Fred Hutch Cancer Center

Immunotherapy for Lymphoma

Mazyar Shadman, MD MPH

Associate Professor

Fred Hutch Cancer Center and University of Washington

Seattle, WA

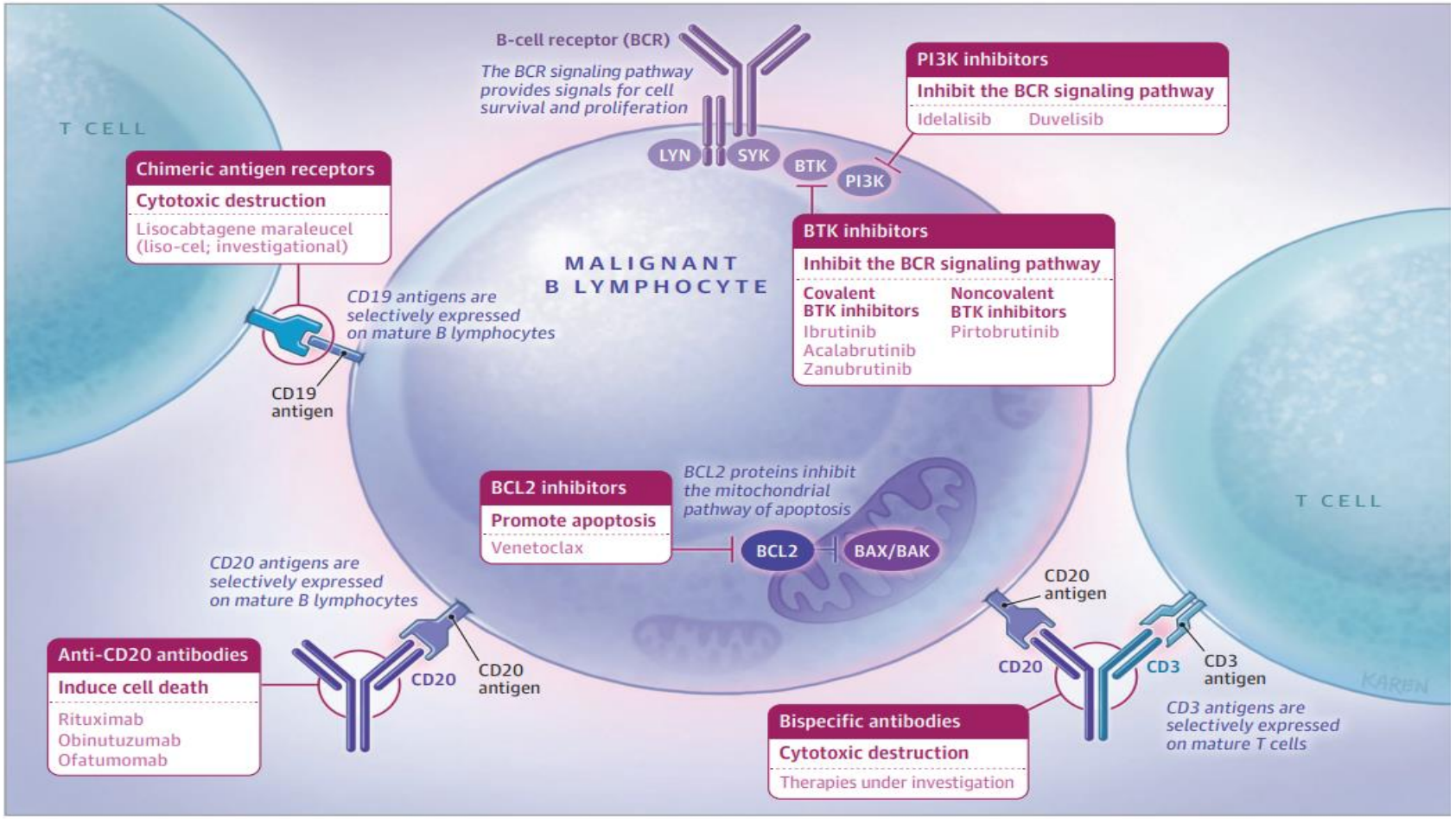
UW Medicine

Disclosures

Research funding from: Mustang Bio, BMS, Pharmacyclics, Genentech, AbbVie,TG Therapeutics, BeiGene, AstraZeneca, Genmab, MorphoSys/Incyte, Vincerx

