Bispecific Antibody Therapy in Non-Hodgkin Lymphoma and Toxicity Management

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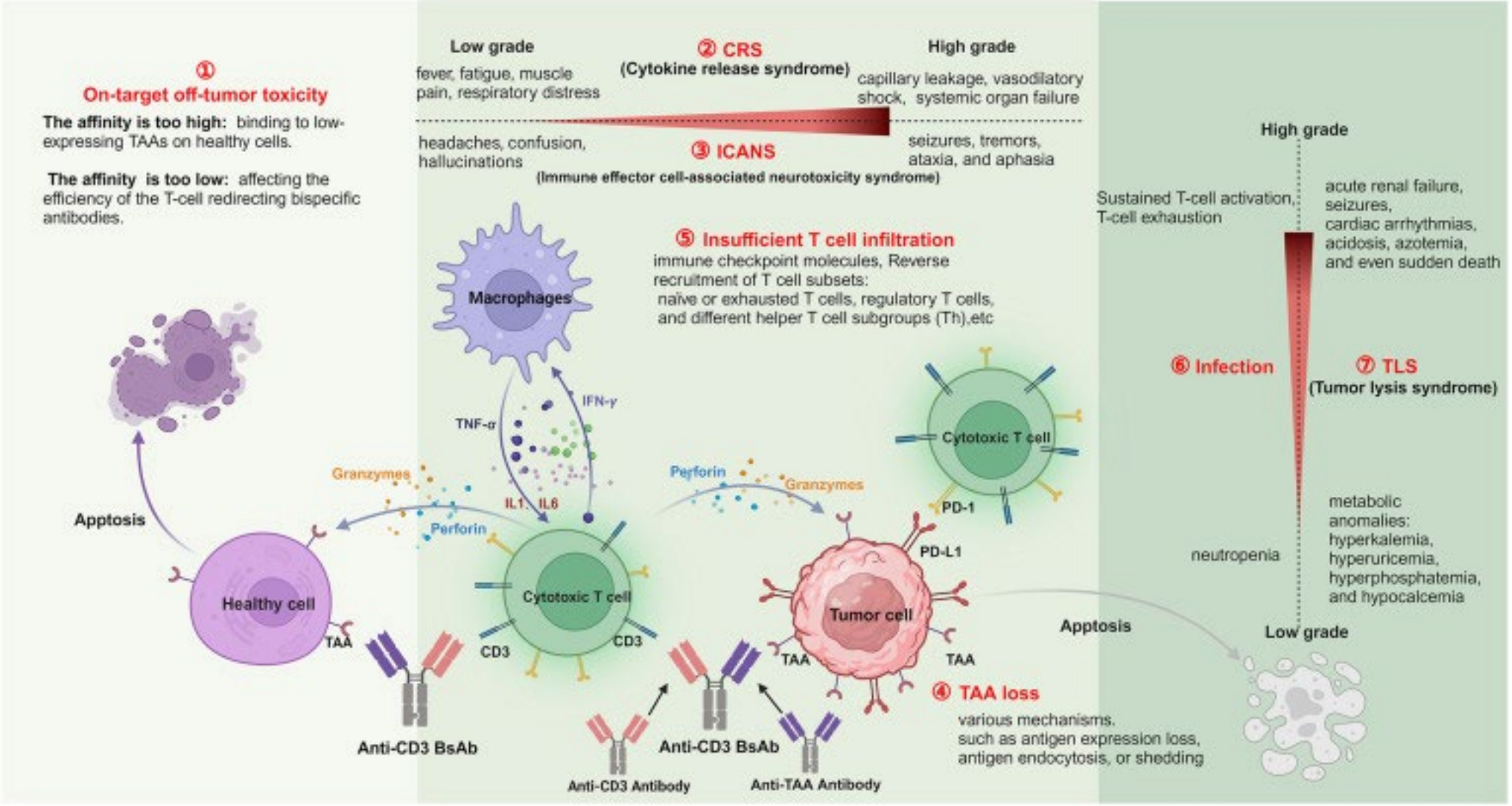
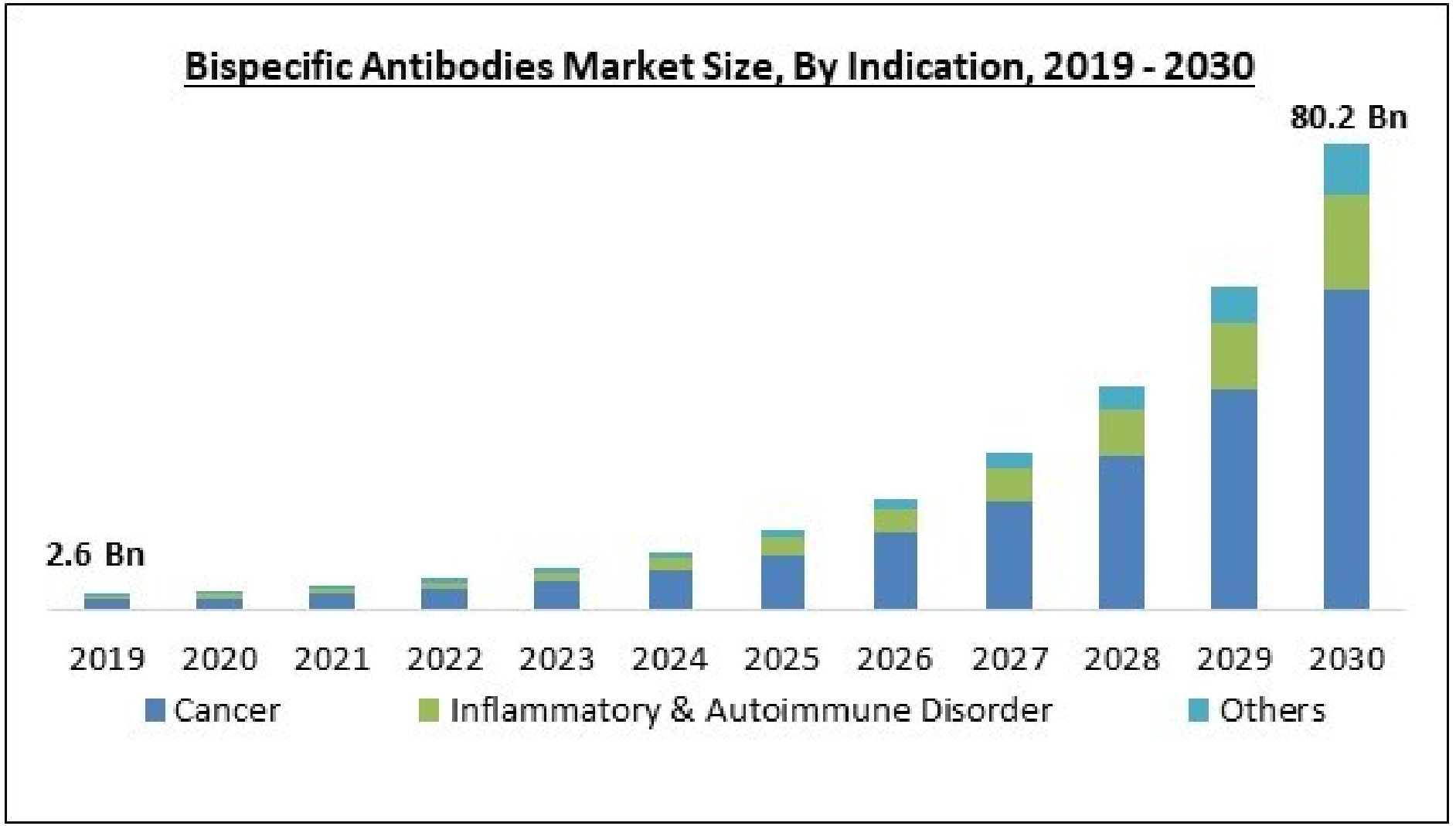
Learning Objectives

- ✓ Describe the mechanism of action of CD20×CD3 bispecific antibodies in B-cell malignancies
- ✓ Review strategies to manage cytokine release syndrome and ICANS
- ✓ Review FDA-approved bispecific antibodies in relapsed/refractory FL and DLBCL
- ✓ Identify appropriate candidates for bispecific antibody therapy based on clinical characteristics

Bispecific T-cell Engagers: Mechanism of action




Bispecific Antibodies Market Size, By Indication, 2019 - 2030
80.2 Bn
2.6 Bn
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030
Cancer
Inflammatory & Autoimmune Disorder
Others

Side effects of Bispecific T-cell Engagers

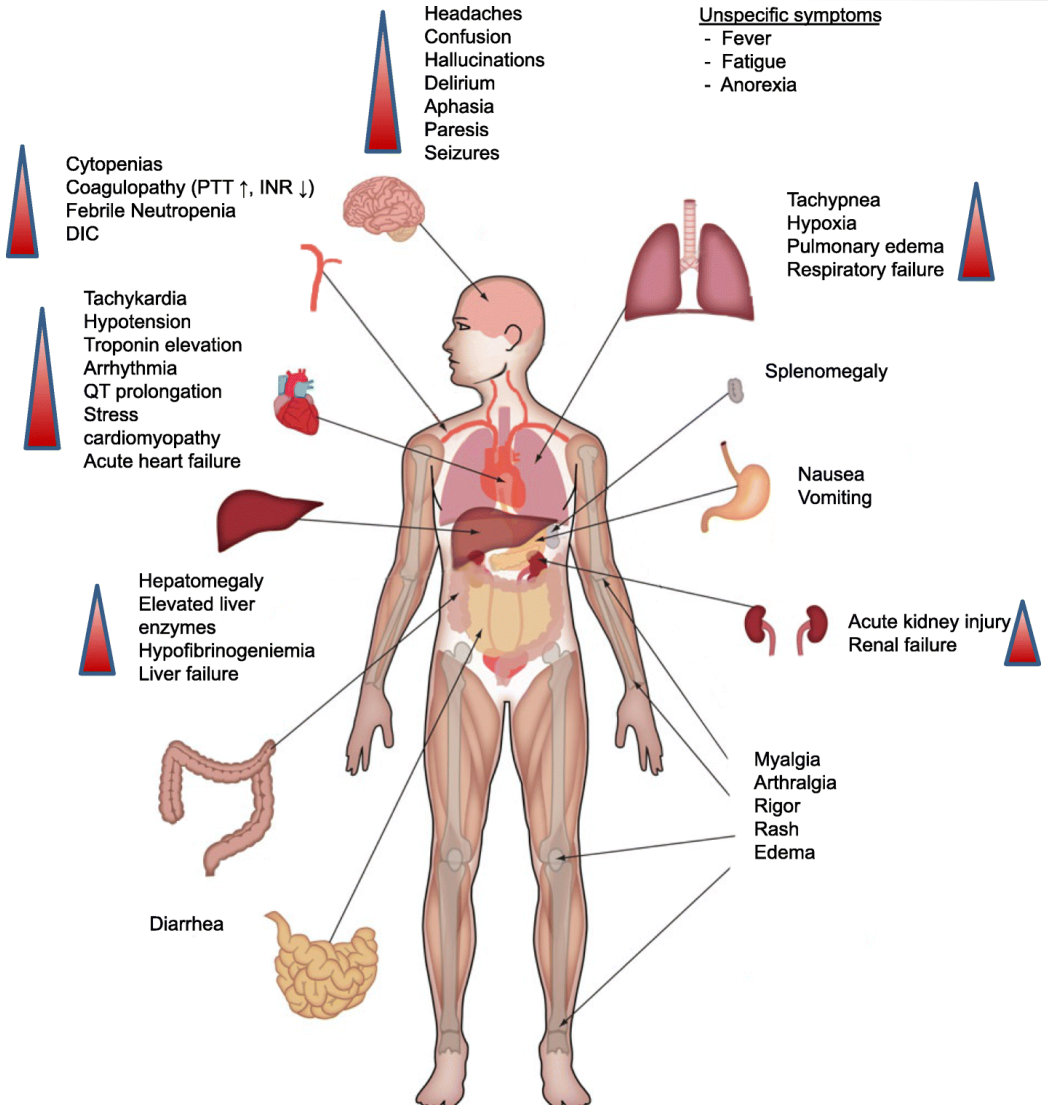
Side effects can include:

- **CRS (Cytokine Release Syndrome)**
- **Neurological toxicity (rare and reversible)**
- **Infections**
- **Cytopenias**

Side effects of Bispecific T-cell Engagers: CRS

Cytokine Release Syndrome:

