Advances in Bispecific Antibody Treatment in B-cell NHL - Pharmacology

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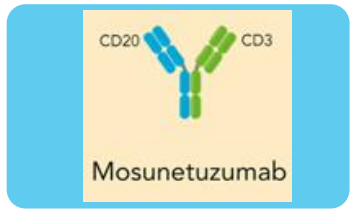
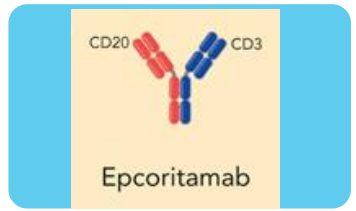
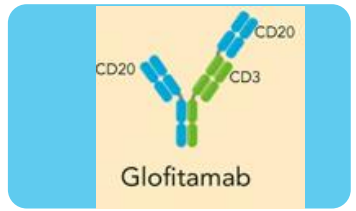
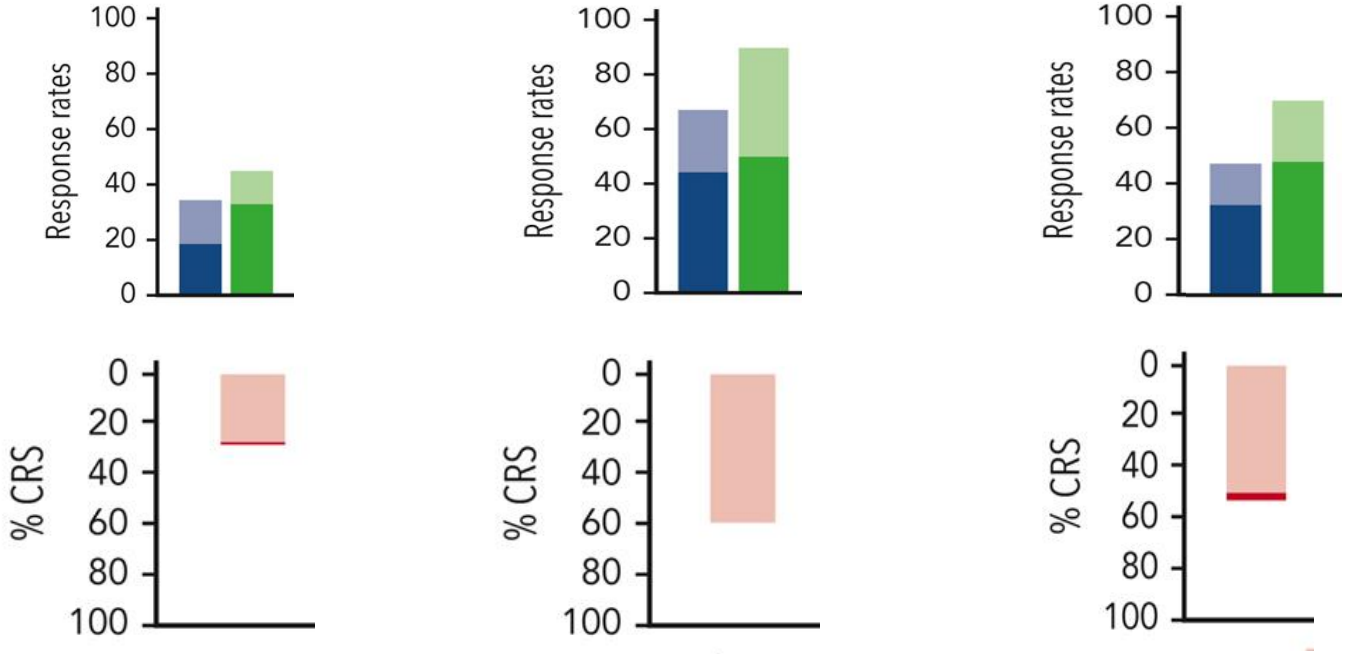
Bispecific antibodies (BsAb) in NHL