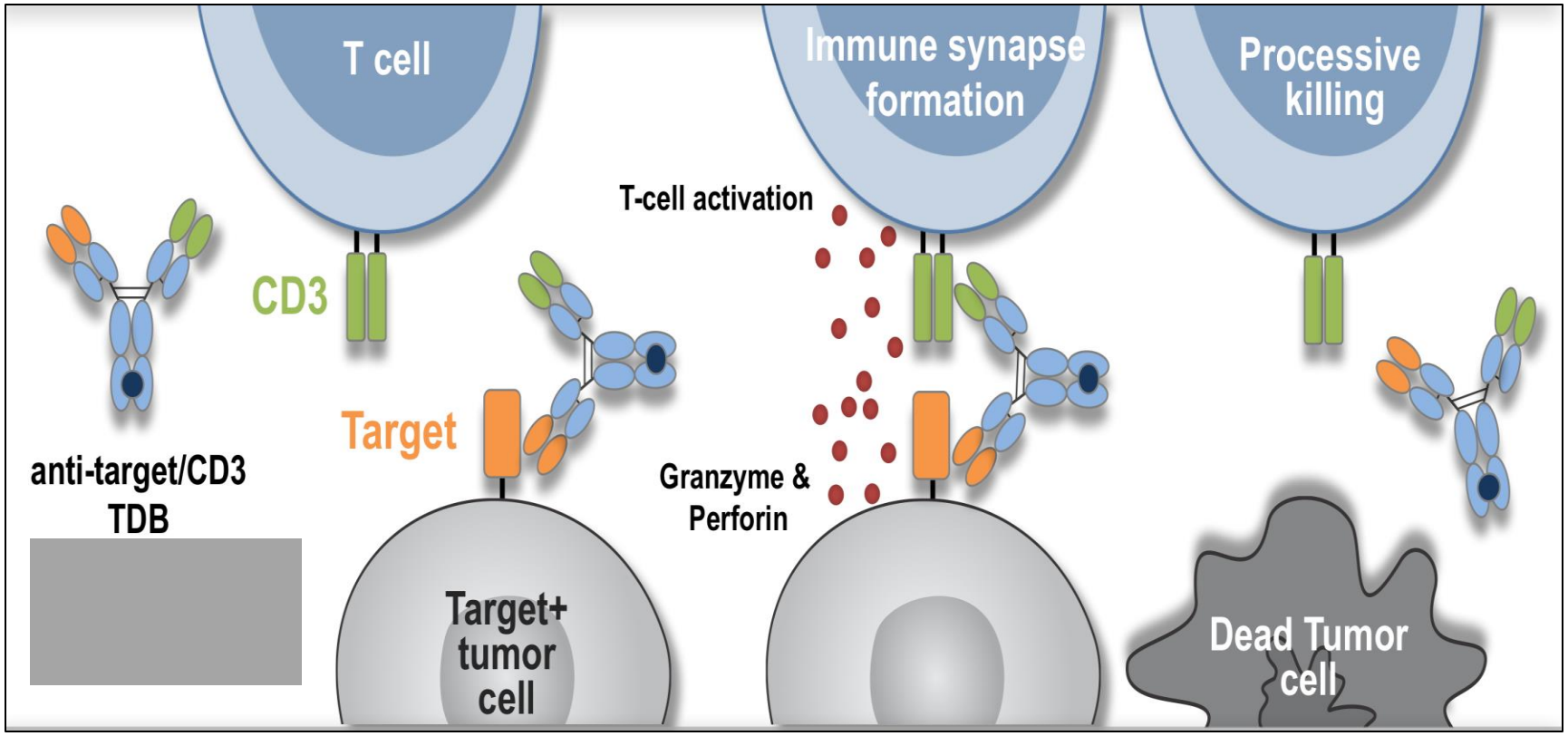
Consulting for: AbbVie, Genentech, AstraZeneca, Pharmacyclics, BeiGene, BMS, MorphoSys/Incyte, Kite, Eli Lilly, Genmab, Mustang Bio, Regeneron, ADC therapeutics, Fate Therapeutics, Nurix and MEI Pharma