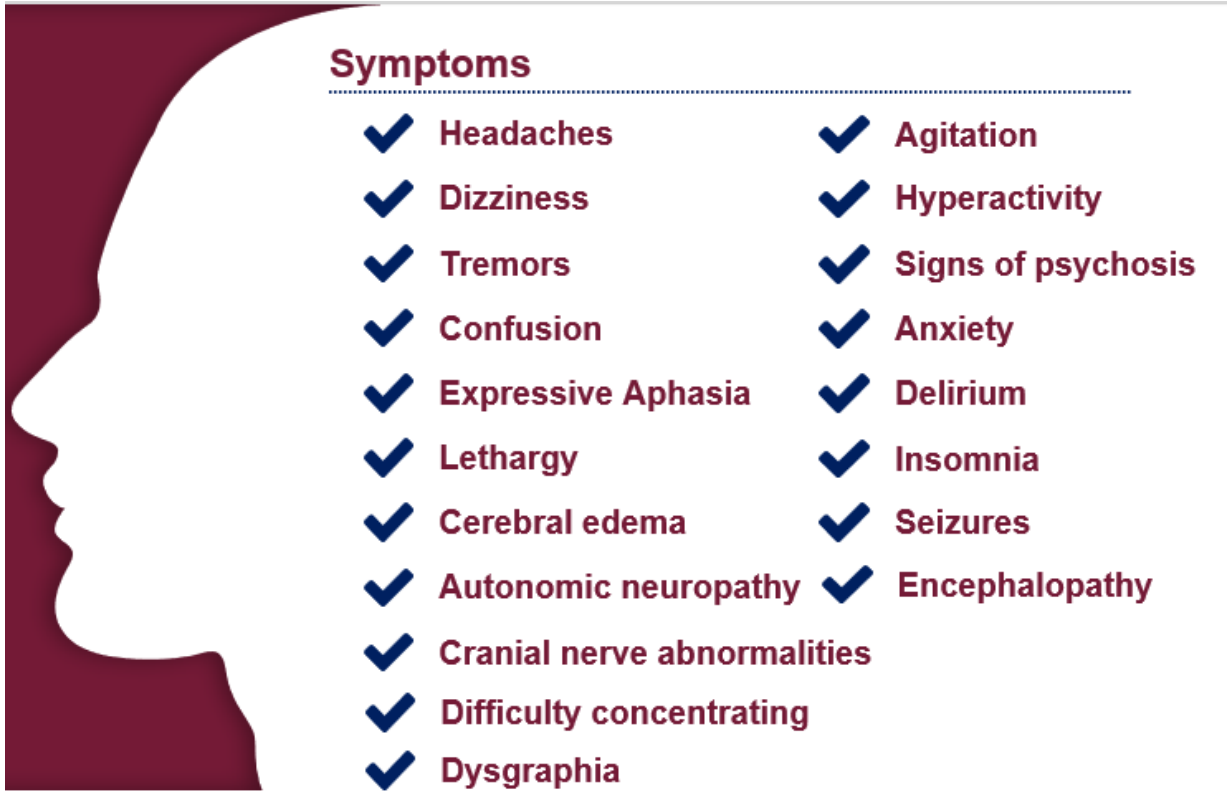
- **Caused by inflammatory response with release of cytokines including IL6**
- **Typically occurs during first cycle**
- **Initially starts with a fever, tachycardia, and fatigue when starting therapy.**
- **Reversible and can be controlled by Toci and/or Dexamethasone**



Side effects of Bispecific T-cell Engagers: Neurological Toxicity

Neurotoxicity Syndrome (ICANS)

- **Neurological adverse events in clinical trials have been rare, generally mild, and self-resolving within hours of their onset**
- **Typically occurs during first cycle**
- **Reversible**
- **No role for Toci. Typically treated with dexamethasone (or anakinra for refractory cases).**



Grading CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥ 38°C (100.4°F)			
With either:				
Hypotension	None	Not requiring vasopressors	Vasopressor with or without vasopressin	Multiple vasopressors (excluding vasopressin)
And/ or				
Hypoxia	None	Low flow nasal cannula ≤ 6L/min or blow-by	High flow nasal cannula > 6L/min, facemask, nonrebreather mask, Venturi mask	Positive pressure (CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT Consensus grading criteria for CRS

Toxicities: Immune effector cell-associated neurotoxicity syndrome (ICANS)

ASCTC consensus grading of ICANS

	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (unarousable or unable to perform ICE)
Level of Consciousness	Awakens spontaneously	Awakens to voice	Awakens to tactile stimulus	**Unarousable** to vigorous or repetitive stimuli; **stupor or coma**
Seizure	N/A	N/A	**Any clinical seizure** focal or generalized that resolves rapidly; or nonconvulsive seizure on EEG that resolve with intervention	Life threatening **prolonged seizure** (>5mins) or repetitive clinical or electrical seizures without return to baseline in between
Motor Finding	N/A	N/A	N/A	**Deep focal motor weakness** (hemiparesis or paraparesis)
Elevated ECP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	**Diffuse cerebral edema**, or cranial nerve palsy or papilledema or Cushing's triad or decerebrate or decorticate posturing

ICE score: Immune effector cell-associated encephalopathy.

	Task	Points
Orientation	Orientation to year, month, city, hospital	**4**
Naming	Name 3 objects (eg: point to clock, pen, button)	**3**
Commands	Ability to follow simple commands (eg: "show me 2 fingers" or "touch your finger to your nose")	**1**
Writing	Ability to write a standard sentence (eg: our national bird is a bald eagle)	**1**
Attention	Ability to count backwards from 100 by 10	**1**
Total		**10**

ASTCT Consensus grading criteria for ICANS

CRS management summary Algorithm

Grade	Definition	Management	Setting
Grade 1	Fever ≥100.4°F, no hypotension/hypoxia	Acetaminophen, blood cultures, consider antibiotics if neutropenic	Consider inpatient admission/ Outpatient possible
Grade 2	Fever + hypotension (no pressors) or hypoxia (low-flow O2 < 6L)	Tocilizumab +/- Dexamethasone, IV fluids. Empiric antibiotics.	Emergency department and inpatient admission
Grade 3	Fever + hypotension requiring one pressor, or high-flow O2 >6L	ICU, dexamethasone 10mg q6h, tocilizumab, vasopressors	ICU required
Grade 4	Life-threatening, multiple pressors, positive pressure or mechanical ventilation	Aggressive ICU care, pulse dose steroids, tocilizumab	ICU required

Key Considerations

- Educate patients about CRS symptoms and when to seek medical attention
- Early intervention is critical to prevent progression
- Hold bispecific antibody for Grade 2-4 until resolution to ≤ Grade 1

Management ICANS

Neurological toxicity including ICANS	Action with Current Dose	Management
GRADE 1 (ICE score 7-9, awakens spontaneously)	• Interrupt teclistimab,talquetamab, elranatamab, epcoritamab, tarlatamab (see section F.1 prior to resuming) • Continue blinatumomab, mosunetuzumab, glofitamab	• Inpatient admission • Vigilant supportive care • Aspiration precautions • Consider neurology consultation • Consider **dexamethasone 10mg IV x 1**
GRADE 2 (ICE score 3-6, awakens to voice)	• Interrupt therapy (see section F.1 prior to resuming)	• Inpatient admission • Start **steroids (dexamethasone 10mg IV Q 6 hr)** • Can give **tocilizumab 8mg/kg x 1 (ONLY if concurrent CRS)** • Neurology consultation if refractory to 4 doses of dex; (EEG, MRI brain, Lumbar puncture)

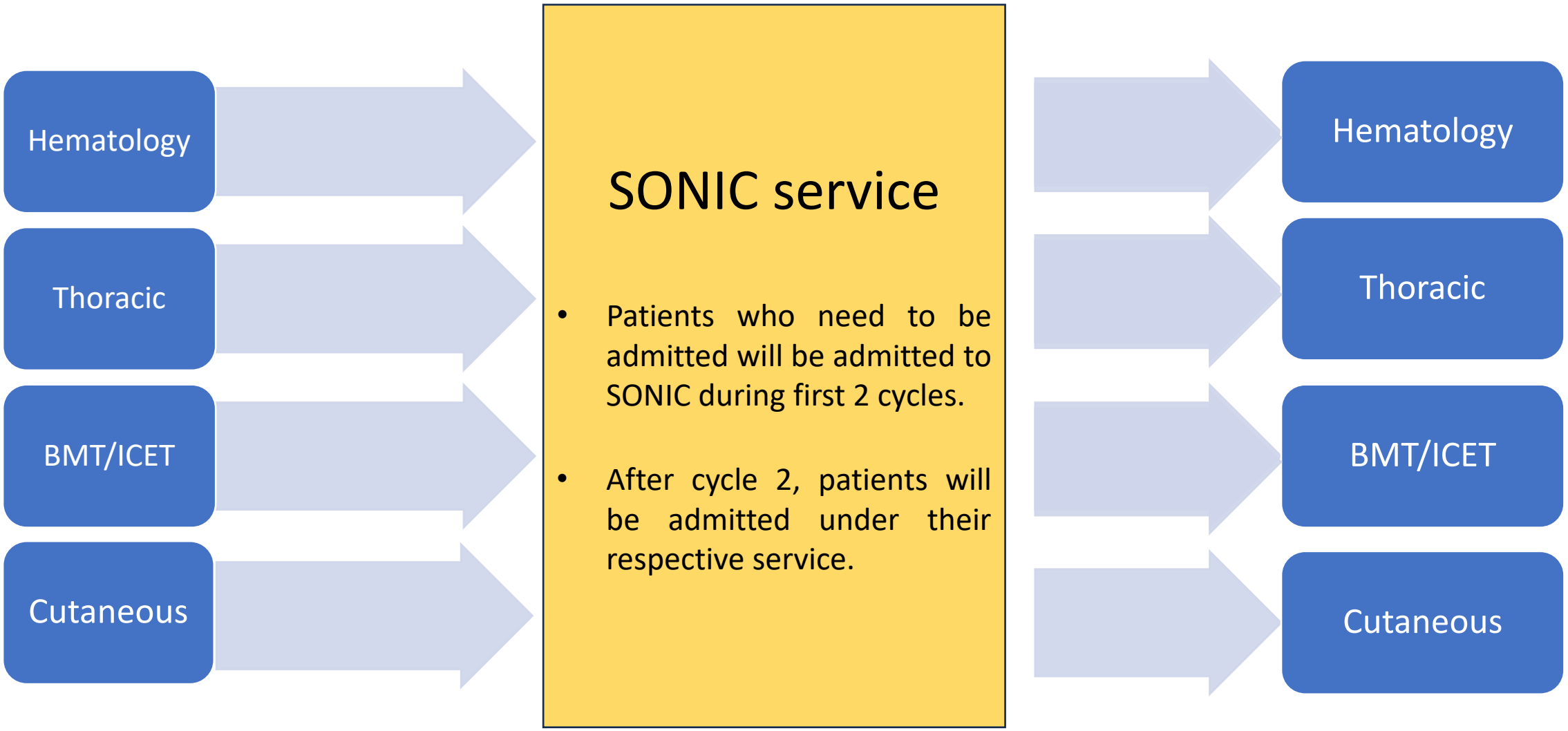
Management ICANS

GRADE 3 (ICE score 0-2, awakens to tactile stimuli, any clinical seizure that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention, focal/local edema on neuroimaging)	• Interrupt therapy (see section F.1 prior to resuming)	• Inpatient admission • Symptomatic management transfer to ICU • **Give Steroids (dexamethasone 10mg IV Q 6 hrs)** • Can give **tocilizumab 8mg/kg x 1 (ONLY if concurrent CRS)** • Neurology consultation(EEG, MRI brain, Lumbar puncture) • Consider repeat neuroimaging every 2-3 days if patient has persistent grade 3 ICANS
GRADE 4 (ICE score 0, unarousable to vigorous stimuli, stupor, life-threatening prolonged seizure >5 min, repetitive clinical or electrical seizures without returning to baseline, deep focal motor weakness, diffuse cerebral edema, cranial nerve palsy, papilledema, or decerebrate, or decorticate posturing or Cushing's trial)	• Permanently discontinue	• Inpatient admission • ICU monitoring, consider mechanical ventilation to protect airways • **Start steroids (dexamethasone 10mg IV Q 6) if not already done, can consider high dose steroids** to methylprednisolone 1000mg/day IV until improvement to grade 1 then taper • Neurology consultation (EEG, MRI brain, Lumbar puncture) • Consider repeat neuroimaging every 2-3 days if patient has persistent grade ≥3 ICANS

SONIC Program: Specialized, Oncology, Non-cellular, Immunotherapy, Comprehensive care