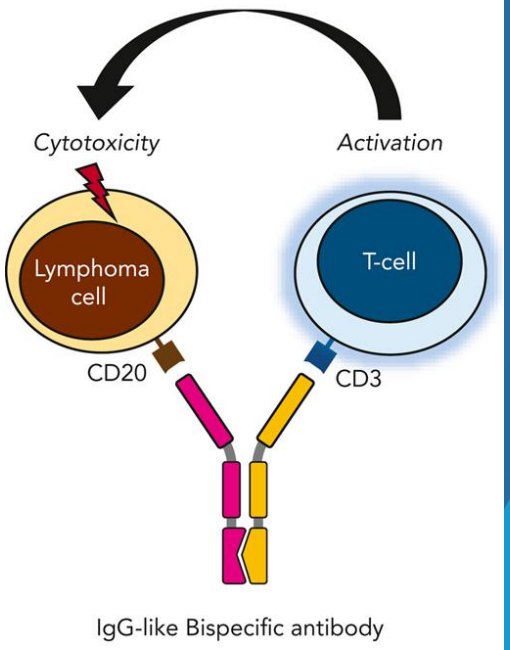
Blinatumumab











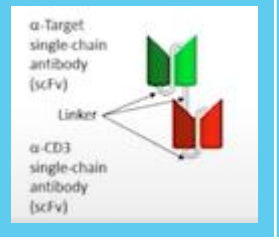
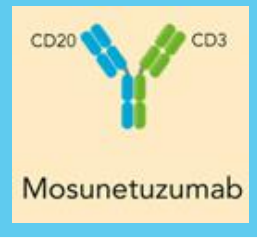
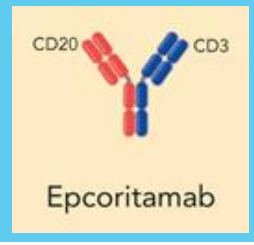
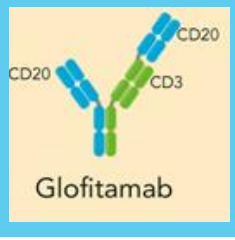
- Aggressive NHL, CR
- Aggressive NHL, PR
- Indolent NHL, CR
- Indolent NHL, PR

- Other common adverse events (AE): Neutropenia, diarrhea, fatigue, anemia;
- ICANS-like syndrome, TLS, HLH: rare (<5%)

* data for aggressive NHL and indolent NHL reported in aggregate

Falchi. *Blood* (2023) 141 (5): 467–480.

Structure of BsAbs

	Blinatumumab 			
Format	• 1st generation • Two scFv joined by a glycine-serine linker • Short half-life (1.5-2 hours) → continuous IV infusion	• 2nd generation • Silent Fc region • IgG1	• 2nd generation • Silent Fc region • IgG1 Fc modified to minimize Fc-dependent effector functions/control Fab-arm exchange of mAb half-molecules	• 2nd generation • Silent Fc region • IgG1
CD19/CD3 or CD20/CD3 Ratio	1:1 CD19:CD3	1:1 CD20:CD3	1:1 CD20:CD3 ratio	2:1 CD20-CD3 ratio
Technology	-	Knobs-into-holes	Controlled Fab-arm exchange	Head-to-tail fusion
CD20 Ab Clone	-	Rituximab epitope	Ofatumumab epitope	Obinutuzumab epitope

Ig, immunoglobulin; scFv, single-chain variable fragment; mAb, monoclonal antibody; Fc, fragment crystallizable; FcγR, Fc gamma receptor; Fab, Fragment antigen-binding

Schuster, Hematol Oncol. 2021

Pharmacology/FDA Status

	Mosunetuzumab	Epcoritamab (GEN3013)	Glofitamab (RG6026)
Half-life	~16.1 days	~ 8.8 days	~ 10 days
Drug Interactions	Release of cytokines may suppress activity of CYP450 enzymes • Monitor for increased exposure of CYP450 substrates		
FDA Status	• FL: FDA Accelerated Approval on 12/22 • Aggressive NHL: coming soon	• LBCL: FDA granted priority review for BLA w/ PDUFA date 5/21/23 • FL: FDA grants orphan drug status for R/R follicular lymphoma treatment on 3/1/22	LBCL: 1/23 FDA accepted BLA and granted priority review (expected FDA will decide by 7/2023)
NCCN	Third-line and subsequent therapy	-	-

BLA, Biologics license application; PDUFA, Prescription Drug User Fee Act; FL, follicular lymphoma; LBCL, large B-cell lymphoma; NHL, Non-hodgkin's lymphoma; CYP, Cytochrome; NCCN, National Comprehensive Cancer Network; FDA, Food and Drug Administration; R/R, relapse/refractory