Treatment options for B-cell lymphoma

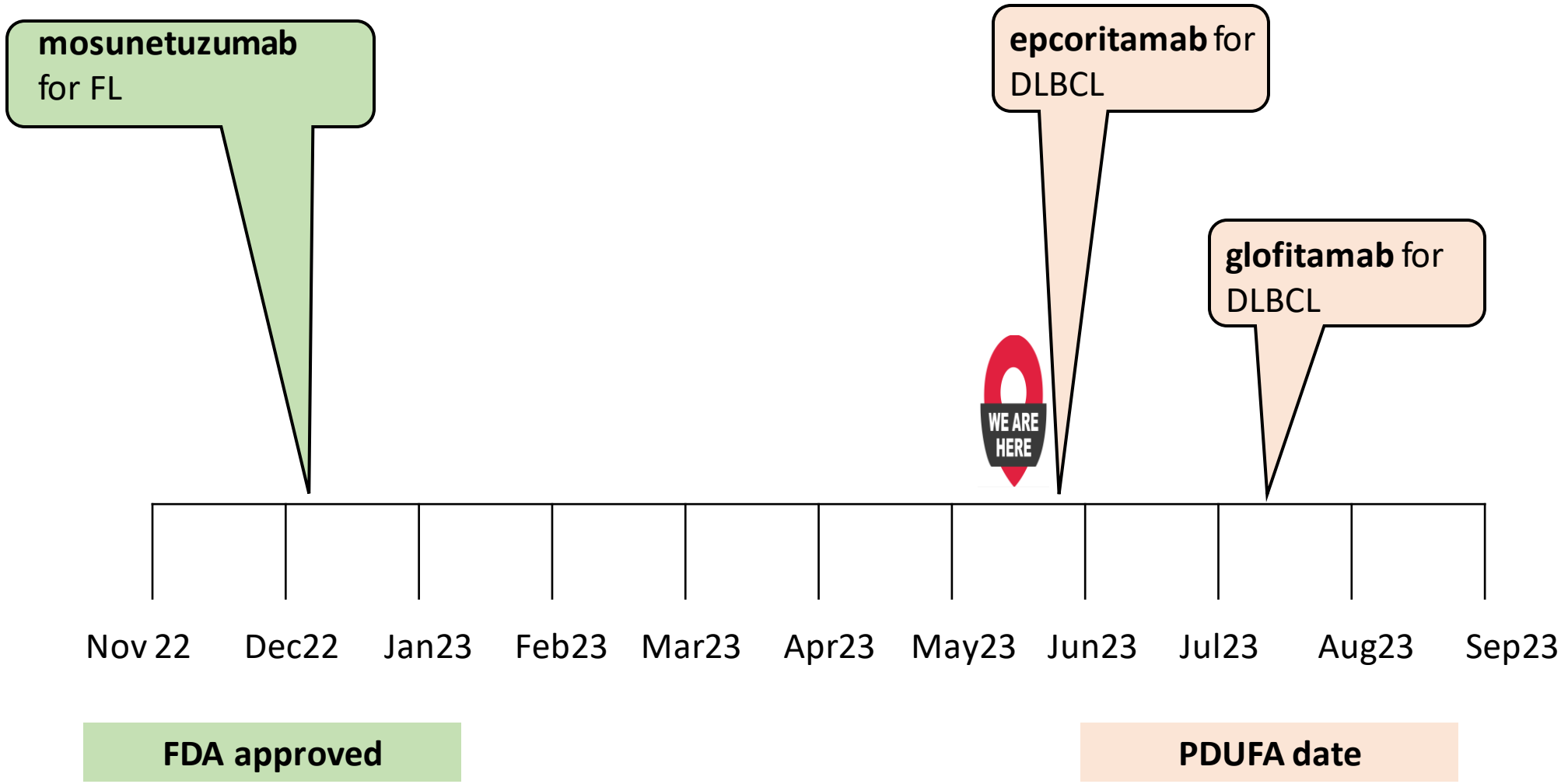


Shadman, JAMA, 2023

Bispecific Antibodies



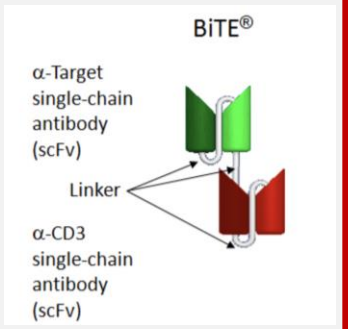
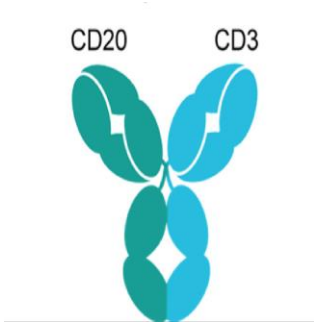
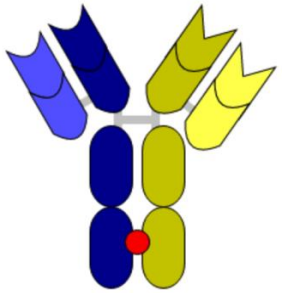
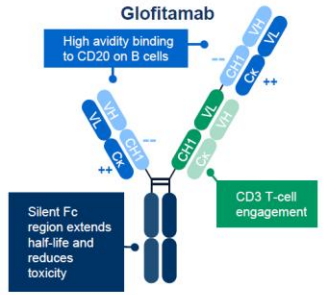
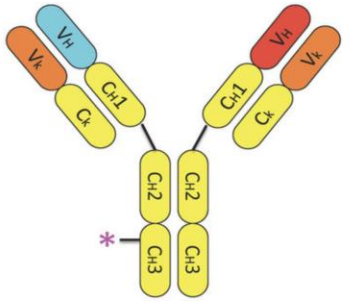
Bispecific Antibodies for Lymphoma