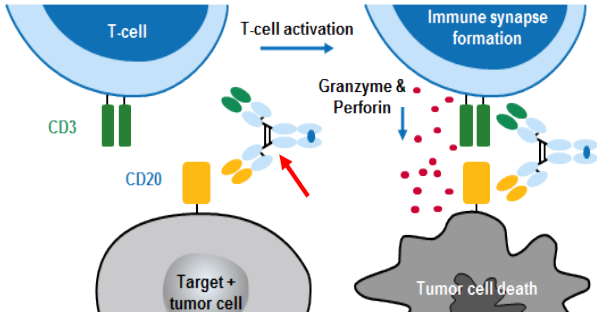
Given the unique toxicities of these agents, a multidisciplinary team was needed to administer these new immune therapies and shared by different departments/clinics. This led to the SONIC program initiative

SONIC Service Structure



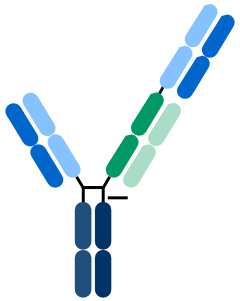
Bispecific T-cell Engagers for B-NHL

Mosunetuzumab (CD3xCD20)



Approved in FL

Glofitamab (CD3xCD20)

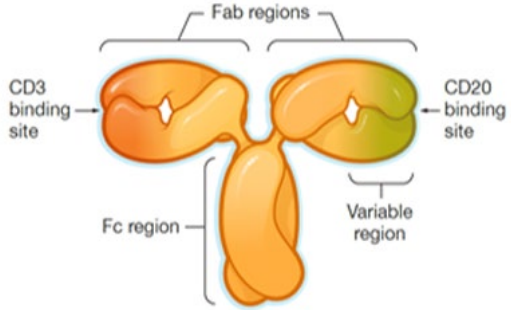


Approved in DLBCL

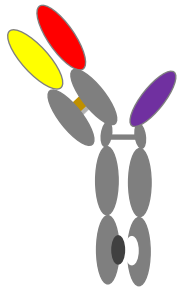
Epcoritamab (CD3xCD20)

Approved in DLBCL and FL

Odronextamab (CD3xCD20)



TNB-486 (CD3xCD19)



Fc Tail

Plamotamab (CD3xCD20)

Bispecific antibodies in Follicular lymphoma

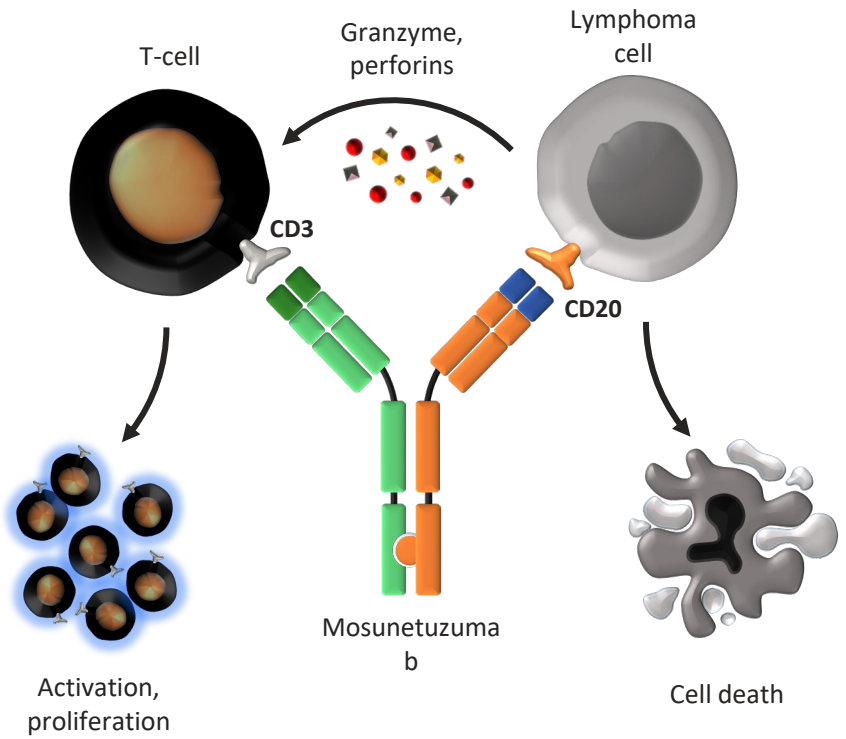
Mrs. J is a 62-year-old woman with grade 2 follicular lymphoma, initially treated with bendamustine and rituximab, followed by lenalidomide-rituximab over five years. She now presents with progressive, symptomatic lymphadenopathy and B symptoms after two prior lines of therapy. Imaging shows widespread but non-bulky disease; ECOG 1; mild cytopenias. She has HTN, DM, HL, and A.fib.

What would you treat her with:

- CART
- Mosunetuzumab
- Epcoritamab
- RCHOP
- Zanubrutinib/Obinutuzumab
- Tazemetostat

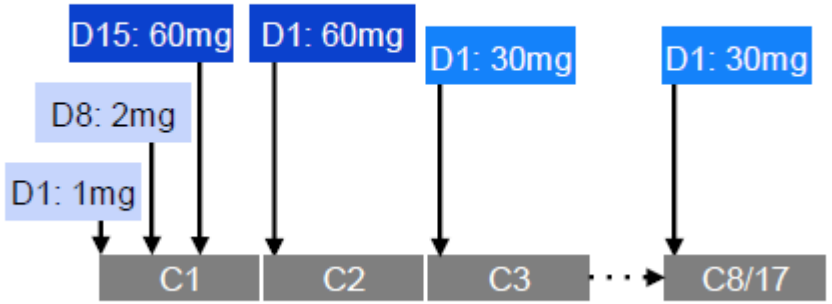
Mosunetuzumab (CD20 x CD3 T-cell Engager)

- Mosunetuzumab **(first-in-class)** is now FDA approved for the treatment of **relapsed/refractory follicular lymphoma (R/R FL)** after ≥2 prior systemic therapies.
- Redirects T cells to engage and eliminate malignant B cells
- Off the Shelf outpatient treatment



Mosunetuzumab administration

- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Re-treatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization

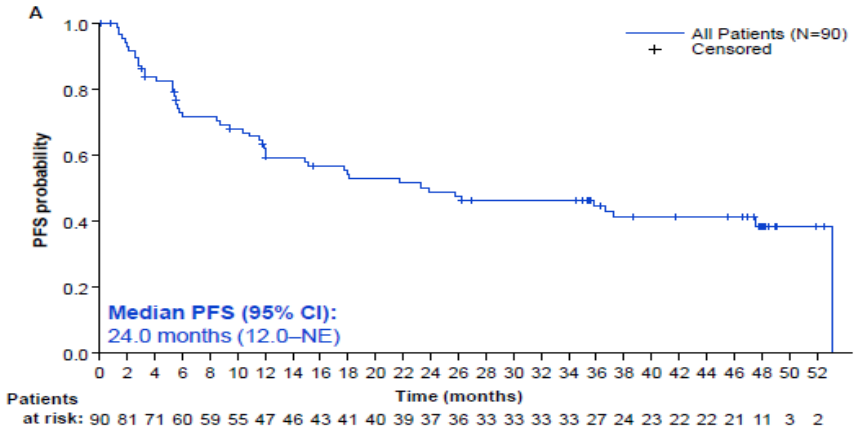


Bartlett et al. ASH 2022; Budde et al. The Lancet Oncology 2022; Sun LL, et al: Sci Transl Med 2015;7:287ra70; Hernandez G, et al. ASH 2019

