jiroveci pneumonia

Nooka AK, et al. Cancer. 2024;130(6):886-900. | Mazahreh F, et al. Blood Adv. 2023;7(13):3069-3074.

Infection prevention

	NCCN Recommendations	Comments
Hypogamma-globulinemia	Administer IVIG starting second cycle to maintain IgG >400 mg/dL	0.4 g/kg every 4 weeks. Also consider if recurrent or severe infection
Neutropenia	Consider antibiotic prophylaxis during first cycle. Consider yeast prophylaxis with ANC <0.5 and mold prophylaxis in high risk	Also consider filgrastim for absolute neutrophil count (ANC) <0.5 x 10^9 /L
Herpes/Zoster	Administer prophylaxis indefinitely	Acyclovir, valacyclovir
Cytomegalovirus	Monitor viral load if suspicious for CMV-related disease or patient is high risk	Consider baseline IgG/IgM testing. Treat as per standard guidelines for reactivation
Hepatitis B virus	Administer prophylaxis for history of infection	Entecavir, tenofovir
PJP	Administer prophylaxis starting first cycle until CD4 >200/mm3 or end of therapy	TMP/SMX, atovaquone, dapsone, pentamidine

Raje N, et al. Blood Cancer J. 2023;13(1):116. | National Comprehensive Cancer Network Clinical Practice Guidelines for Prevention and Treatment of Cancer-Related Infections. V2.2023.

Talquetamab toxicities

Skin

- **Examples:** dry skin (50-90%), rash (30-40%), exfoliation, fissures, pruritis
- **Timing:** onset 3-7 weeks. Most are not painful, mild, and resolve in 3-6 weeks
- **Management:** Heavy moisturizers, ammonium lactate or urea, steroid (topical or oral), antihistamines, avoid hot showers and friction, reduce treatment dose/frequency, dermatology consult. Hold therapy if grade 3-4

Nails

- **Examples**: onycholysis, onychomadesis, discoloration, ridging, cracking. Overall occurs in 30-60%
- **Timing:** onset 4-15 weeks. Most are not painful, and 20-30% resolve
- **Management:** nail hardeners, moisturizers, topical vitamin E oil, avoid friction

Mouth

- **Examples:** dry mouth (30-60%), dysgeusia (60-70%), dysphagia (25-40%), decreased appetite, weight loss (30-60%)
- **Timing:** onset 2-4 weeks. 30% resolve
- **Management:** Mouth rinses (e.g., dexamethasone, bicarb), saliva substitutes, sugar-free candies, cevimeline, small meals, nutritional support, different flavor profiles, dysphagia diet, monitor weight, reduce treatment dose/frequency, nutrition consult

Laheij AMGA, et al. Support Care Cancer. 2023;32(1):20. | Talquetamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2023

Step-up phase schedule

	Step-up 1	Step-up 2	Step-up 3	First treatment
Tec[a, b]	Day 1 *(0.06 mg/kg)*	Day 4 *(0.3 mg/kg)*	-	Day 7 *(1.5 mg/kg)*
Tal[a, b] (w)	Day 1 *(0.01 mg/kg)*	Day 4 *(0.06 mg/kg)*	-	Day 7 *(0.4 mg/kg)*
Tal[a, b] (2w)	Day 1 *(0.01 mg/kg)*	Day 4 *(0.06 mg/kg)*	Day 7 *(0.4 mg/kg)*	Day 10 *(0.8 mg/kg)*
Elra[c]	Day 1 *(12 mg)*	Day 4 *(32 mg)*	-	Day 8 *(76 mg)*

Administer pre-medications prior to all doses in step-up phase

[a] May be administered 2-4 days after previous dose and may allow up to 7 days for resolution of adverse events

[b] Patients SHOULD be hospitalized for 48 hours after each dose due to risk of CRS/ICANS

[c] Patients SHOULD be hospitalized for 48 hours after step-up 1 and 24 hours after step-up 2

Teclistamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2022 | Elranatamab [prescribing information]. Pfizer Inc. New York, NY. 2023 | Talquetamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2023

Administration and subsequent schedule

- Subcutaneous injection in abdomen
- Up to 2 mL per syringe

	Treatment Dose	Initial Frequency	Decreasing Frequency for Responders	Maximum Delay to Avoid Re-Stepping-Up
Teclistamab	1.5 mg/kg	Weekly	For CR+ for 6+ months: every 2 weeks	4 weeks
Talquetamab	0.4 mg/kg	Weekly	N/A	4 weeks
	0.8 mg/kg	Every 2 weeks	N/A	4 weeks
Elranatamab	76 mg	Weekly	For Cycles 7+ (week 25+) AND PR+ for 2+ months: every 2 weeks	6 weeks

Teclistamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2022 | Elranatamab [prescribing information]. Pfizer Inc. New York, NY. 2023 | Talquetamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2023

Preparation

	Dosing	Vial Sizes	Preparation	Storage
Teclistamab	Weight-based	30mg/3mL (10mg/mL); 153mg/1.7mL (90mg/mL)	Remove from fridge and equilibrate to room temp for at least 15 minutes For teclistamab and talquetamab, swirl for 10 seconds to mix	Room temp or fridge for 20 hours
Talquetamab	Weight-based	3mg/1.5mL (2mg/mL); 40mg/1mL		Fridge for 24 hours followed by room temp for 24 hours
Elranatamab	Flat dose	44mg/1.1mL (40mg/mL); 76mg/1.9mL (40mg/mL)		Fridge for 4 hours

Teclistamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2022 | Elranatamab [prescribing information]. Pfizer Inc. New York, NY. 2023 | Talquetamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2023

REMS program

- Requirements
  - Prescriber: training and certification, patient education, report serious adverse events of CRS/ICANS
  - Pharmacy/healthcare settings: authorized representative, training and certification, verify prescriber certification prior to dispensing
  - Patients: receive patient wallet card
- Websites
  - https://www.tec-talrems.com/
  - https://www.elrexfiorems.com/

Teclistamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2022 | Elranatamab [prescribing information]. Pfizer Inc. New York, NY. 2023 | Talquetamab [prescribing information]. Janssen Biotech Inc. Horsham, PA. 2023

Patient case

- 62 M with history of CKD, afib, ECOG 1, and IgG kappa MM who has progressed through VRd/ASCT/len, DKd, elo-Pd, selinexor with increasing Mspike and new lesions on PET requiring new line of therapy
  - What are his next options?
  - Which bispecific antibody would be preferred?

Choice of therapy

- Past/future BCMA-directed therapy vs GPRC5D-directed therapy
- Toxicity profile: infection vs taste/skin
- Dosing schedule/duration of hospitalization
- Cost/formulary
  - Tal/tec - 340b purchasing
  - Elra – free supply for step-up doses

Patient case

- 62 M with history of CKD, afib, ECOG 1, and IgG kappa MM who has progressed through VRd/ASCT/len, DKd, elo-Pd, selinexor with increasing Mspike and new lesions on PET requiring new line of therapy
  - What are his next options?
  - Which bispecific antibody would be preferred?
  - What supportive care would he require?