Bispecific Antibodies for Lymphoma

- FL
  - **Mosunetuzumab** for 3rd line FL **(FDA approved)**
- DLBCL
  - **Epcoritamab** for 3rd line DLBCL **(Approval is expected)**
  - **Glofitamab** for 3rd line DLBCL **(Approval is expected)**

Bispecific Antibodies for Lymphoma

The Original: Proof of Concept	The Emerging: Viable Future Therapies?			
Blinatumomab	**Epcoritamab**	**Mosunetuzumab**	**Glofitamab**	**Odronextamab**
				
CD3 (scFV) x CD19 (scFV)	DuoBody- CD3 x CD20 BsAb	CD3 x CD20 Knobs-in-hole Fc BsAb	)3 (Fab) x CD20 (Fab x2) Fc BsAb	CD3 x CD20 Common LC Fc BsAb
	PDUFA: 5/21/23 For DLBCL	**Approved: 12/22/22 For FL**	**PDUFA: 7/1/23 For DLBCL**	

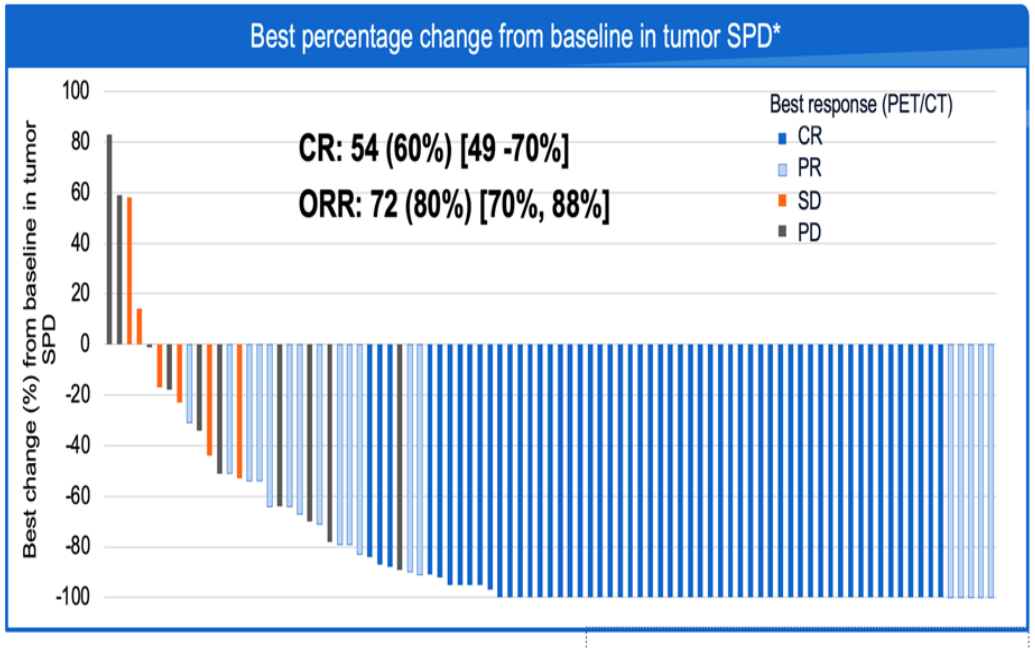
Mosunetuzumab for r/r FL

N	**90**
Median age	**60 (53-67)**
Prior lines	**3 (2-4)**
Prior CAR-T	**3%**
Prior ASCT	**21%**
Bulky disease (>6cm)	**34%**
POD24	**52%**