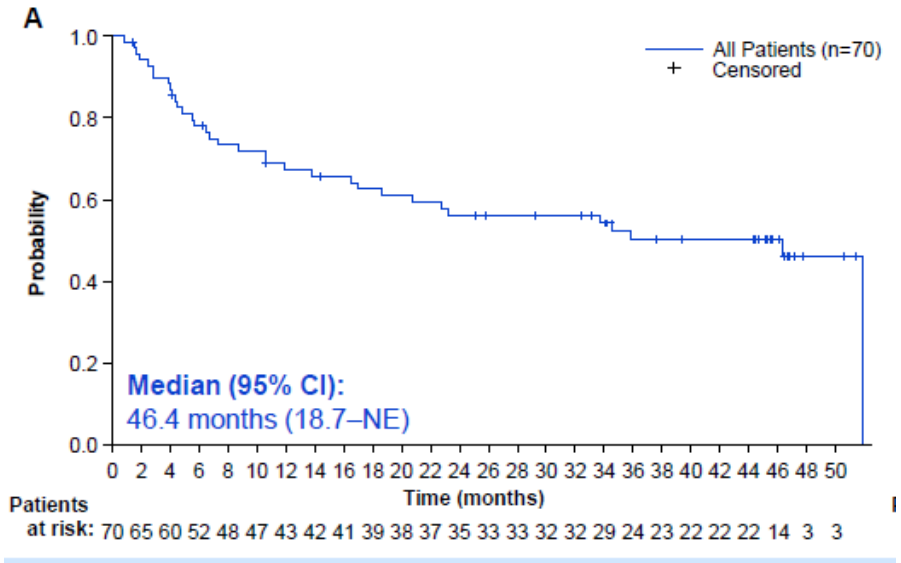
Mosunetuzumab: Efficacy

ORR	78%
CR	60%
Median FU	49.4

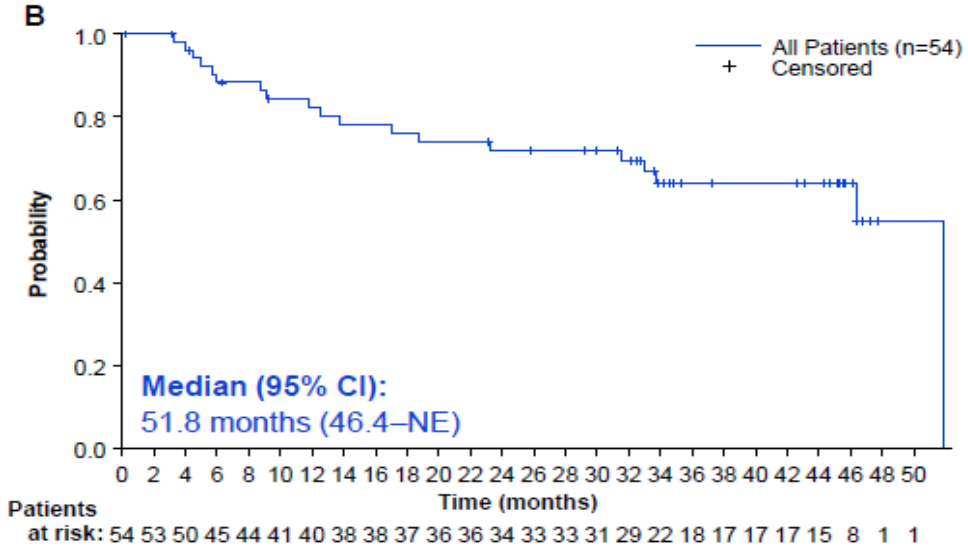
mPFS: 24 months



mDOR: 46.4



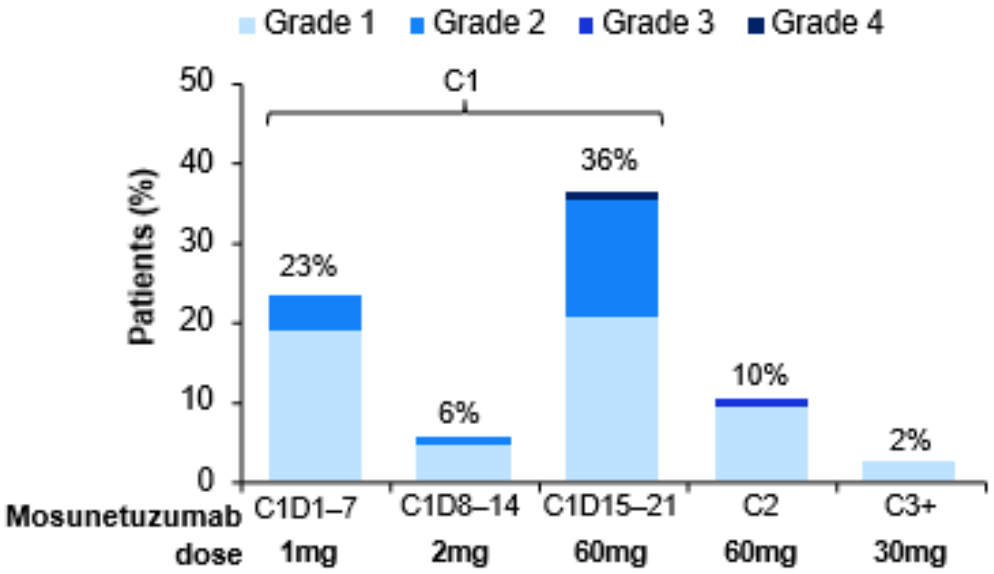
mDOCR: 51.8 months



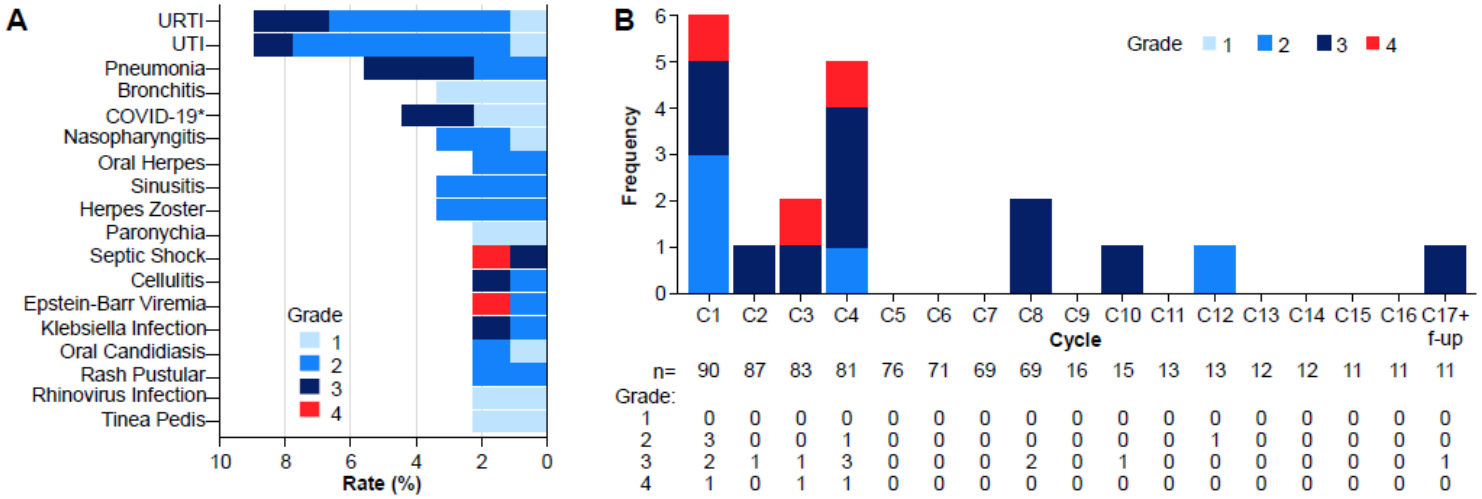
Shadman et al. ASH 2024; Budde et al. The Lancet Oncology 2022;

Mosunetuzumab: Safety profile

CRS by cycle and grade



Infections (≥2% incidence) by grade (A) and serious infections by grade and cycle (A)



*Includes all COVID-19 narrow terms (terms that are highly likely to represent the condition of interest).
COVID-19, coronavirus disease; f-up, follow-up.

CRS mostly low grade (Grade 3/4: 2%) and occurred during Cycle 1
ICANs 3% (all grade 1-2)

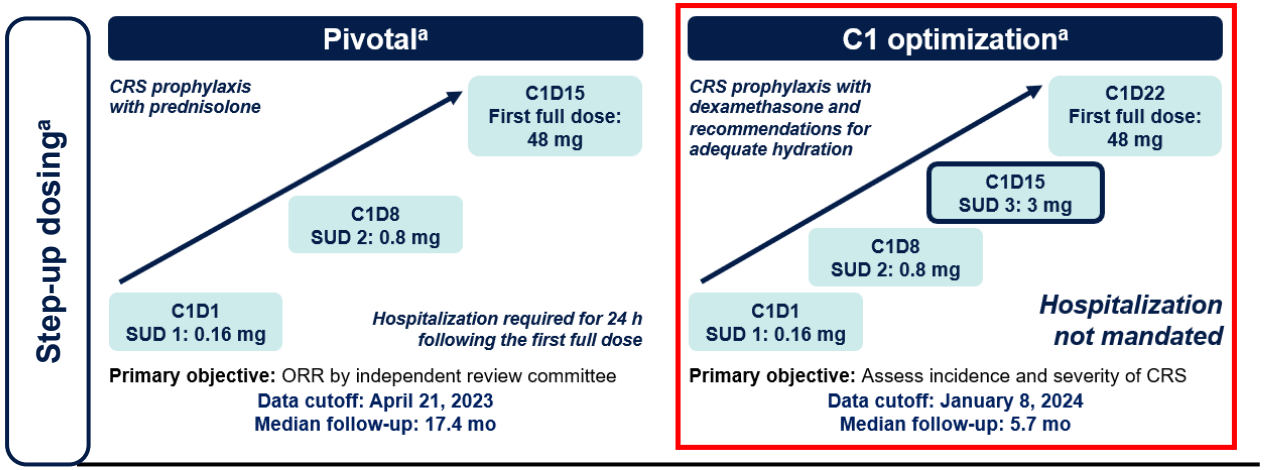
Serious infections were reported in 20.0% of patients
No infectious deaths
Most serious infections (73.7%) occurred in the first 4 cycles

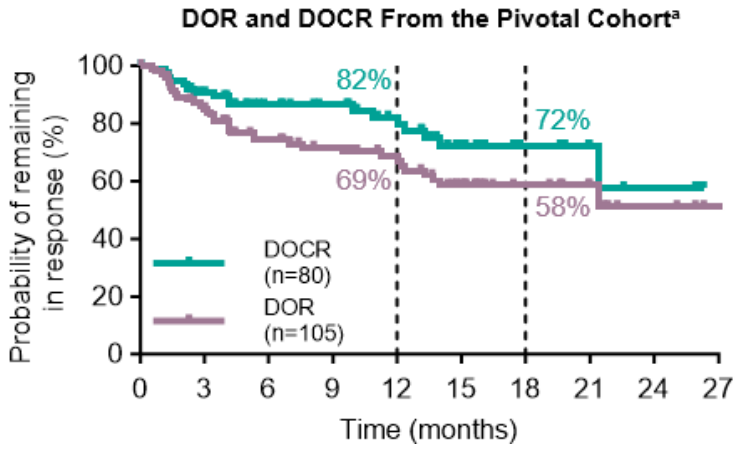
Shadman et al. ASH 2024; Budde et al. The Lancet Oncology 2022;

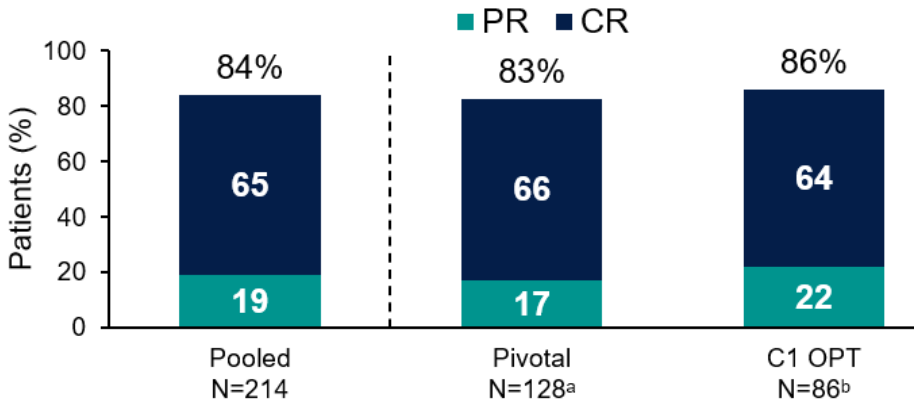
Epcoritamab: EPCORE NHL-1 Follicular Lymphoma Dose Optimization Cohort (3 SUD) in R/R FL

Key inclusion criteria

- R/R CD20⁺ FL grade 1–3A
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 regimen with an anti-CD20 mAb
- Prior treatment with an alkylating agent or lenalidomide
- FDG-avid disease by PET/CT
- Prior CAR T allowed







MRD-Negativity Rate	n (%)
Pooled (n=135)	89 (66)
Pivotal (n=91)	61 (67)
C1 OPT (n=44)	28 (64)

Based on MRD-evaluable population per clonoSEQ® PBMC assay with 10^{-6} cutoff.

	Pivotal N=128	C1 OPT N=86
CRS,[a] n (%)	85 (66)	42 (49)
Grade 1	51 (40)	34 (40)
Grade 2	32 (25)	8 (9)
Grade 3	2 (2)	0
Treated with tocilizumab, n (%)	31 (24)	10 (12)
Leading to epcoritamab discontinuation, n (%)	**0**	**0**
CRS resolution, n/n (%)	**85/85 (100)**	**42/42 (100)**
Median time to resolution, d (range)	2 (1–54)	2 (1–14)
ICANS, n (%)	8 (6)[b]	0

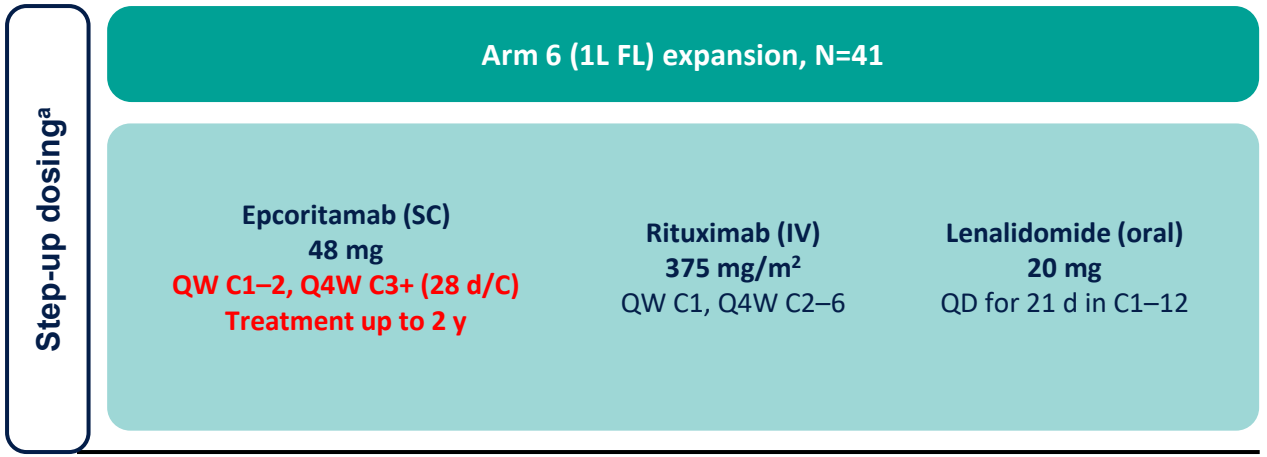
Vose et al. ASCO 2024

Emerging data in Frontline setting in Follicular Lymphoma

Epcoritamab With Rituximab + Lenalidomide (R^2) in Previously Untreated (1L) Follicular Lymphoma: EPCORE NHL-2 Arms 6

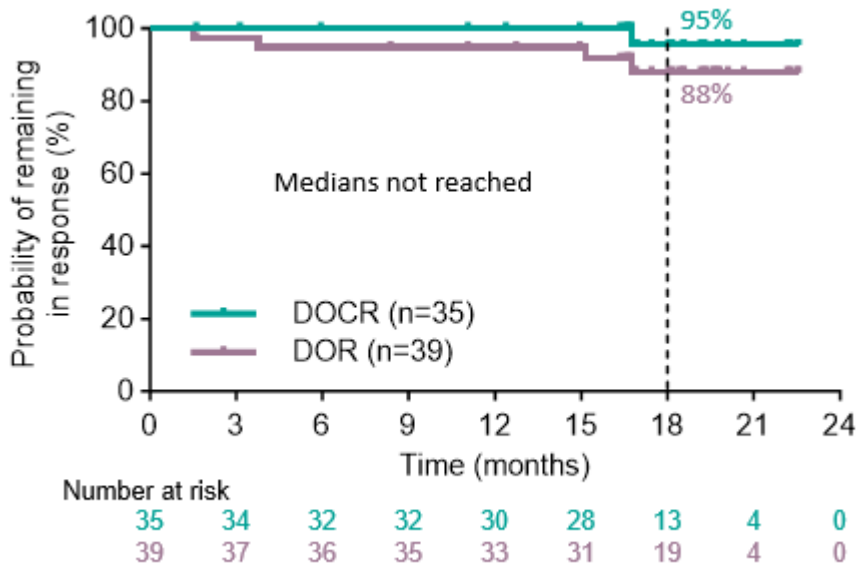
Key inclusion criteria

- CD20+ FL
  - Grade 1, 2, or 3A
- 1L FL **(arm 6, 1L FL)**
- ECOG PS 0–2
- Measurable disease by CT or MRI **(arm 6, 1L FL)**
- Adequate organ function