Future directions

- Move to earlier lines
- Use in combinations
- Outpatient initiation
- Tocilizumab premedication
- Sequencing
- Overcoming resistance/T-cell exhaustion
- Increasing dosing interval

MSK outpatient operations

- Inclusion/exclusion criteria
  - Performance status, comorbidities, disease burden, caregiver support, distance from hospital
  - Limited to specific treatment sites
- Provider assessment schedule
  - In person visit before each step-up dose and telehealth assessment daily for 2 days after
- Patient supplies and education
  - Thermometer, blood pressure cuff, pulse oximeter. Must demonstrate competency
  - Prescription for dexamethasone and non-antipyretic pain medications
  - Avoid medications that can contribute to altered mental status
  - Vital signs log, symptom chart, wallet card
- Outpatient observation unit
  - Able to administer tocilizumab/steroids and manage low grade CRS

Bispecific T-Cell Engagers in Lymphoma

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Treatment Paradigms for B-cell Non-Hodgkin lymphomas (NHL)

- Chemotherapy
- Immunotherapy
- Antibody–drug conjugates
- Small molecules
- Chimeric antigen receptor T-cell (CAR-T) therapy
- Bispecific T-cell engager therapies (BiTEs)

Falchi L, et al. *Blood*. 2023.

BiTEs Currently Approved for NHL

BiTEs	FDA approved	Indication
Mosunetuzumab	December 22, 2022	R/R FL ≥2 prior lines
Epcoritamab	May 19, 2023	R/R DLBCL (including transformed) and HGBCL ≥2 prior lines
Glofitamab	June 15, 2023	R/R DLBCL and transformed FL ≥2 prior lines

R/R = relapsed/refractory

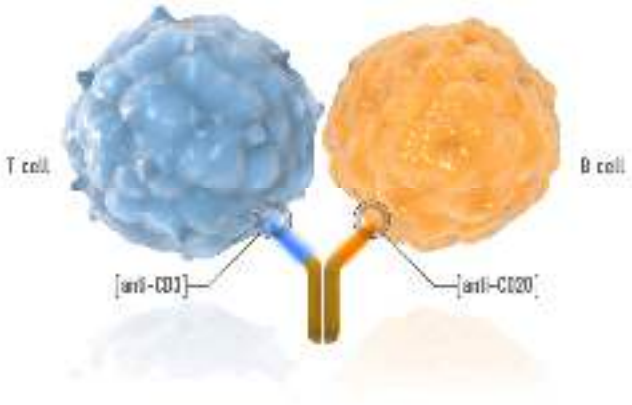
FL = follicular lymphoma

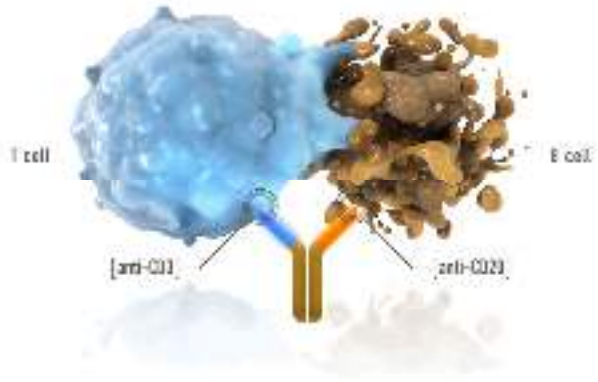
DLBCL = diffuse large B-cell lymphoma

HGDCL = high-grade B-cell lymphoma

Mosunetuzumab

- Indication: R/R follicular lymphoma ≥2 prior lines
- Mechanism of Action (MOA)
  - CD20 on B-cells
  - CD3 on T-cells





Falchi L, et al. *Blood*. 2023.
Lunsumio. Patient and Caregiver Site. 2024.

Mosunetuzumab

GO29781 - Phase II, single-arm, multicenter study

Key inclusion criteria:

- R/R FL ≥2 prior therapies including an anti-CD20 therapy and an alkylating agent
- ECOG 0–1

Dose and Schedule (21-Day Treatment Cycles)		
Day of Treatment		Dose, IV
Cycle 1 (step-up)	Day 1	1 mg
	Day 8	2 mg
	Day 15	**60 mg**
Cycle 2	Day 1	60 mg
Cycles 3+	Day 1	30 mg

Budde LE, et al. *Lancet*. 2022.
Lunsumio [prescribing information]. Genentech, Inc; 2023.

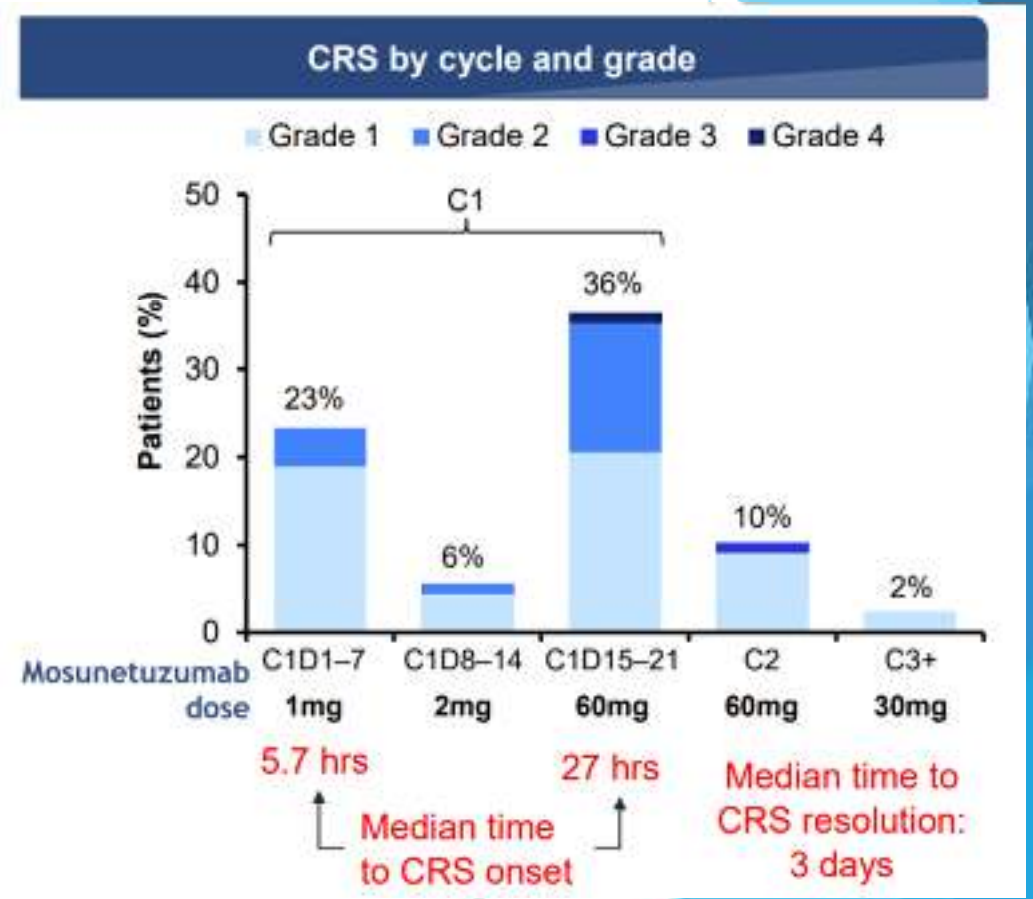
Mosunetuzumab - Efficacy

- N = 90
- Overall response rate (ORR): 80%
- Complete response (CR) rate: 60%
- Median time to response: 1.1 months
- Median duration of response (DOR): 22.8 months
- Median progression free survival (PFS): 24 months

Budde LE, et al. *Lancet*. 2022.

Mosunetuzumab - Safety

Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Cytokine release syndrome (CRS)	44	2.2
Neurologic toxicity	39	3
ICANS	1	0
Neutropenia	58	40
Infections	24	3.3
Rash	39	4.4
Musculoskeletal pain	28	1.1



Budde LE, et al. *Lancet*. 2022.
Lunsumio [prescribing information]. Genentech, Inc; 2023.
Budde LE, et al. ASH; 2021.

ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome

Mosunetuzumab: Logistical Considerations

- No mandatory hospitalizations for administration unless symptomatic
- Outpatient monitoring of CRS/ICANS
  - NewYork-Presbyterian Hospital - Columbia protocol:
    - C1D1 dose: administer in the early AM and remain on campus for a 6-hour post-infusion RN vitals check or be called at the end of the day by an RN
    - C1D15 dose: return to clinic for RN/NP visit 24-hours post-infusion for vitals check or telemedicine visit
- IV administration time:

Dose and Schedule (21-Day Treatment Cycles)			
Day of Treatment		Dose	**Infusion Duration**
Cycle 1 (step-up)	Day 1	1 mg	Administer over a minimum of **4 hours.**
	Day 8	2 mg	
	Day 15	60 mg	
Cycle 2	Day 1	60 mg	Administer over **2 hours** if infusions from Cycle 1 were well-tolerated.
Cycles 3+	Day 1	30 mg	

Lunsumio [prescribing information]. Genentech, Inc; 2023.

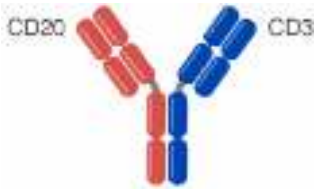
Mosunetuzumab: Logistical Considerations

- Premedications:
  - Corticosteroid, Antihistamine, Antipyretic for all Cycle 1 doses
  - Cycle 2+: as above for patients who experienced any grade CRS with the previous dose
- Administer prophylactic antimicrobials according to guidelines
- 2 vial sizes: 1 mg/mL and 30 mg/30 mL
- Restarting therapy after dose delay specific recommendations per PI
- Fixed duration of treatment:
  - 8 cycles if CR after cycle 8
  - 17 cycles if PR/SD after cycle 8

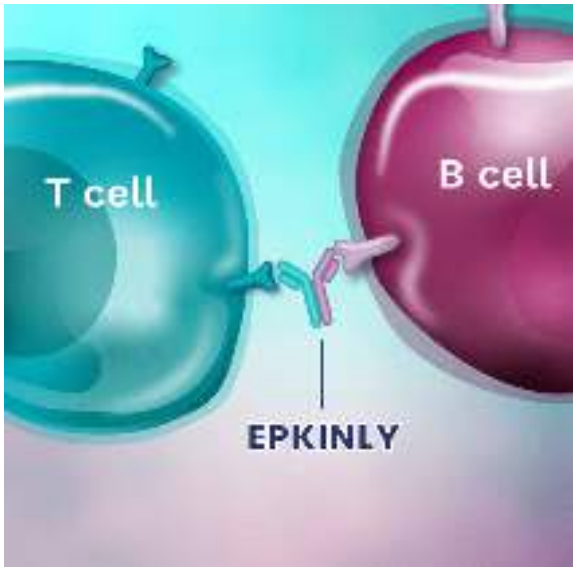
CR = complete response
PR = partial response
SD = stable disease

Budde LE, et al. *Lancet*. 2022.
Lunsumio [prescribing information]. Genentech, Inc; 2023.

Epcoritamab



- Indication:
  - R/R DLBCL (including transformed) and HGBCL ≥2 prior lines
- MOA:
  - CD20 on B-cells
  - CD3 on T-cells



Falchi L, et al. *Blood*. 2023.
Epkinly. Patient and Caregiver Site. 2024.

Epcoritamab

EPCORE NHL-1 - Phase I/II, single-arm, multicenter study

Key inclusion criteria:

- CD20+ mature B-cell neoplasm R/R ≥2 prior therapies including an anti-CD20 therapy
- ECOG 0–**2**

Dose and Schedule (28-Day Treatment Cycles)		
Day of Treatment		Dose, SC
Cycle 1 (step-up)	Day 1	0.16 mg
	Day 8	0.8 mg
	Day 15	**48 mg**
	Day 22	48 mg
Cycle 2 and 3	Day 1, 8, 15 and 22	48 mg
Cycle 4-9	Days 1 and 15	48 mg
Cycles 10+	Day 1	48 mg

Thieblemont C, et al. *JCO*. 2022.
Epkinly. [prescribing information]. AbbVie Inc; 2023.

Epcoritamab: Efficacy

Updated results from the pivotal EPCORE NHL-1 trial:

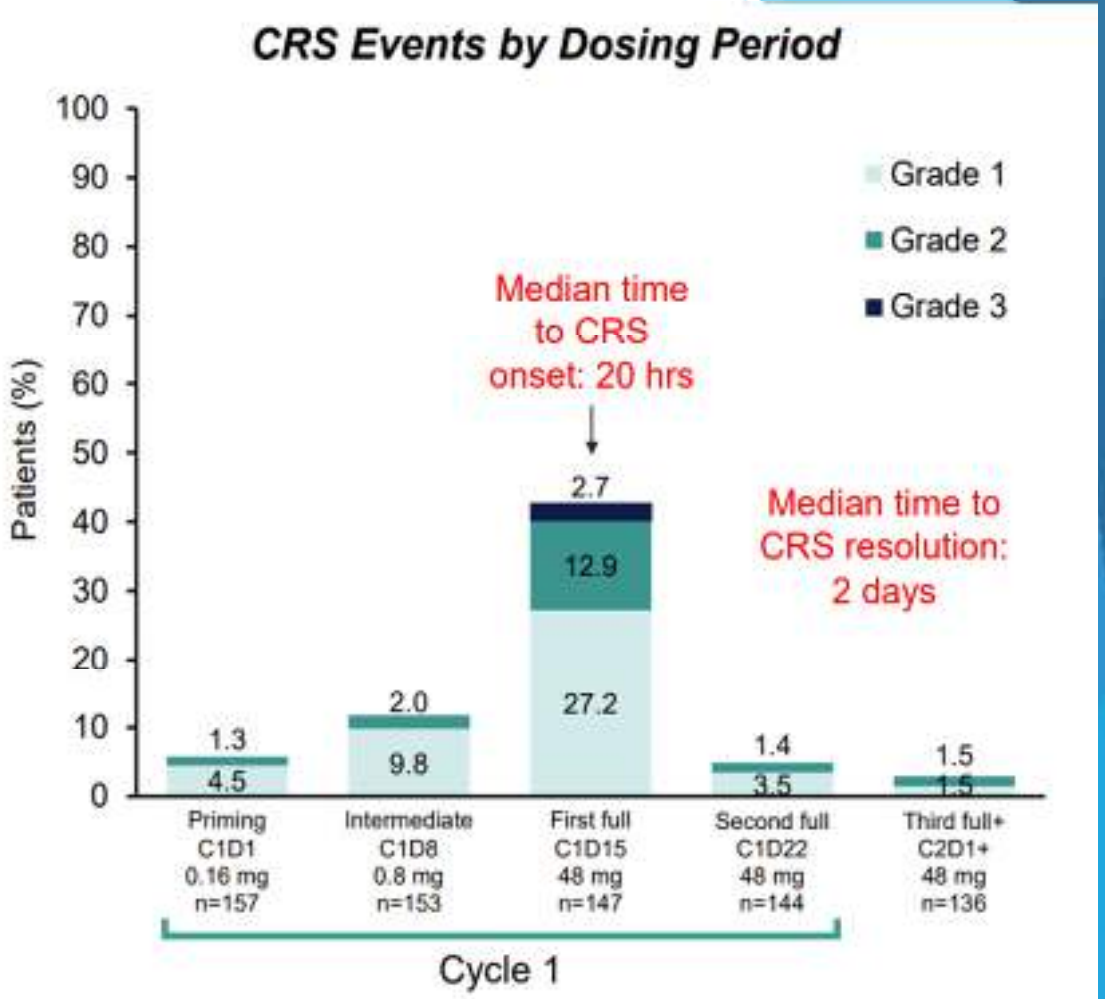
- N = 157
- ORR: 63%
- CR: 39%
- Median time to CR: 2.7 months
- Median OS: 18.5 months
- Median duration of CR: 20.8 months
- Median PFS: NR

NR = not reached

Karimi Y, et al. *JCO*. 2023.
Thieblemont C, et al. *JCO*. 2022.
Epkinly. [prescribing information]. AbbVie Inc; 2023.