Route	IV
Cycles	21 days
Duration	7-17 cycles

Budde, Lancet, 2022

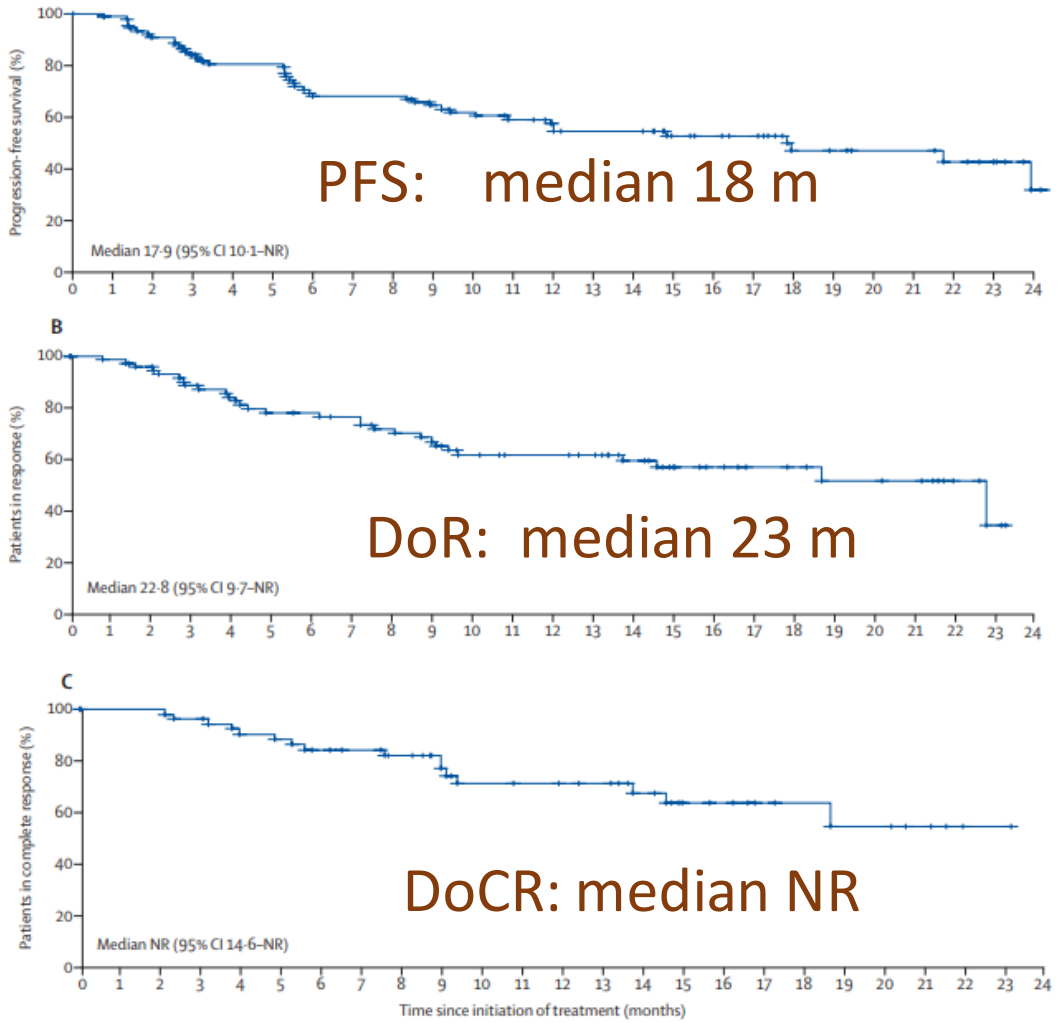
Mosunetuzumab for r/r FL



Median time to CR:
3 mo (1.2, 18.9)

Median DoR:
22.8 months (range: 9.7, NE)

Median PFS:
17.9 months (95% CI: 10.1, NE)



Budde, Lancet, 2022

Mosunetuzumab for r/r FL

N (%)	N=90
AE	90 (100%)
Mosunetuzumab related*	83 (92.2%)
Grade 5 (fatal) AE	2 (2.2%)†
Mosunetuzumab related*	0
AE leading to discontinuation of treatment	4 (4.4%)‡
Mosunetuzumab related*	2 (2.2%)‡
ICANS*	4 (4.4%)
Grade 3†	0

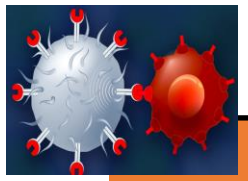
N (%)	N=90
CRS (any Grade)*	40 (44.4%)
Grade 1	23 (25.6%)
Grade 2	15 (16.7%)
Grade 3	1 (1.1%)
Grade 4	1 (1.1%)†
Serious AE of CRS (any Grade)	21 (23.3%)‡
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–23.7)
C1D15–21	26.6 (0.1–390.9)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	10 (11.1%)
Tocilizumab for CRS management	7 (7.8%)