- **Primary objective:**
  - **Arm 6:** Antitumor activity (ORR)[b]
- **Key secondary endpoints:**
  - **Arm 6:** Safety/tolerability, DOR, DOCR, PFS, OS

	N=41[a]
Overall response, n (%)	39 (95)
Complete response, n (%)	35 (85)
Partial response, n (%)	4 (10)
Progressive disease, n	0
Median time to response, mo (range)	2.7 (1.2–5.5)
Median time to complete response, mo (range)	2.8 (1.4–11.4)



Leslie et al, ASH 2024

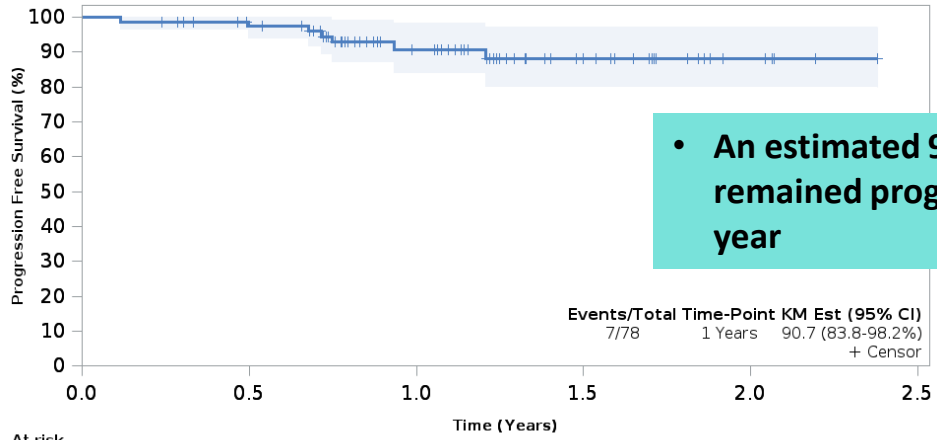
MITHIC-FL1 Trial (Phase 2): **Subcutaneous** Mosunetuzumab in Newly Diagnosed Follicular Lymphoma:

Endpoints:
- **Primary:** CR rate per Lugano
- **Secondary:** ORR, safety, PFS, DOR, TTNT, OS
- **Exploratory:** PD, ctDNA monitoring

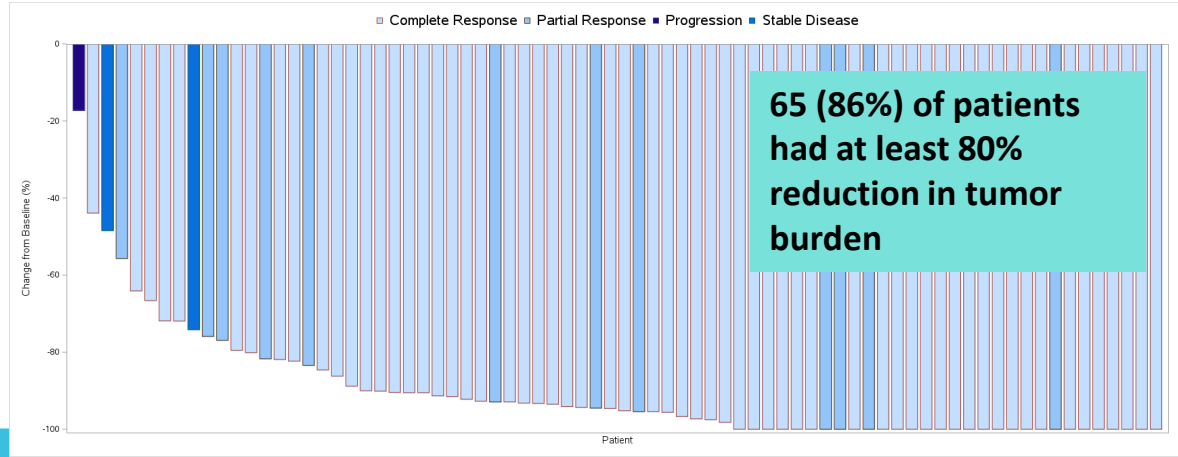
Eligibility:
- ≥18 years; PS 0-2
- CD20+ previously untreated FL,
- G1-3A, stage II–IV
- **Need of therapy per GELF criteria**

Duration of therapy:
CR after 8 cycles can stop.
PR after C8: can receive up to 17 cycles.

Response type	Response evaluable (N=76)	Intention-to-treat (N=78)
Overall response	96%	94%
Complete response	80%	78%
Partial response	16%	15%
Stable disease	3%	3%
Progressive disease	1%	1%
Non-evaluable	n/a	3%



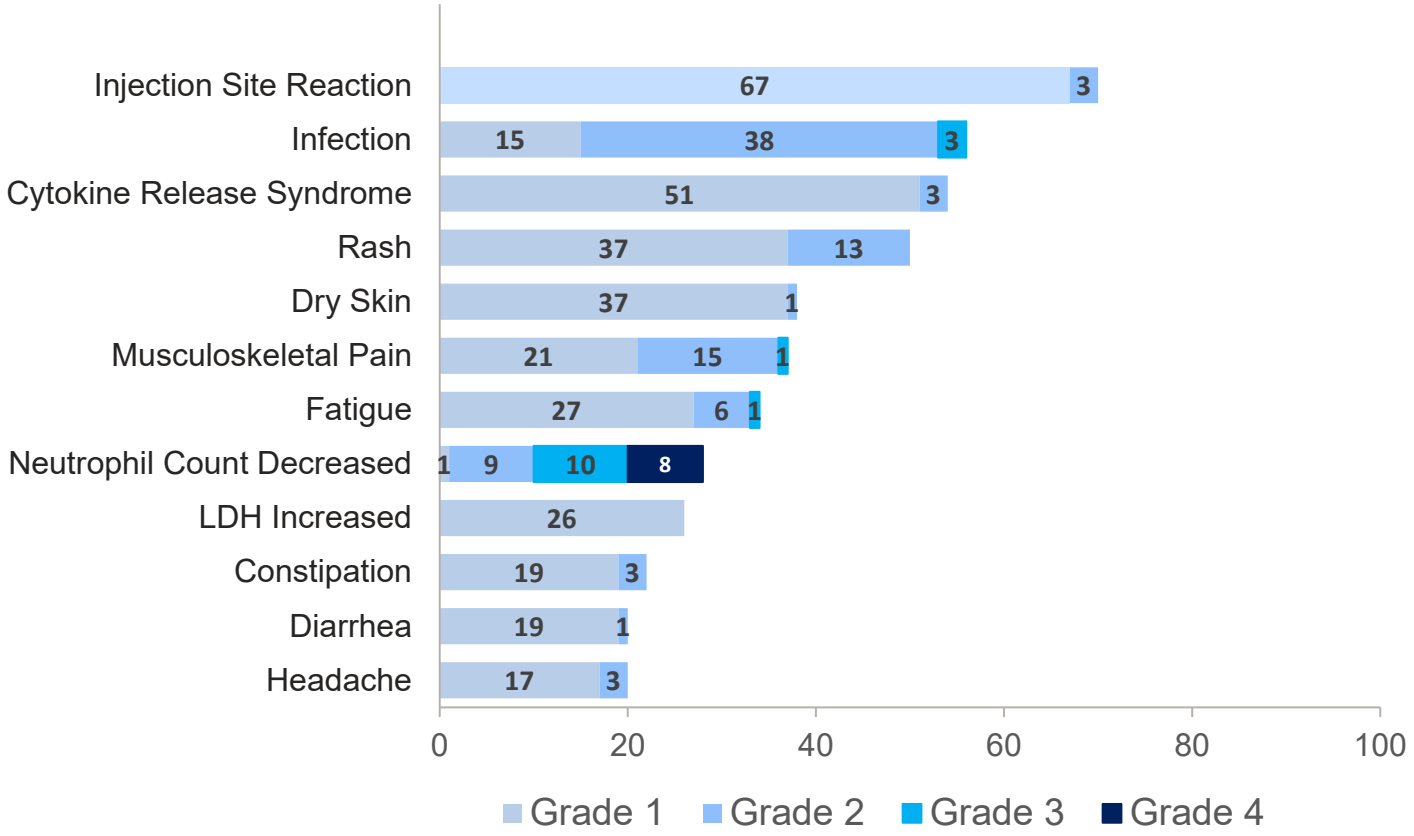
- **An estimated 91% of patients remained progression-free at 1 year**



65 (86%) of patients had at least 80% reduction in tumor burden

Falchi et al, ASH 2024

SC Mosunetuzumab: Most adverse events were mild



- **No new safety signal observed**
  Median number of mosunetuzumab cycles: 8 (1-17)
- No ICANS-like toxicities
- No tumor lysis syndrome
- One episode of G2 tumor flare reaction

Febrile neutropenia G3 (4%); ventricular tachycardia G5 (1%), dyspnea (G1-2 10%, G3 1%), platelet count decreased (G1-2 14%, G3 1%), syncope G3 (1%), hyperglycemia (G1-2 11%, G3 1%), ALC decreased (G1-2 3%, G3 1%), peritonitis (G3 1%), fracture (G3 1%), anemia (G1-2 12%, G3 1%).

Bispecific antibodies in DLBCL

Mr. T is a 58-year-old man with DLBCL, treated with R-CHOP and was in CR for 9 months and was treated with CAR-T cell therapy for early relapsed disease. Disease progressed after 10 months of CAR-T, but he maintains ECOG 1 and good organ function. He has residual peripheral neuropathy and CKD.

What would you treat him with:

- Glofitamab +/- Gem/Ox
- Epcoritamab +/- Gem/Ox
- Mosun/Polatuzumab
- Loncastuximab
- Brentuximab/R2
- Tafasitamab/Lenalidomide
- Polatuzumab/BR

NCCN Guidelines (Relapsed disease < 12 mo or primary refractory disease)

Candidates for CAR T-Cell Therapy

CAR T-cell therapy

- Axicabtagene ciloleucel (CD19-directed) (category 1)
- Lisocabtagene maraleucel (CD19-directed) (category 1)

Bridging Therapy Options (≥1 cycles as needed until CAR T-cell product is available)

- DHA + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, carboplatin or cisplatin) ± rituximab
- GemOx ± rituximab
- ICE ± rituximab
- Polatuzumab vedotin ± rituximab ± bendamustine
- ISRT (can be used as monotherapy or sequentially with systemic therapy)

Non-Candidates for CAR T-Cell Therapy

Preferred regimens (in alphabetical order)

- Epcoritamab + GemOx
- Glofitamab + GemOx
- Polatuzumab vedotin ± bendamustine ± rituximab
- Polatuzumab vedotin + mosunetuzumab
- Tafasitamab + lenalidomide (excluding primary refractory disease)

Other recommended regimens (in alphabetical order)

- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, carboplatin or cisplatin) ± rituximab
- Gem Ox (gemcitabine, oxaliplatin) ± rituximab (if unable to receive epcoritamab-bysp or glofitamab-gxbm)
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

Useful in certain circumstances

- Brentuximab vedotin for CD30+ disease
- Ibrutinib[n] (non-GCB DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)

NCCN Guidelines- 2L Therapy (Relapsed Disease > 12 months)

Intention to Proceed to Transplant

Preferred regimens (in alphabetical order)

- DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, carboplatin or cisplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab

Other recommended regimens (in alphabetical order)

- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- Gem Ox (gemcitabine, oxaliplatin) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

No Intention To Proceed To Transplant

Preferred regimens (in alphabetical order)

- CAR T-cell therapy (CD19-directed) With bridging therapy as needed; (if eligible)
  - Lisocabtagene maraleucel
- Glofitamab + Gem Ox
- Polatuzumab vedotin ± bendamustine ± rituximab
- Polatuzumab vedotin + mosunetuzumab
- Tafasitamab + lenalidomide

Other recommended regimens (in alphabetical order)

- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- GDP (gemcitabine, dexamethasone, carboplatin or cisplatin) ± rituximab
- GemOx ± rituximab
- Rituximab

Useful in certain circumstances

- Brentuximab vedotin for CD30+ disease
- Ibrutinib (non-GCB DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)

STARGLO Phase 3 Study of Glofit + GemOx vs R-GemOx in 2L DLBCL

Key Eligibility Criteria
- R/R DLBCL NOS after ≥1 prior therapy
- ASCT-ineligible patients with 1 prior LOT
- ECOG PS 0-2