Epcoritamab: Safety

Adverse Reaction	All Grades (%)	Grade ≥3 (%)
CRS	51	2.5
ICANS	6.4	0.6
Neutropenia	50	32
Thrombocytopenia	48	12
Infections	15	15
AST elevation	48	4.6
Musculoskeletal pain	28	1.3
Nausea	20	1.3



Thieblemont C, et al. *JCO*. 2022.
Epkinly. [prescribing information]. AbbVie Inc; 2023.
Karimi Y, et al. SOHO. 2023.

Epcoritamab: Logistical Considerations

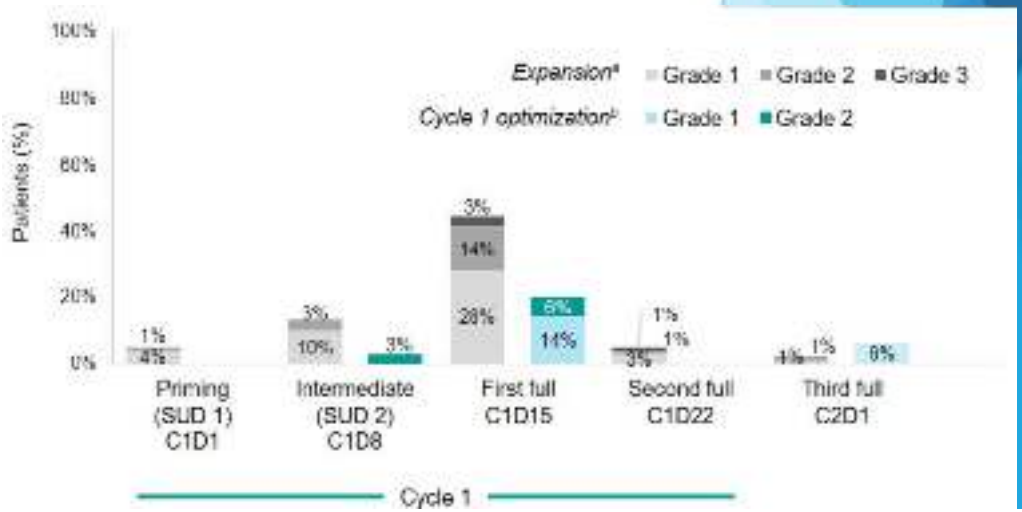
- Premedications:
  - Cycle 1:
    - Corticosteroid (Prednisolone 100 mg PO or IV or Dexamethasone 15 mg PO or IV)
      - Prior to injection and for **3 consecutive days following administration**
    - Antihistamine
    - Antipyretic
  - Cycle 2+: for patients who experienced grade 2 or 3 CRS with the previous dose
    - Corticosteroid (Prednisolone 100 mg PO or IV or Dexamethasone 15 mg PO or IV)
      - Prior to injection and for 3 consecutive days following administration

Epkinly. [prescribing information]. AbbVie Inc; 2023.

Epcoritamab: Mitigating the Risk of CRS Optimization Cohort

- Dexamethasone 15 mg PO or IV as premed and as CRS ppx for 3 days post C1 doses
- 2-3 L of fluid 24h prior to dose
- 500 ml IV fluids prior to administration
- Hold antihypertensives 24h prior to dose
- Self-monitoring of temperature 3 times daily for 4 days after dose
- Hospitalization not required

Adverse event	Expansion, N=157	Optimization, n=36
CRS (%)	51	22
ICANS (%)	6.4	1.7



Vose JM, et al. ASH 2023. Poster

Epcoritamab: Logistical Considerations

- Patients should be hospitalized for at least 24 hrs for C1D15 dose or if CRS with previous step-up dose
- Outpatient monitoring of CRS/ICANS
- PJP and consider herpes virus prophylaxis prior to starting
- Subcutaneous administration
- Step-up doses require dilution
- 2 vial sizes: 4 mg/0.8 mL and 48 mg/0.8 mL
- Restarting therapy after dose delay specific recommendations per PI
- Duration of treatment: until disease progression or unacceptable toxicity

PJP = Pneumocystis jirovecii Pneumonia

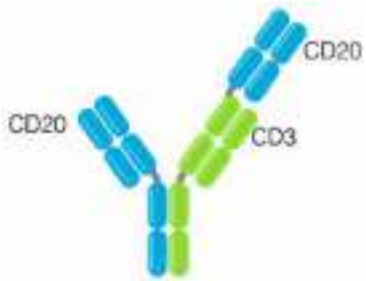
Epkinly. [prescribing information]. AbbVie Inc; 2023.

Audience participation

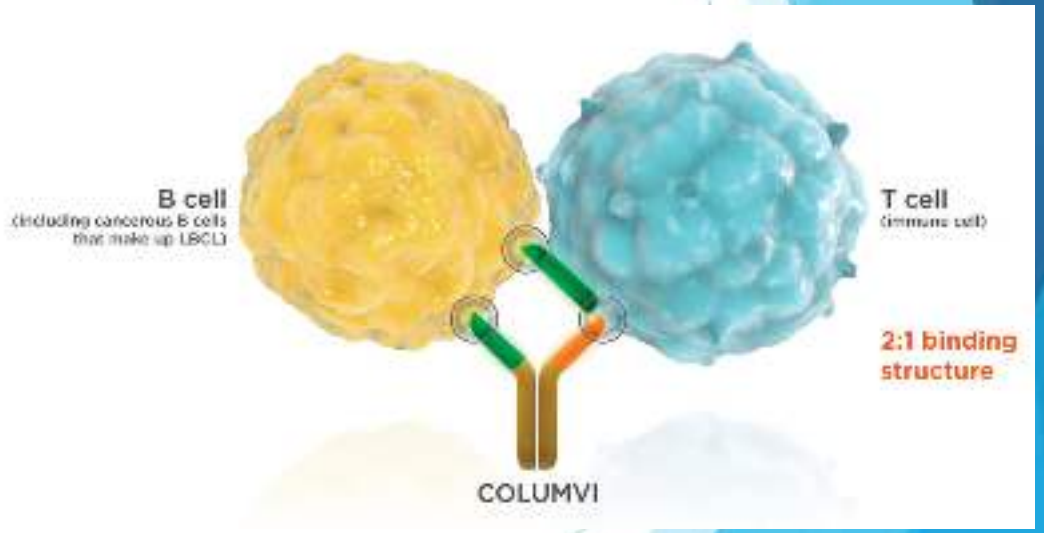
True or false?

All BiTEs approved for NHL have identical antibody structure

Glofitamab



- Indication:
  - R/R DLBCL and transformed FL ≥2 prior lines
- MOA:
  - Novel 2:1 tumor–T-cell binding configuration
  - Bivalent CD20 on B-cells
  - Monovalent CD3 on T-cells



Falchi L, et al. *Blood*. 2023.
Columvi. Healthcare Professionals Site. 2024.