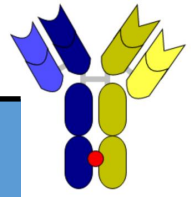
- **Mosunetuzumab had a manageable safety profile. AEs leading to discontinuation were uncommon.**

*AE considered related to treatment by the investigator; †mosunetuzumab unrelated: malignant neoplasm progression and unexplained death (1 patient each); ‡mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each); AE, adverse event; Gr, Grade ;

Budde, Lancet, 2022

CAR-T vs. bispecific antibody therapy for FL





	tisagenlecleucel	axicabtagene Ciloleucel	mosunetuzumab
Age	57 (49-64)	60(53-67)	60 (29-90)
High-risk FLIPI (≥3)	60%	44%	44%
POD24%	63%	55%	52%
Prior treatments	4 (2-13)	3 (2-4)	3 (2-10)
ORR	86%	94%	78%
CR	68%	79%	60%
CRS (grade>3)	0%	6%	1%
ICANS (grade>3)	1%	15%	0%
Infections (grade 3)	9%	18%	14%
PFS	2-year: 57%	3-year: 54.4%	2-year: 48%

One time treatment

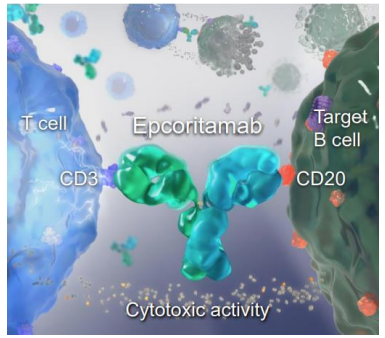
8-17 cycles , retreatment is possible

Dreyling, ASH, 2022, abstract #608; Jacobson, Lancet Oncol, 2022 ; Jacobsen, ASCO, 2021, abstract#7515; Neelapu, ASH, 2022, abstract#4660; Budde, Lancet, 2022 ; CAR-T image source: Yale University website

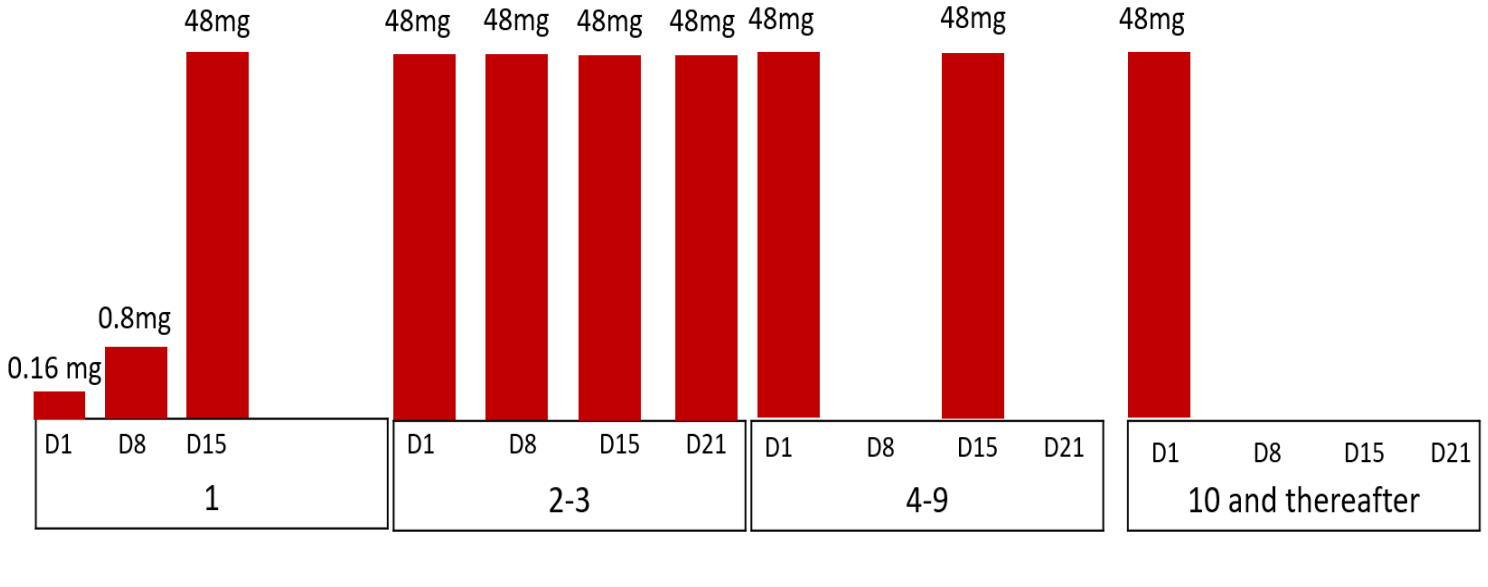
Mosunetuzumab study: Take home points

- Mosunetuzumab is an effective and time-limited IV (SC in future) for patients with relapsed FL
- Alternative to CAR-T
- Based on this study, the drug received accelerated approval in patients with relapsed FL after 2 prior lines of treatment