R 2:1
N=274

Glofit + GemOx
Glofitamab SUD cycle 1, 30 mg day 1 cycle 2+
Gemcitabine 1000 mg/m² IV
Oxaliplatin 100 mg/m² IV
- Cycle 1: Obin pre-tx day 1; GemOx day 2; Glofit 2.5 mg day 8; Glofit 10 mg day 15
- Cycles 2-8: Glofit 30 mg and GemOx day 1

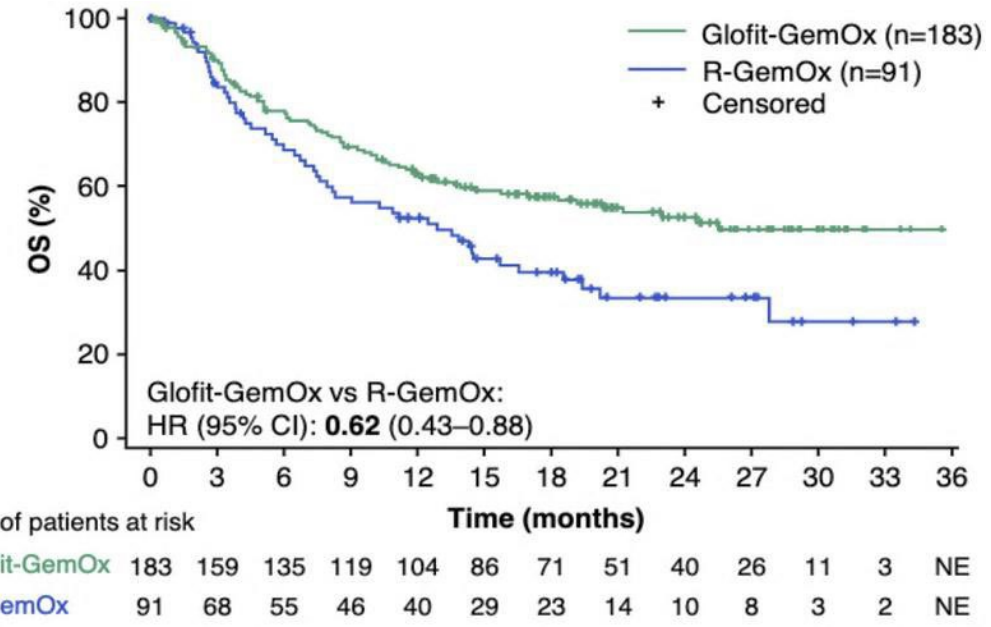
→ **Glofit**
30 mg, day 1
cycles 9-12

Cycles 1-8 (21-day cycles)

R-GemOx
Rituximab 375 mg/m²
Gemcitabine 1000 mg/m² IV
Oxaliplatin 100 mg/m² IV
- Cycles 1-8: day 1

Primary endpoint: OS
Key secondary endpoints: PFS, CR, DoCR (all by IRC), AEs

OS: Updated Analysis (Primary Endpoint)



OS Analyses		Glofit-GemOx (n=183)	R-GemOx (n=91)
Updated	Median (95% CI), months	25.5 (18.3-NE)	12.9 (7.9-18.5)
	HR (95% CI)	0.62 (0.43-0.88)	
	P value	0.006	
	24-month (95% CI), %	52.8 (44.8-60.7)	33.5 (22.2-44.9)
	Median follow-up	20.7 months	

Abramson JS, et al. EHA 2024. Abstract LB3438.

Glofitamab in combination with polatuzumab vedotin in R/R DLBCL Phase Ib/II study (NCT03533283)

Phase Ib/II study in patients with R/R LBCL and ≥1 prior therapy

Key inclusion criteria

- DLBCL, HGBCL, trFL, or PMBCL
- ECOG PS 0–2
- ≥1 prior therapies, including:
  - Anti-CD20 antibody
  - CAR T-cell therapy

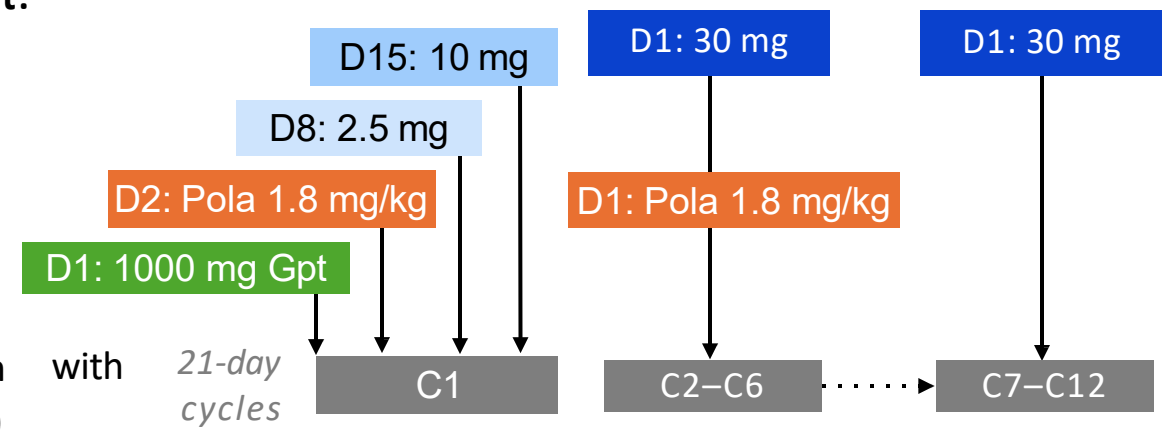
Glofitamab IV administration

Fixed-duration treatment:

- Up to 12 cycles

CRS mitigation:

- Obinutuzumab IV pre-treatment
- C1 step-up dosing
- 24-hour hospitalization first Glofit dose (C1D8)



Endpoints

- **Primary:** Best ORR* by IRC and MTD and/or RP2D for Glofit
- **Key secondary:** efficacy (best ORR by INV, DoR, DoCR, PFS by IRC and INV, and OS) and safety
- **Exploratory:** ctDNA

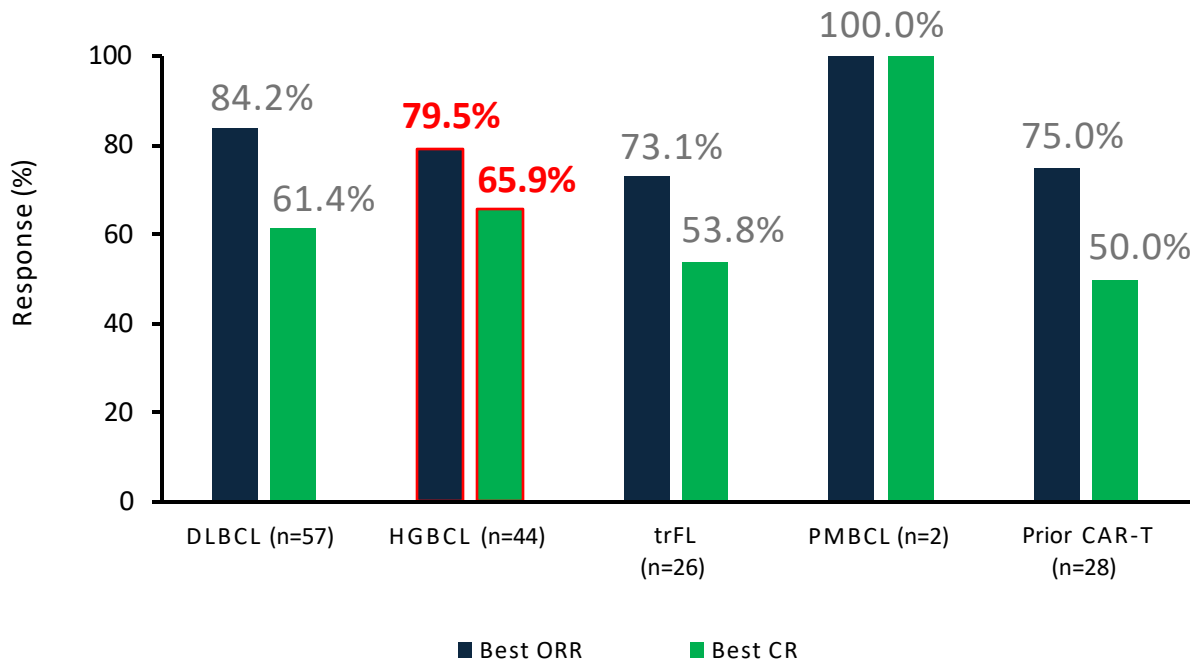
*By PET-CT (Lugano criteria).[1] C, cycle; CRS, cytokine release syndrome; D, day; DoR, duration of response; DoCR, duration of complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pre-treatment; INV, investigator; IRC, independent review committee; IV, intravenous; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall surv ival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; trFL, transformed follicular lymphoma.

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

Efficacy

n (%) [95% CI]	By INV N=129	By IRC N=129
ORR	104 (**80.6**) [72.7–87.1]	101 (**78.3**) [70.2–85.1]
CR	80 (**62.0**) [53.1–70.4]	77 (**59.7**) [50.7–68.2]
PR	24 (18.6) [12.3–26.4]	24 (18.6) [12.3–26.4]
PD	16 (12.4) [7.3–19.4]	16 (12.4) [7.3–19.4]
DOR, median (months) [95% CI]	24.3 [15.0–37.8]	26.4 [10.9–44.3]

Best ORR and CR by histology and prior CAR T-cell therapy (INV-assessed)



Impressive responses observed (**66% CR**) amongst patients with HGBCL

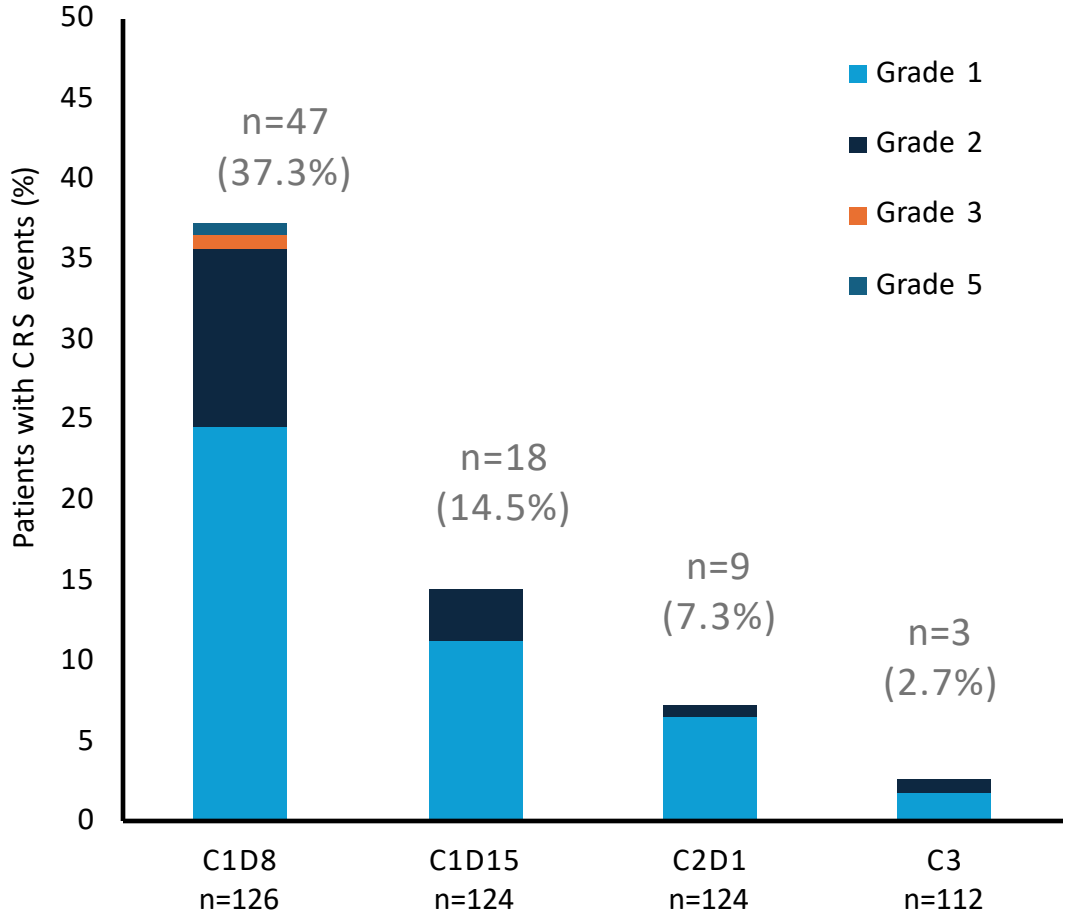
Clinical cut-off date: September 2, 2024. High concordance was observed between INV- and IRC-assessed response rates.
Response rates determined using Lugano 2014 criteria[1] with PET-CT.
CI, confidence interval; PD, progressive disease; PR, partial response.