Glofitamab

Phase II, single-arm, multicenter study

Key inclusion criteria:

- DLBCL, transformed FL, HGBCL, PMLBCL: R/R ≥2 prior therapies including an anti-CD20 therapy and anthracycline
- ECOG 0–1

Dose and Schedule (21-Day Treatment Cycles)		
Day of Treatment		Dose, IV
Cycle 1 (step-up)	Day 1	**Obinutuzumab 1,000 mg**
	Day 8	2.5 mg
	Day 15	10 mg
Cycles 2-12	Day 1	30 mg

Dickinson MJ, et al. *NEJM*. 2022.
Columvi. [prescribing information]. Genentech, Inc; 2023.

PMLBCL = primary mediastinal large B-cell lymphoma

Glofitamab - Efficacy

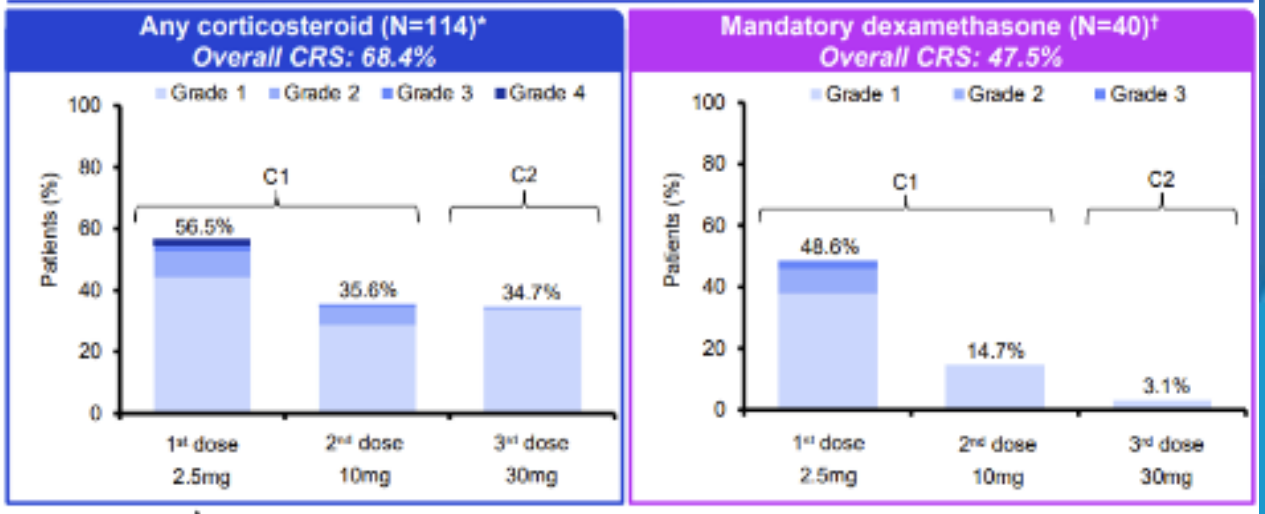
- N = 155
- ORR: 51.6%
- CR: 39.4%
- Median time to response: 42 days
- Median PFS: 4.9 months
- Median OS: NR
- Median duration of CR: 26.9 months

Dickinson MJ, et al. *NEJM*. 2022.
Dickinson MJ, et al. ICML; 2023.

Glofitamab - Safety

Adverse Reaction	All Grades (%)	Grade ≥3 (%)
CRS	64	4
ICANS	8	3
Neutropenia	38	27
Thrombocytopenia	25	7.7
Anemia	30.5	6.5
Musculoskeletal pain	21	2.1

CRS by steroid premedication



Mandatory dexamethasone: no Grade ≥2 CRS with 10mg or 30mg glofitamab

Median time to CRS onset: 13.6 hrs

Median time to CRS resolution: 30.5 hrs

Dickinson MJ, et al. *NEJM*. 2022.
Dickinson MJ, et al. ICML; 2023.
Dickinson MJ, et al. EHA; 2022.
Columvi. [prescribing information]. Genentech, Inc; 2023.

Glofitamab Logistical Considerations

- Pretreatment with Obinutuzumab
- Patients should be hospitalized for Cycle 1 Day 8 (2.5 mg step-up dose) and for subsequent infusions as recommended
- Outpatient monitoring of CRS/ICANS
- NewYork-Presbyterian Hospital - Columbia protocol:
  - Mandatory hospitalization for at least 24 hrs for C1D8 dose
  - Hospitalize for at least 24 hrs for C1D15 if any grade CRS with C1D8 dose
  - Hospitalize for at least 24 hrs for any doses C2D1 or beyond if ≥grade 2 CRS with prior dose
  - If no history of prior CRS, then for C1D15:
    - administer in early AM if possible and RN call at end of day C1D15
    - Patient should return to clinic for RN/NP visit 24-hours post-infusion for vitals check or telemedicine visit

Dickinson MJ, et al. *NEJM*. 2022.
Columvi. [prescribing information]. Genentech, Inc; 2023.

Glofitamab Logistical Considerations

Infusion Duration (21 day cycles)			
Day of Treatment		Dose, IV	Duration of infusion
Cycle 1 (step-up)	Day 1	Obinutuzumab	
	Day 8	2.5 mg	**4 hours***
	Day 15	10 mg	
Cycle 2	Day 1	30 mg	**4 hours**
Cycles 3-12	Day 1	30 mg	**2 hours****

*For patients who experience CRS with their previous dose may extend up to 8 hours

**If the patient experienced CRS with the previous dose, the duration of infusion should be maintained at 4 hours

Dickinson MJ, et al. *NEJM*. 2022.
Columvi. [prescribing information]. Genentech, Inc; 2023.

Glofitamab Logistical Considerations

- Premedications:
  - Cycle 1-3:
    - Dexamethasone 20 mg IV
    - Antihistamine
    - Antipyretic
  - Cycle 4+:
    - Dexamethasone 20 mg IV for patients who experienced any grade CRS with the previous dose
    - Antihistamine
    - Antipyretic

Columvi. [prescribing information]. Genentech, Inc; 2023.

Glofitamab Logistical Considerations

- Tumor lysis syndrome (TLS) prophylaxis:
  - Anti-hyperuricemics and hydration
- Consider PJP and antiviral prophylaxis
- Consider prophylaxis for cytomegalovirus infection in patients at increased risk
- 2 vial sizes: 2.5 mg/2.5 mL and 10 mg/10 mL
- 0.2-micron in-line filter
- Fixed treatment duration: 12 cycles

Columvi. [prescribing information]. Genentech, Inc; 2023.

Epcoritamab and Glofitamab Logistical Considerations Summary

BiTE	Epcoritamab	Glofitamab
Administration	SC Post dose steroid for C1	IV (2–8-hour infusion) Obinutuzumab pre-treatment
Prophylaxis	PJP and antiviral	TLS, PJP and antiviral, CMV (for high risk)
Duration	Until progression/toxicity	Fixed duration of 12 cycles treatment

Epkinly. [prescribing information]. AbbVie Inc; 2023.
Columvi. [prescribing information]. Genentech, Inc; 2023.