Epcoritamab for R/R DLBCL



N	**157**
Median age	**64 (20-83)**
Prior lines	**3 (2-11)**
Prior CAR-T	**38.9%**
Prior ASCT	**19.7%**
Primary refractory	**61.1%**
Refractory to previous treatment	**82.8%**

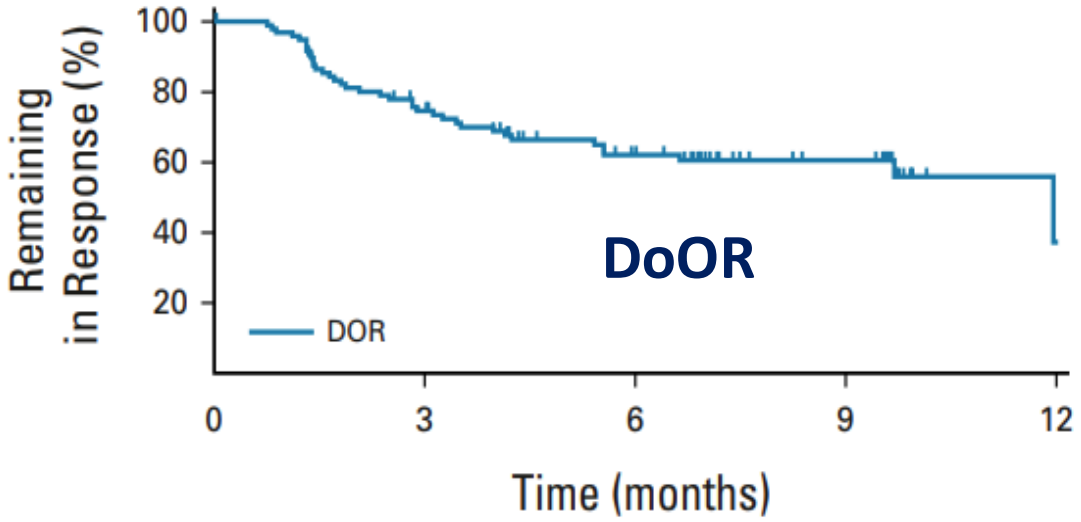


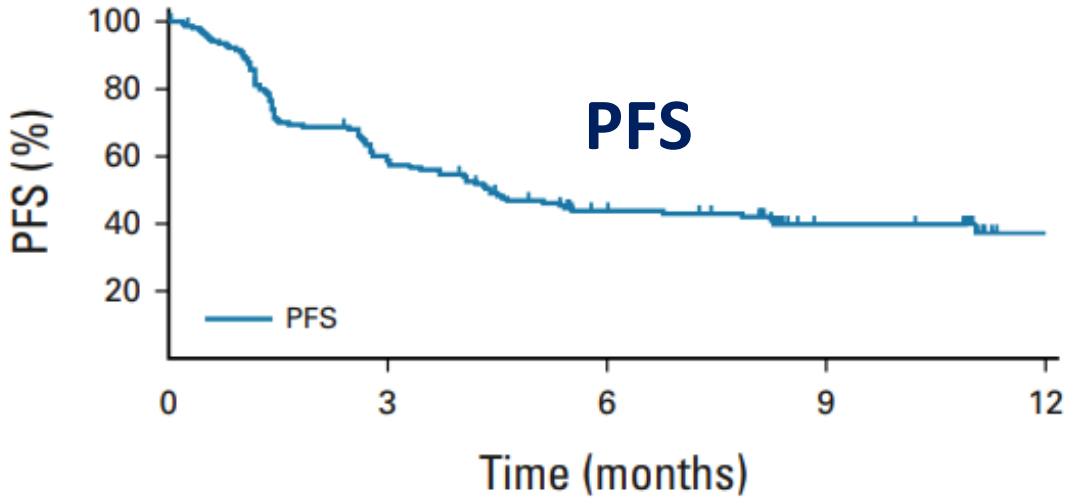
Route	SubQ
Cycles	28 days
Duration	Until PD or intolerance