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

CRS events were mainly low-grade, occurred early during step-up dosing, and resolved within ~2 days

N (%)	N=126*
CRS by grade[†]	**56 (44.4)**
Grade 1	35 (27.8)
Grade 2	19 (15.1)
Grade 3	1 (0.8)
Grade 4	0
Grade 5	1 (0.8)[‡]
Median time to CRS after glofitamab dose, hours (range)	
2.5 mg	16.3 (5.4–42.1)
10 mg	34.6 (8.9–86.0)
30 mg	36.2 (18.5–55.9)
CRS management	
Tocilizumab	19 (33.9)
Corticosteroids	8 (14.3)
Fluids	13 (23.2)
Single pressor	2 (3.6)
Low flow oxygen	11 (19.6)
High flow oxygen	1 (1.8)
Intensive care unit	3 (5.4)

CRS by cycle and grade



Clinical cut-off date: September 2, 2024. *Glofitamab exposed patients. [†]By ASTCT grade. [‡]Occurred in the context of unresolved infection, patient declined further CRS management at Grade 3.

Mosun + Pola (NCT03671018): Randomized Phase 2

Key inclusion criteria

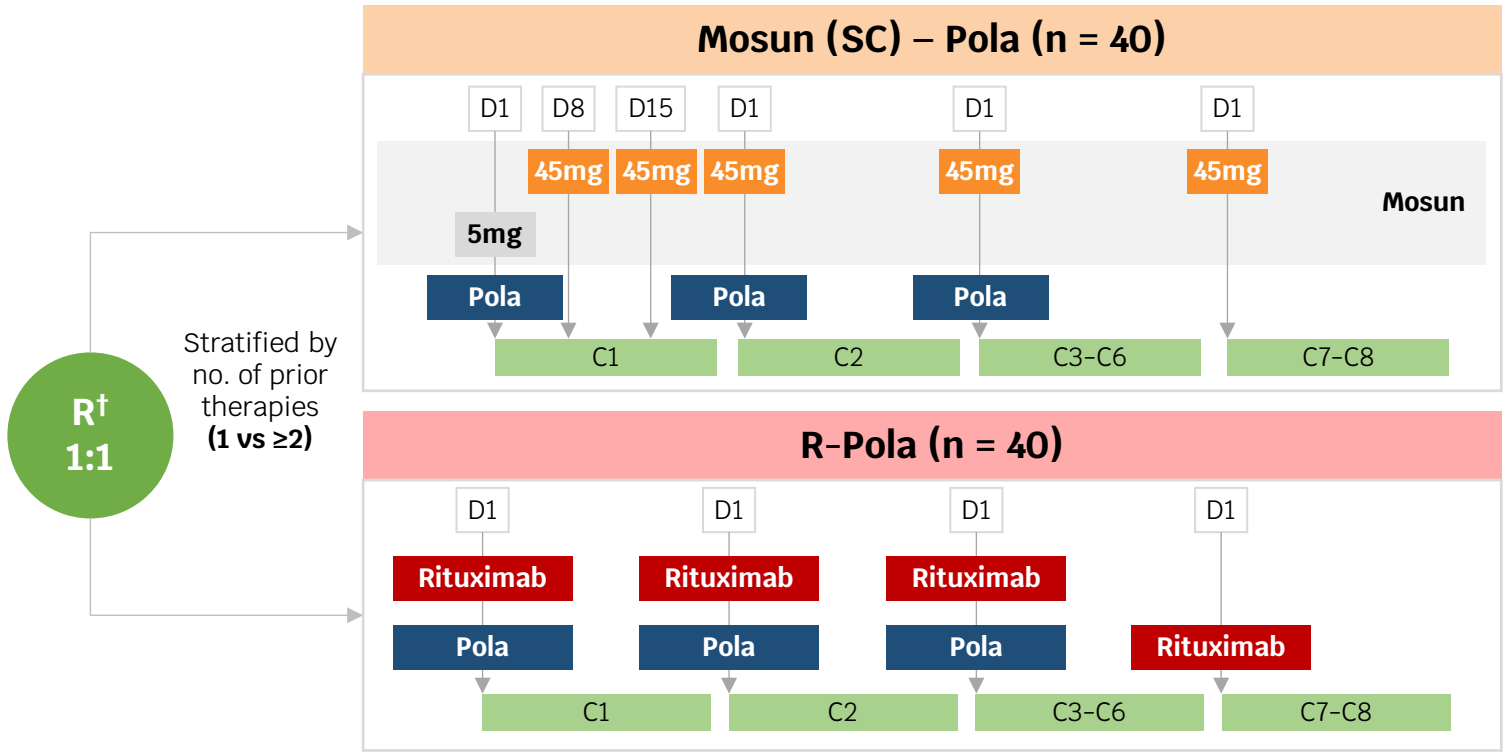
- Confirmed LBCL (DLBCL, HGBCL, or FL Grade 3b; trFL included)
- ≥1 prior line of therapy, including an anti-CD20-directed therapy

Objectives

- Efficacy and safety of Mosun-Pola
- Primary endpoint: best ORR[1] by IRC

Mosun-Pola Fixed duration administration

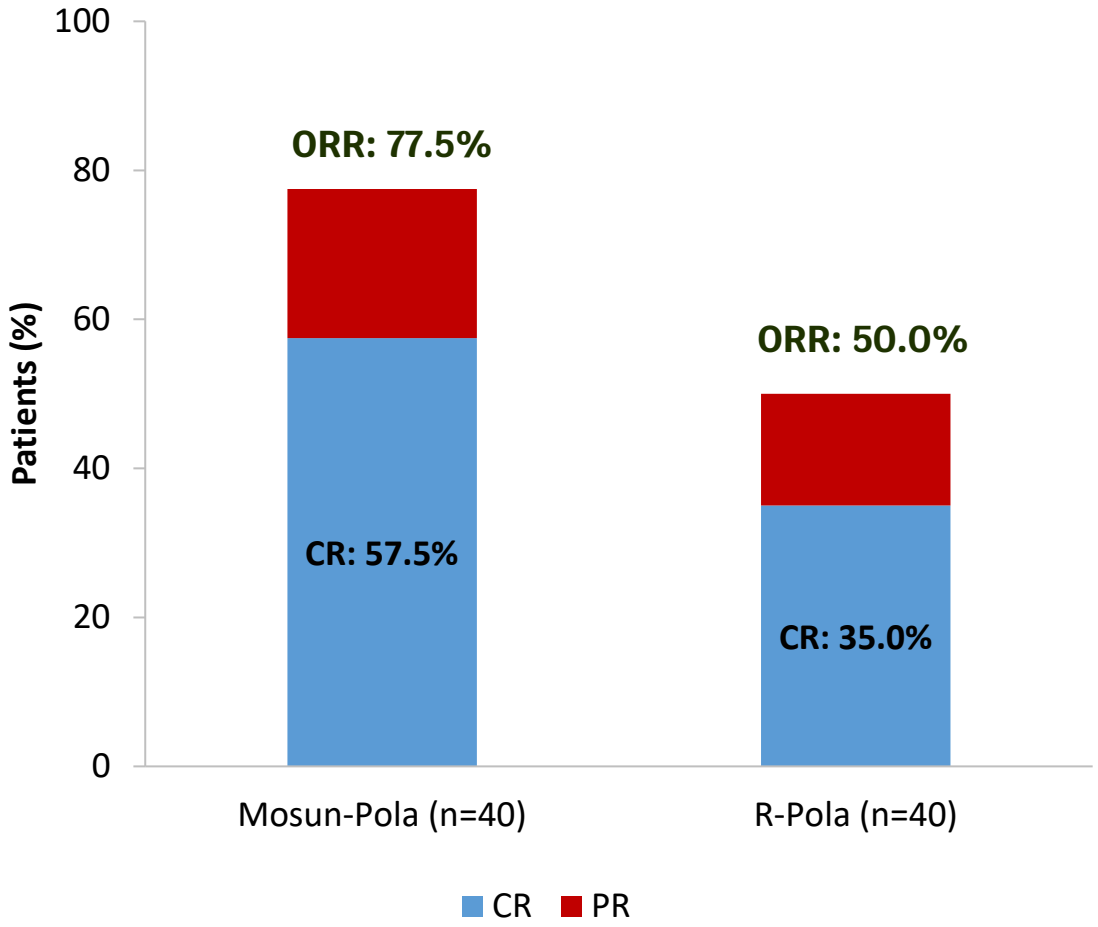
- **Mosun:** SC with step-up dosing in C1; total of 8 cycles
- **Pola:** 1.8mg/kg IV on D1 of C1-6
- **Rituximab:** IV (375mg/m^2) on D1 of C1-8
- **No mandatory hospitalization**
- **Premedications for CRS:** mandatory corticosteroids at C1; not required for C2 and beyond*
- **Retreatment:** permitted if there is PD following completion of treatment for pts on M-Pola achieving CR
- **Potential crossover:** Pts on R-Pola with PD during treatment/at EOT or with stable disease at EOT could cross over to receive Mosun-Pola (up to 8 cycles of cumulative Pola)



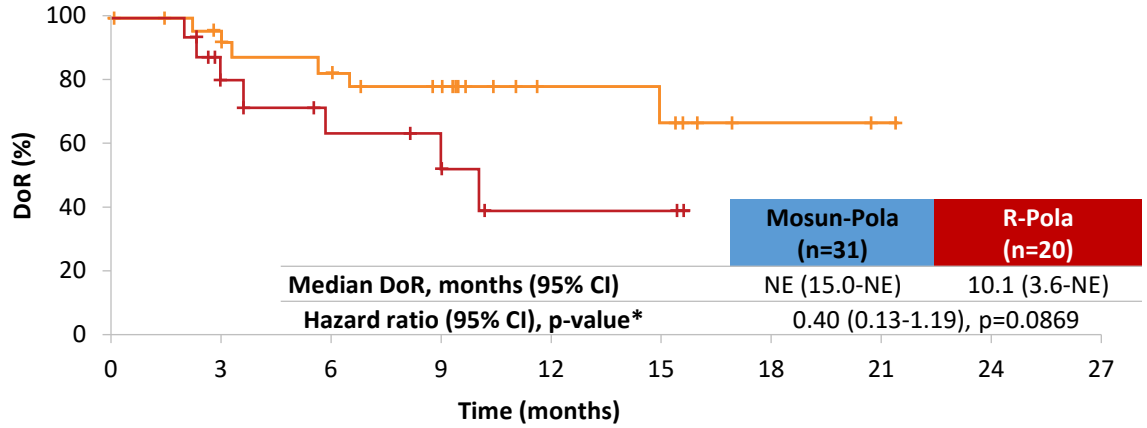
Budde LE, Olszewski AJ, Assouline S, Lossos IS, Diefenbach C, Kamdar M, Ghosh N, Modi D, Sabry W, Naik S, Mehta A, Nakhoda SK, Smith SD, Dorritie K, Jia T, Pham S, Huw LY, Jing J, Wu H, Ead WS, To I, Batlevi CL, Wei MC, Chavez JC. Mosunetuzumab with polatuzumab vedotin in relapsed or refractory aggressive large B cell lymphoma: a phase 1b/2 trial. Nat Med. 2024 Jan;30(1):229-239. doi: 10.1038/s41591-023-02726-5. Epub 2023 Dec 10. PMID: 38072960; PMCID: PMC10803244.