Future of BiTEs

- Combination therapy
- Earlier line of therapy
- Optimal duration of BiTE therapy
- Treatment sequencing
- Strategies to minimize toxicity
- Biomarkers of response and resistance
- Predictors of CRS

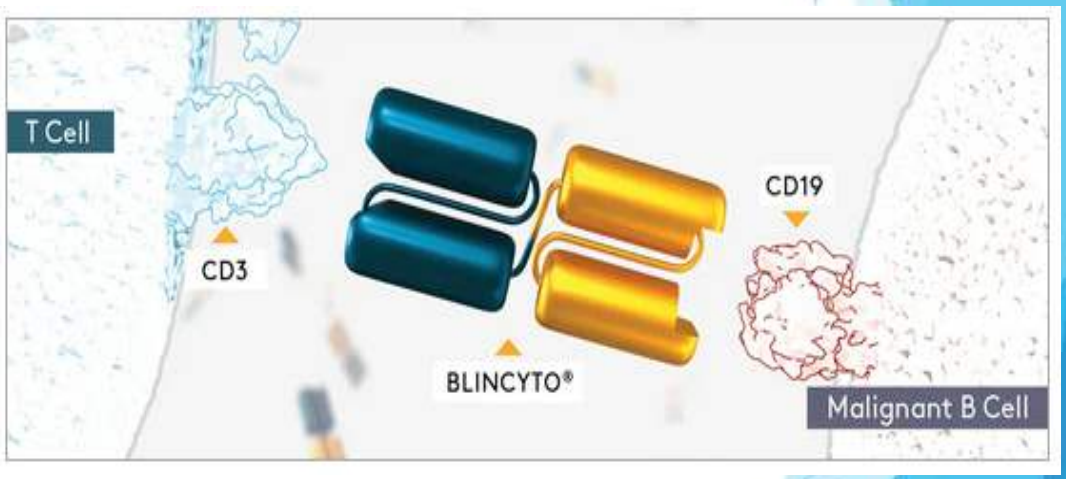
Falchi L, et al. *Blood*. 2023.

Conclusion

- Physician and patient education
- Minimize risk factors for CRS/ICANS
- Ensure appropriate prophylaxis

Blinatumomab (Blincyto)

- First Bispecific T-cell Engager (BiTE®)
- FDA-approved indications:
  - 2014: Philadelphia chromosome negative (Ph-) relapsed or refractory (r/r) CD19-positive B-cell precursor acute lymphoblastic leukemia (B-ALL)
  - 2017: Ph+ r/r CD19-positive B-ALL
  - 2018 (accelerated): CD19-positive B-ALL in first or second complete remission (CR1 or CR2) with minimal residual disease (MRD) greater than or equal to 0.1% [full approval in 2023]



https://www.blincytohcp.com/mechanism-of-action
Blincyto (blinatumomab). Amgen Inc; 2024.

Relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia

Ph Negative (TOWER)

- Randomized, ph III trial
- Adults with relapsed/refractory Ph negative B-cell ALL
- Blinatumomab (N=271) vs standard chemotherapy (N=134)
- Median OS: 7.7 mo vs 4 mo (HR 0.71; p=0.01)
  - HSCT censored: 6.9 mo vs 3.9 mo
- Remission: 44% vs 25%; p<0.001
- 6-mo event-free survival: 31% vs 12%; p<0.001

Ph Positive (ALCANTARA)

- Ph II, single-arm trial
- Adults with relapsed/refractory Ph positive B-cell ALL
- Failed/intolerant to 2nd generation or later TKIs
- Blinatumomab (N=45)
- Remission within 2 cycles: 36%
  - 88% MRD negative
- Relapse-free survival: 6.7 mo
- Median OS: 7.1 mo

N Engl J Med. 2017;376(9):836-847.
J Clin Oncol. 2017;35(16):1795-1802.

MRD+ B-ALL: BLAST Study

- Open-label, single-arm ph II trial (Europe and Russia)
- ≥18 years with B-cell precursor ALL in first or later hematologic CR and with persistent or recurrent MRD $\geq 10^{-3}$ after a minimum of 3 blocks of intensive chemotherapy (N=116)
  - Only 5 patients with Ph+ disease
- Complete MRD response after cycle 1 (N=113): 78%
- HSCT in CR: 67%
- Relapse-free survival, median: 18.9 months
  - MRD- 23.6 mo vs MRD+ 5.7 mo
- Overall survival, median: 36.5 months
  - MRD- 38.9 mo vs MRD+ 12.5 mo

Blood. 2018;131(14):1522-1531.

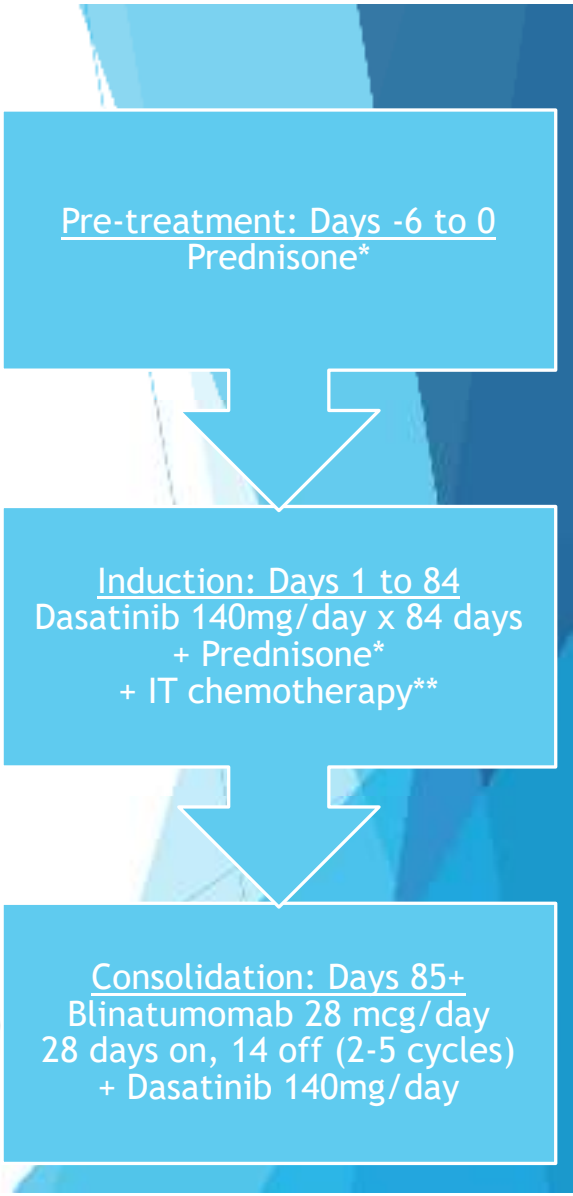
Blinatumomab

	r/r B-ALL		MRD+ B-ALL	
Dosing	≥45 kg	<45 kg	≥45 kg	<45 kg
	Cycle 1: 9 mcg/day x 7 days 28 mcg/day x 21 days Cycle 2+: 28 mcg/day x 28 days	Cycle 1: 5 mcg/m^2/day x 7 days 15 mcg/m^2/day x 21 days Cycle 2+: 15 mcg/m^2/day x 28 days	28 mcg/day	15 mcg/m^2/day
	Induction/consolidation: 28 days on, 14 off Continuation: 28 days on, 56 off		28 days on, 14 off	
Duration	1 – 2 induction cycles (42 days) 3 consolidation cycles (42 days) Up to 4 continuation cycles (84 days)		1 induction cycle (42 days) Up to 3 consolidation cycles (42 days)	
Setting	Hospitalization recommended: • First 9 days of cycle 1 • First 2 days of cycle 2		Hospitalization recommended: • First 3 days of cycle 1 • First 2 days of cycle 2 • Any interruption of ≥ 4 hours	
Premedication (Dexamethasone)	Adults: 20mg 1 hour before 1st dose of each cycle, prior to a step up dose (C1D8) or after interruption of 4+ hours Peds: 5 mg/m^2 (max 20 mg) at same time points		Adults: 20mg 1 hour before 1st dose of each cycle or after interruption of 4+ hours Peds: 5 mg/m^2 (max 20 mg) at same time points	

Blincyto (blinatumomab). Amgen Inc; 2024.