Agent	Mosunetuzumab		Epcoritamab (GEN3013)	Glofitamab (RG6026)	
MOA	T-cell engaging BsAb targeting CD3 receptor expressed on T cells & CD20 expressed on the surface of lymphoma cells and some healthy B-lineage cells. Redirects T-cells to engage & eliminate malignant B-cells by releasing proinflammatory cytokines & inducing lysis				
Indication	• FL: R/R in adults after ≥2 prior lines of therapy • Aggressive NHL: coming soon		• LBCL: R/R after ≥2 prior lines of therapy	• LBCL: R/R after ≥2 prior lines of therapy	
Administration	Cycle 1: IV over 4 hrs (minimum) • SQ coming soon	Cycles 2+: IV over 2 hrs if previously tolerated	• Cycle 1-3: SQ weekly • Cycle 4-9: SQ every 2 weeks • Cycle 10+: SQ every 4 weeks	Cycle 1 day 1: IV over 4 hrs	Subsequent dosing: IV over 2 hrs if previously tolerated
	21-day cycles x 8 cycles (if achieve CR) or 17 cycles (if achieve a PR or SD)		28-day cycles until disease progression or unacceptable toxicity	21-day cycles x 12 cycles	
Step-Up Dosing	Cycle 1: • D1 = 1 mg IV • D8 = 2 mg IV • D15 = 60 mg IV	Cycle 2: • D1 = 60 mg Cycle 3+: • D1 = 30 mg	Cycle 1: • D1 = 0.16 mg • D8 = 0.8 mg • D15+ = 48 mg	Cycle 1: • D1 = 2.5 mg • D8 = 10 mg	Cycle 2+: • D1 = 30 mg
Pre-medications or Pre-treatment	Mandatory cycles 1 & 2; only if previously experienced CRS for cycles 3+ • Dexamethasone 20 mg IV 1 hr prior • Diphenhydramine 50-100 mg PO/IV and • Acetaminophen 500-1000 mg PO 30 mins prior		Mandatory for cycle 1; optional beyond • Prednisone 100 mg PO (or IV equivalent) 30-120 mins prior d1-4, d8-11, d15-18, d22-25 • Diphenhydramine 50 mg PO/IV and • Acetaminophen 650-1000 mg PO d1, 8, 15, 22	Pre-treatment: Obinutuzumab 1000 mg IV on D-7 • Methylprednisolone 80 mg • Diphenhydramine 50 mg PO/IV • Acetaminophen 650-1000 mg PO 30 mins prior	
Hospitalization	Not required		Required for cycle 1	Required for cycle 1	

Adverse Effects – CRS/ICANS

	Mosunetuzumab		Epcoritamab (GEN3013)	Glofitamab (RG6026)
CRS	***FL (N=90):*** • 44%; G≥3: 2.2% • Onset: ○ C1D1: 5 hrs (1h-3d) ○ C1D8: 28 hrs (5h-3d) ○ C1D15: 25 hrs (0.1h-16d) ○ C2D1: 46 hrs (12h-3d) • Duration: median 3d (1-29) • Incidence: ○ C1D1 (1mg): 15% ○ C1D8 (2 mg): 5% ○ C1D15 (60 mg): 33% ○ C2D1 (30 mg): 5% ○ Subsequent doses: 1% • Management: ○ Tocilizumab or corticosteroids: 23% ○ Tocilizumab and corticosteroids: 10%	***Aggressive NHL* (N=197):** • 27.4%; G≥3: 1% ○ Serious: 7.1%; G≥3: 1% • Duration: median 2d (1-20) • Management: ○ Tocilizumab: 1.5%	***R/R LBCL (N=157):*** • 49.7%; G≥3 2.5% • Onset: ○ C1D15: 20 hrs • Duration: median 2d • Incidence: ○ C1D1 (0.16 mg): 5.8% ○ C1D8 (0.8 mg): 11.8% ○ C1D15 (48 mg): 42.8% ○ C1D22 (48 mg): 4.9% ○ C2D1 (48 mg): 3% • Management: ○ Tocilizumab: 14% ○ Corticosteroids: 10.2%	***R/R LBCL (N=154)*** • 63%; G≥3: 3.9% • Onset: from C1D8: 13.5 hrs (6.2-51.8) • Incidence: ○ C1D8-14: 54.5% ○ C1D15-21: 30.4% ○ C2: 26.8% ○ C3: 0.9% ○ C4+: 2% • Management: ○ Tocilizumab: 20.1% ○ Corticosteroid: 17.5%
ICANS/ Neurotoxicity	***FL*** • ICANS: G1-2: 3% • Neurotoxicity: 39%; G3: 3%	***Aggressive NHL*** • ICANS: none • Neurotoxicity: G3: 4.1%	• ICANS: 6.4%; G5: 0.6% • Neurotoxicity: 13.4%; G≥3: 0.6%	• ICANS: 7.8%; G≥3: 2.6% • Neurotoxicity: 38.3%; G≥3: 3.2%
Neutropenia	***FL***: G3-4: 38%	***Aggressive NHL***: 28.4%; G≥3: 25.4% • Serious: 2.5%; G≥3: 2.5%	• 21.7%; G≥3 14.6%	• 37.7%; G≥3: 26.6%

CRS, cytokine release syndrome; ICANS: Immune effector cell-associated neurotoxicity syndrome

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