Mosun + Pola (NCT03671018): Key Efficacy Outcomes

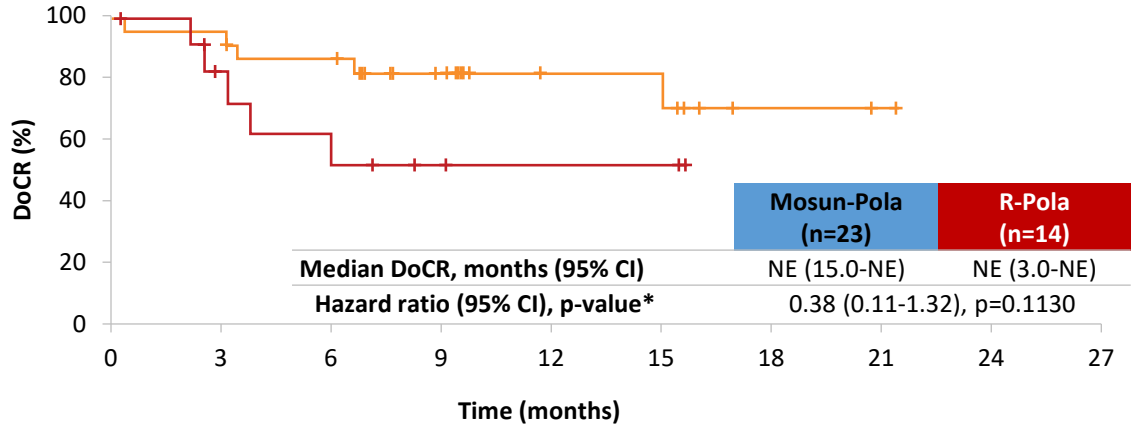
Efficacy endpoint results



DoR by IRC assessment



DoCR by IRC assessment



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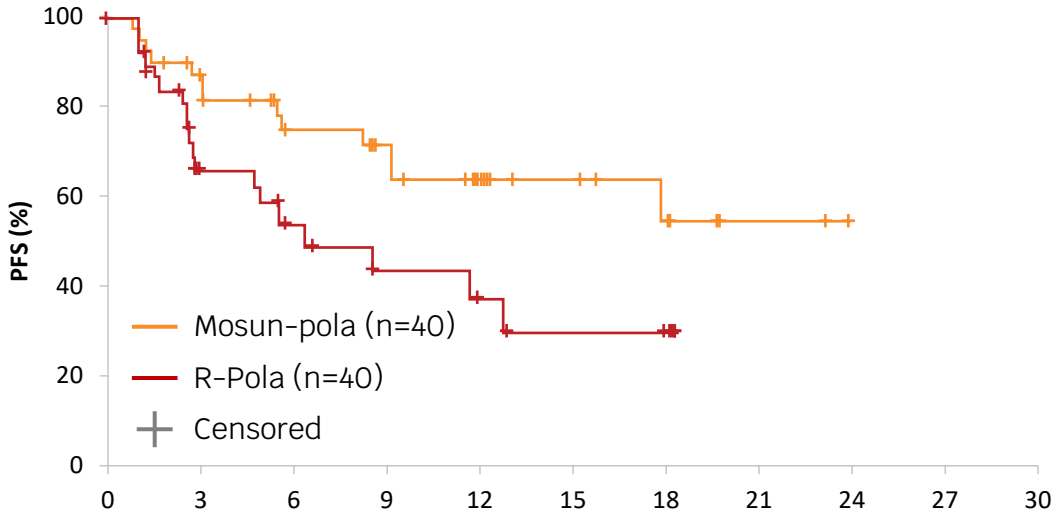
Mosun + Pola (NCT03671018): PFS and OS at 12 months

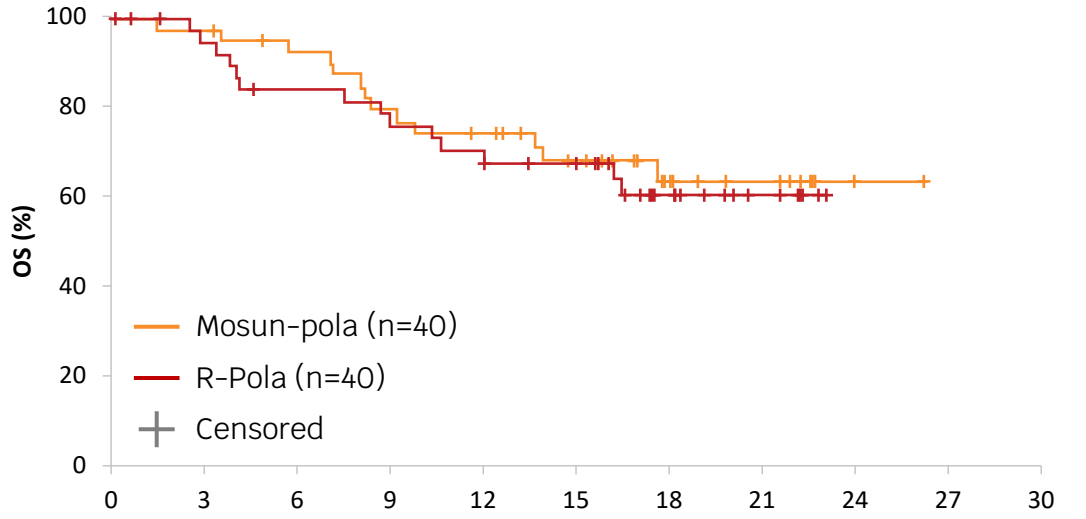
IRC-assessed PFS



No. at risk											
Mosun-pola	40	32	22	19	13	9	6	2	NE	NE	NE
R-Pola	40	18	11	7	5	3	3	NE	NE	NE	NE

	Mosun-Pola (n=40)	R-Pola (n=40)
Median PFS, months (95% CI)	NE (9.2-NE)	6.4 (4.7-NE)
Hazard ratio (95% CI), p-value†	0.45 (0.22-0.92), p=0.0250	
9-month event-free rate, % (95 % CI)	71.7 (56.6-86.8)	43.8 (24.4-63.3)
12-month event-free rate,% (95% CI)	64.2 (47.4-80.9)	37.6 (17.4-57.7)

OS*



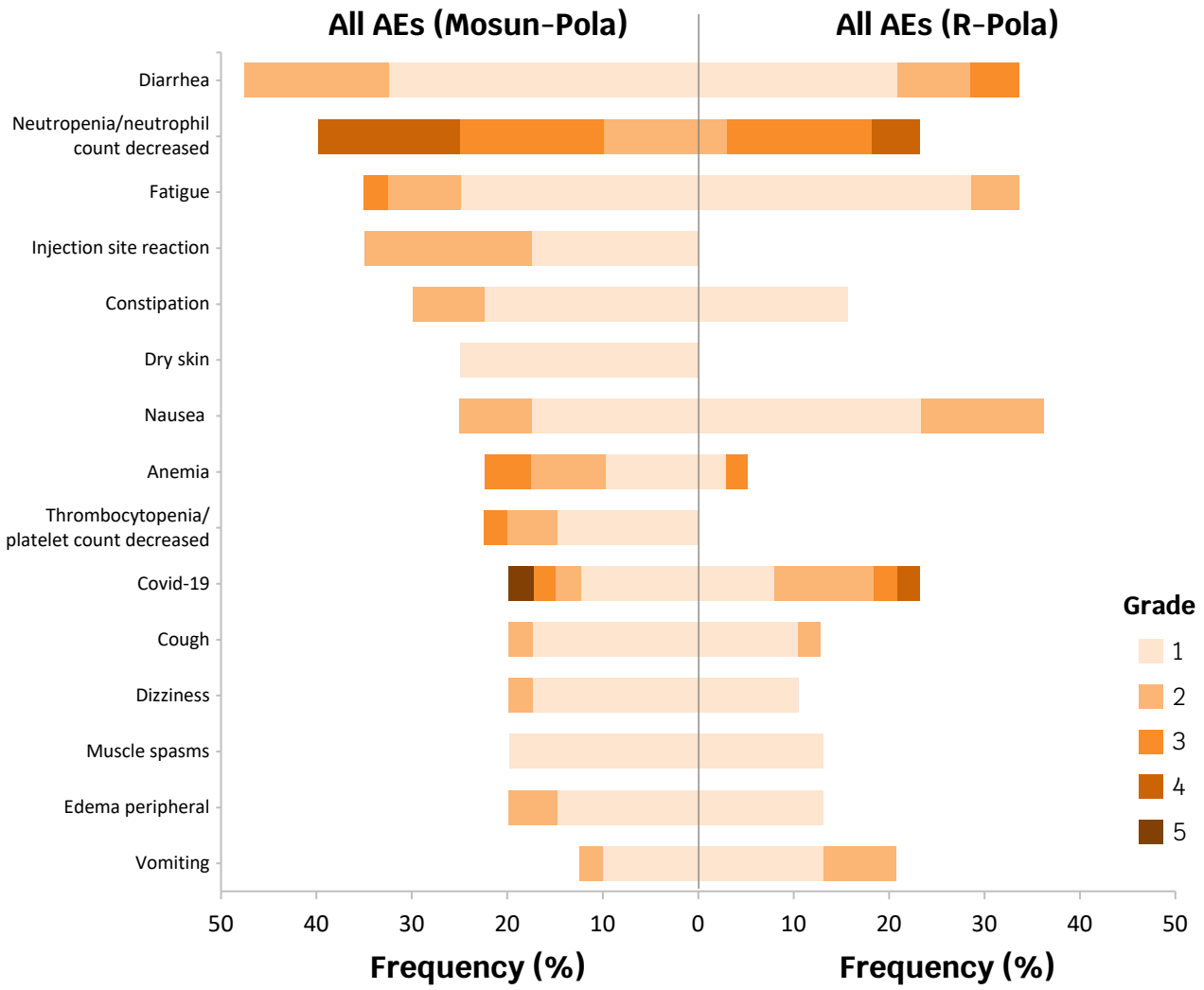
No. at risk											
Mosun-pola	40	39	35	30	27	21	12	7	1	NE	NE
R-Pola	40	35	30	27	23	21	12	5	NE	NE	NE

	Mosun-Pola (n=40)	R-Pola (n=40)
Median OS, months (95% CI)	NE (17.6-NE)	NE (16.2-NE)
Hazard ratio (95% CI), p-value†	0.85 (0.40-1.80), p=0.6644	
9-month event-free rate, % (95 % CI)	79.1 (66.2-92.0)	75.4 (61.4-89.4)
12-month event-free rate,% (95% CI)	73.8 (59.9-87.8)	67.0 (51.7-82.3)

Budde LE, Olszewski AJ, Assouline S, Lossos IS, Diefenbach C, Kamdar M, Ghosh N, Modi D, Sabry W, Naik S, Mehta A, Nakhoda SK, Smith SD, Dorritie K, Jia T, Pham S, Huw LY, Jing J, Wu H, Ead WS, To I, Batlevi CL, Wei MC, Chavez JC. Mosunetuzumab with polatuzumab vedotin in relapsed or refractory aggressive large B cell lymphoma: a phase 1b/2 trial. Nat Med. 2024 Jan;30(1):229-239. doi: 10.1038/s41591-023-02726-5. Epub 2023 Dec 10. PMID: 38072960; PMCID: PMC10803244.

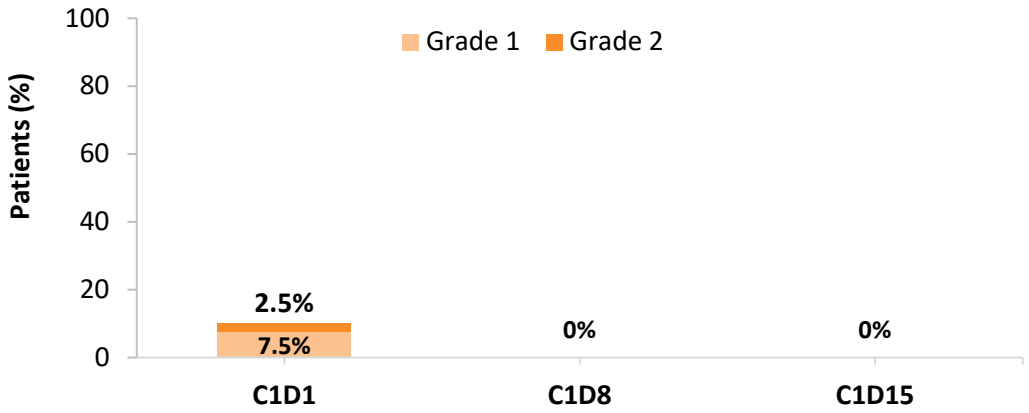
Mosun + Pola (NCT03671018): Safety

AEs occurring in ≥20% of patients by grade



CRS by ASTCT criteria[1]	Mosun-Pola (n=40)
Any grade, n (%)*	4 (10.0)
Grade 1	3 (7.5)
Grade 2	1 (2.5)
Grade ≥3	0
Median CRS duration, days (range)	3 (2-5)
Median time to onset, days (range)	2 (2-3)
CRS management, n (%)	
Corticosteroids	4 (10.0)
Tocilizumab	1 (2.5)
Low-flow oxygen	1 (2.5)
Events resolved, %	100

CRS by cycle and grade



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Key Takeaways

- ❑ Bispecific antibodies provide a novel, effective approach for R/R B-cell NHL patients with response rates of 50-80%
- ❑ Step-up dosing strategies have improved the safety profile, with most CRS events being Grade 1-2
- ❑ CRS management requires a systematic approach with early intervention to prevent progression to higher grades
- ❑ Patient selection should consider prior therapies, performance status, and organ function
- ❑ Post-CAR-T failures represent a promising niche for bispecific antibodies, particularly glofitamab
- ❑ Future directions include combinations and earlier line use to maximize clinical benefit

Thank you!

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