Off-Label:
Newly diagnosed Ph+ B-ALL

- GIMEMA LAL2116, D-ALBA trial (Italy)
- Ph II, single-group study
- Newly diagnosed adult Ph+ B-ALL patients (n=63)
  - Median age (range): 54 years (24 to 82)
  - Day 85: 98% complete hematologic response; 29% molecular response
  - Post cycle 2 consolidation: 52% molecular response (intention-to-treat)
  - Increased complete molecular response (CMR) with more cycles (up to 81%)
- Median follow-up: 18 months
  - Overall survival: 95%; Disease-free survival: 88%
- Median follow-up: 53 months
  - Overall survival: 80.7%; Disease-free survival: 75.8%



N Engl J Med. 2020;383(17):1613-23.
J Clin Oncol. 2023; 42:881-5.

*Prednisone: titrate 20mg/m2/day to 60mg/m2/day day -6 to -3; continue 60mg/m2/day day -2 to +24; taper days +25 to +32
**Prophylactic IT methotrexate + steroid: day 0, day +14, +22, +45, +57, +85

Blinatumomab - Safety

- Black Box Warning
  - CRS
    - R/R ALL: 15% (any grade); 3% (grade 3^{+})
    - MRD+ ALL: 7% (any grade); 1.5% (grade 3^{+})
    - Median onset: 2 days; Resolution: 5 days
  - Neurologic toxicity: 65% (any grade)
    - Grade 3+ 13%
    - Headache and tremor most commonly
    - Onset: within 2 weeks of treatment initiation
- Infection
- Fatal pancreatitis in post-marketing experience
- REMS: at approval in 2014, but removed in 2022

Blincyto (blinatumomab). Amgen Inc; 2024.

Blinatumomab – Operational Pearls

- IV solution stabilizer prior to adding drug
- Continuous infusions – home infusion
  - IV tubing priming with in-line filter
  - Do NOT flush line during bag changes
  - Transitions of care
- 24 hour vs 48 hour vs 168 hour (7-day) preparation
  - Bacteriostatic 0.9% sodium chloride and pediatric population
- Purposeful overfill (270 ml vs 240 mL)
- Subcutaneous formulation on the horizon

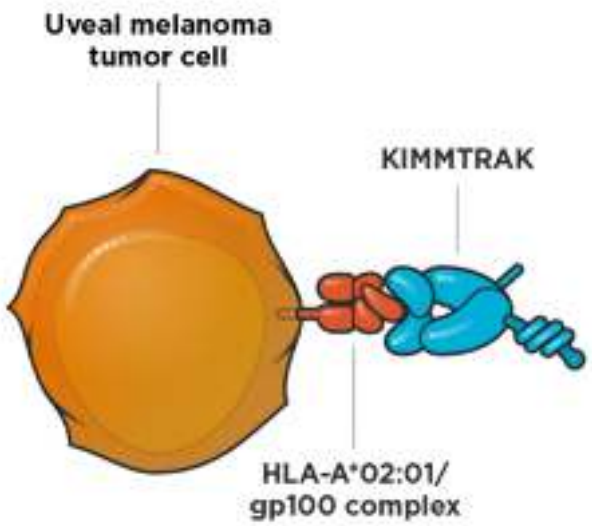
Am J Hematol. 2024;99(4):586-595.
Blincyto (blinatumomab). Amgen Inc; 2024.

True or False:

Blinatumomab 168-hour preparations are appropriate for all patient populations.

Tebentafusp-tebn (Kimmtrak)

- First FDA-approved T-cell–redirecting bispecific fusion protein for a solid tumor
  - Immune-mobilizing monoclonal T-cell receptors against cancer [ImmTAC]
- FDA-approved indications:
  - HLA-A*02:01-positive adult patients with unresectable or metastatic uveal
- HLA-A*02:01 positive: 45% of United States and Europe



HLA-A*02:01–restricted T-cell receptor for glycoprotein 100 (gp100) peptide fused to an anti-CD3 single-chain variable fragment

https://www.kimmtrak.com/#howkimmtrakworks
N Engl J Med. 2021;385(13):1196-1206
Kimmtrak (tebentafusp-tebn). Immunocore; 2023.

Tebentafusp-tebn – IMCgp100-202 Trial

- De novo HLA-A*02:01–positive patients with metastatic uveal melanoma
- Tebentafusp (N=252) vs single agent investigator's choice (N=126) [2:1 ratio]
- First analysis
  - Median OS: 21.7 mo vs 16 mo [HR 0.51 (95% CI, 0.37 - 0.71)]
    - Disease progression as best response before day 100: 15.3 mo vs 6.5 mo [HR 0.43; 95% CI, 0.27 - 0.68)]
  - Median PFS: 3.3 mo vs 2.9 mo [HR 0.73 (95% CI, 0.58 - 0.94)]
- 3 year follow-up analysis (median follow-up: 43.3 mo)
  - 57% tebentafusp continued despite radiographic progression; 16 patients crossed over from control
  - Surviving at 1/2/3 years: 72%/45%/27% vs 60%/30%/18%
  - Disease progression as best response before day 100: 15.1 mo vs 10.1 mo [HR 0.62; 95% CI, 0.44 - 0.89)]

N Engl J Med. 2021;385(13):1196-1206.
N Engl J Med. 2023;389(24):2256-2266.

Tebentafusp-tebn

Dosing	Day 1: 20 mcg IV over 15 – 20 minutes Day 8: 30 mcg IV over 15 – 20 minutes Day 15: 68 mcg IV over 15 – 20 minutes Weekly thereafter: 68 mcg IV over 15 – 20 minutes
Duration	Unacceptable toxicity or "disease progression"
Setting	"Appropriate healthcare setting": first 3 infusions (monitored for at least 16 hours after infusion) Dose 4+: ambulatory setting with at least 30 minutes monitoring after each dose
Premedication	None Dexamethasone 4mg if severe CRS with previous dose

Kimmtrak (tebentafusp-tebn). Immunocore; 2023.

Tebentafusp-tebn - Safety

- Black Box Warning: CRS
  - Doses 1 to 3: "appropriate healthcare setting"
  - Grade 2+: 77%; 60% with CRS episodes with more than 1 dose
  - Onset: 84% on day of infusion
  - Median time to resolution: 2 days
- Dermatologic reactions
  - 91% of patients (mostly grade 1 rash)
  - Grade 2 and 3: 44% and 21%
  - Onset: 1 days
  - Median time to resolution (</= grade 1: 6 days
- Liver Enzymes
  - Increased AST/ALT levels: 65%

Kimmtrak (tebentafusp-tebn). Immunocore; 2023.

Tebentafusp-tebn - Operational Pearls

- 100 mcg / 0.5 mL single-dose vial
- Two-Step preparation
  - Create 250 mcg/mL albumin in 100mL 0.9% sodium chloride bag
    - 5%: 0.5 mL
    - 20%: 0.13 mL
    - 25%: 0.1 mL
  - Add tebentafusp
    - 20 mcg: 0.1 mL
    - 30 mcg: 0.15 mL
    - 68 mcg: 0.34 mL
- 0.2 micron in-line filter

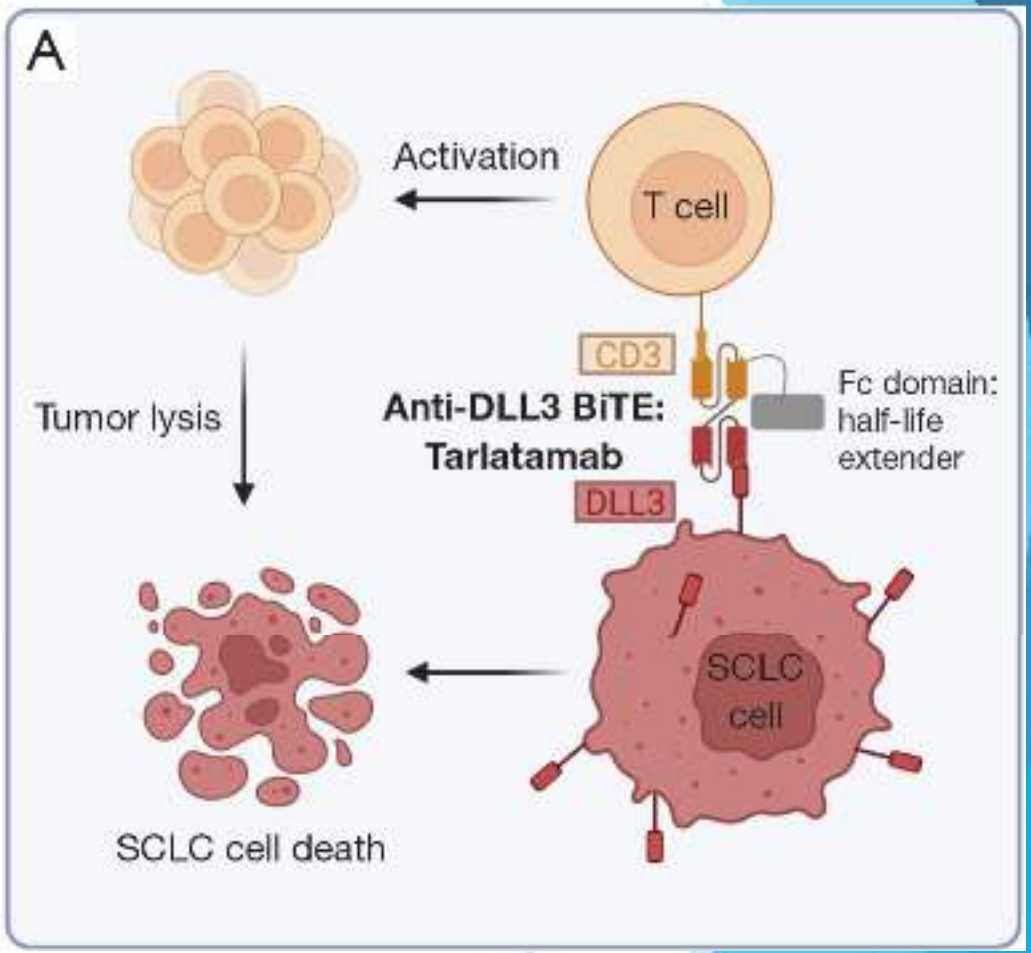
Kimmtrak (tebentafusp-tebn). Immunocore; 2023.

True or False:

Tebentafusp does not require hospitalization for CRS monitoring.

Tarlatamab-dlle (Imdelltra)

- Accelerated FDA approved: May 16, 2024
- Delta-like ligand 3 (DLL3) BiTE®
  - Adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy
- DLL3 expression
  - 85%- 96% of SCLC cells
  - Minimal on normal cells



Transl Lung Cancer Res. 2023;12(5):948-952.
N Engl J Med. 2023;389(22):2063-2075.

Tarlatamab-dlle - DeLLphi-301 trial

- Ph II, open-label trial
- Advanced small cell lung cancer after 2+ lines of therapy
- Three parts
  - Part 1: dose comparison of 10mg (N=88) vs 100mg (N=88)
  - Part 2: qs to 100 patients at selected target dose (10mg) in part 1 (N=12)
  - Part 3: sub-study reducing cycle 1 hospitalization from 48 hrs to 24 hrs (N=34)
- Objective response (10mg vs 100mg): 40% vs 32%
- Disease control (OR plus SD): 70% vs 63%
- Median PFS: 4.9 mo vs 3.9 mo
- Median OS: 14.3 mo vs NR

N Engl J Med. 2023;389(22):2063-2075.

Tarlatamab-dlle

Dosing	Day 1: 1 mg IV over 60 minutes Day 8: 10 mg IV over 60 minutes Day 15: 10 mg IV over 60 minutes Ever 2 weeks thereafter: 10 mg IV over 60 minutes
Duration	Unacceptable toxicity or disease progression
Setting	"Appropriate healthcare setting": first 2 infusions (monitored for 22-24 hours after infusion) "Recommend" remaining within 1-hour of an appropriate healthcare setting for a total of 48 hours from the start of the infusion, accompanied by a caregiver. Cycle 1, Day 15 and beyond: Ambulatory
Supportive medication	Dexamethasone 8mg IV on day 1 and day 8 of cycle 1 prior to tarlatamab administration 0.9% sodium chloride 1000 mL after each tarlatamab infusion in cycle 1 (over 4-5 hours)

Imdelltra (tarlatamab-dlle). Amgen; 2024.
N Engl J Med. 2023;389(22):2063-2075.

Tarlatamab-dlle – Safety (10 mg)

- Black Box Warning
  - CRS: 51% overall
    - Grade 3+: 1%
    - ~5% received tocilizumab; <1% received vasopressors
    - "Most common" after day 1 or day 8 doses
    - Median onset: 13.1 hours after tarlatamab dose
    - Median duration: 4 days
  - ICANS: 8% overall
    - Grade 3+: 0 [5% in 100 mg group]
    - "Most common" after cycle 1 doses
    - Median onset: 5 days
    - Median time to resolution: 6.5 days
- Neutropenia (17%)

N Engl J Med. 2023;389(22):2063-2075.

Tarlatamab-dlle – Operational Pearls

- No REMS program
- IV solution stabilizer required: 13 mL (both doses)
  - Final volume 250 mL 0.9% Sodium Chloride (remove drug and stabilizer volume)
- Remove air from prepared IV bag
- 7-day beyond-use dating refrigerated
- NO in-line filter
- Monitoring based on dose
  - Cycle 1, Day 1 and Day 8: 22-24 hours
  - Cycle 1, Day 15 and Cycle 2: 6-8 hours
  - Cycles 3 and 4: 3-4 hours
  - Cycles 5+: 2 hours

Imdelltra (tarlatamab-dlle). Amgen; 2024.
N Engl J Med. 2023;389(22):2063-2075.

True or False:

Tarlatamab-dlle will be easy to integrate into our existing bispecific t-cell engager practice as the providers caring for these patients are already experts in managing CRS and ICANS.

Bispecific T-Cell Engagers: *Two* BiTE*s* with Lots to Swallow

Round Table Discussion

Round Table Talking points

- Solid tumor specialists and CRS/ICANS management?
- G-CSF and BiTES
- Fever-masking supportive care medications? And potentially neurotoxic supportive care meds?
- Blinatumomab for de novo Ph+ B-ALL patients? Dasatinib or Ponatinib?
- Outpatient initiation for all BiTEs?
- Pre-phase treatment for high disease burden blin patients? Dex? Cy?
- Formulary status for rare medications like tebentafusp?
- Albumin % choice for tebentafusp preparation?
- How fast is P&T turnaround on new oncology medications?
- Managing transitions of care?
- Separate CRS/ICANS per drug or one policy to include all?