Thieblemont, JCO, 2022

Epcoritamab for R/R DLBCL

CR	38.9%
CR in pts with prior CAR-T	34.4%
DoCR months	12 (9.7-NR)
CR at 12 months	-
ORR	63%
DoOR	12 (6.6-NR)
OR at 12 months	-
Median PFS (months)	4.4 (3.0-7.9)
12-month PFS	-
Median OS (months)	NR (11.3-NR)
12-month OS	-
Median time to response	1.4 months
Median time to CR	2.7 months



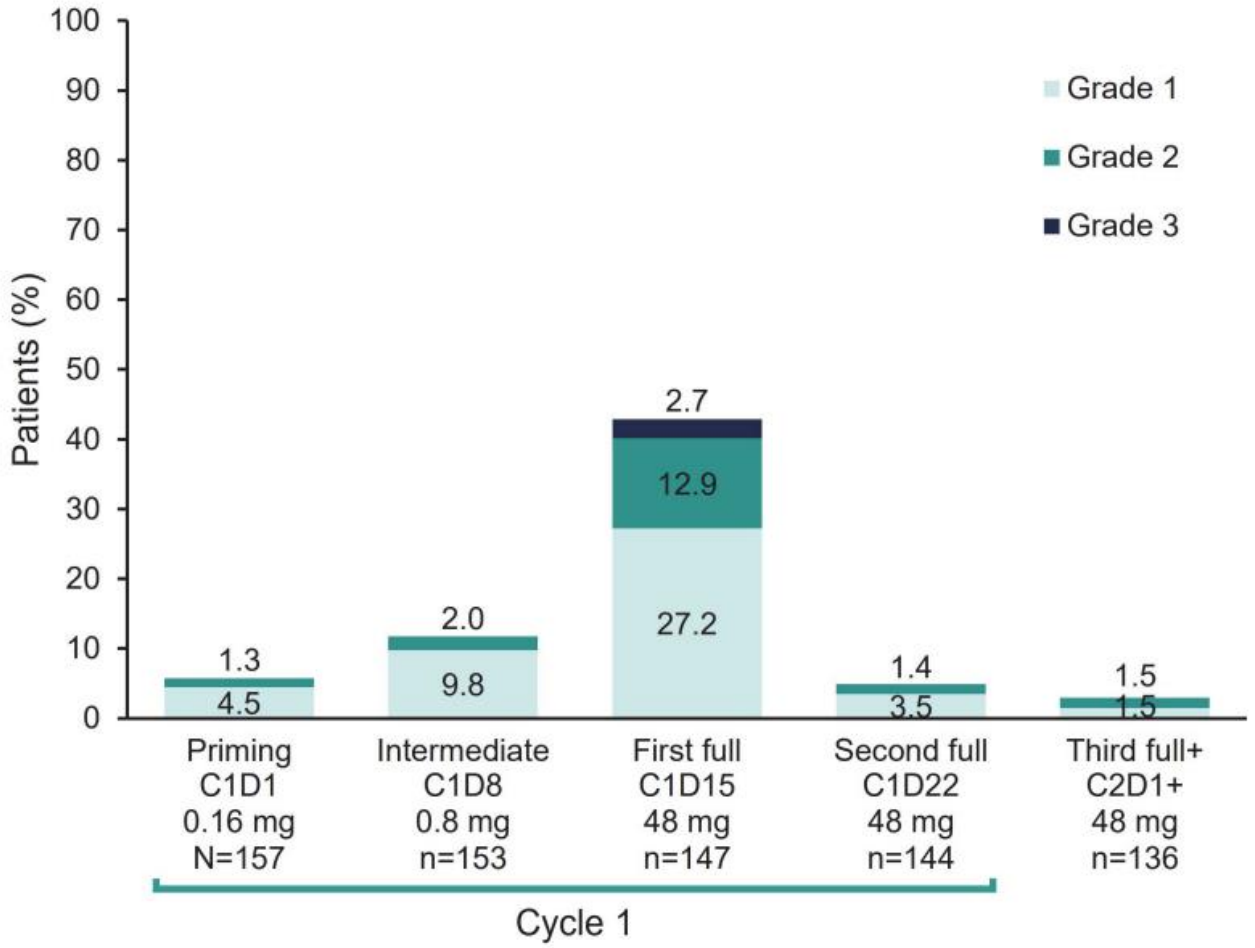


median follow-up of 10.7 months

Thieblemont, JCO, 2022

Epcoritamab for R/R DLBCL

CRS (ASTCT)	**49.7%**
G1	31.8%
G2	15.2%
G3	2.5%
G4	0
ICANS	**6.4%**
G1	4.4%
G2	1.3%
G3	0
G4	0
G5	0.6%



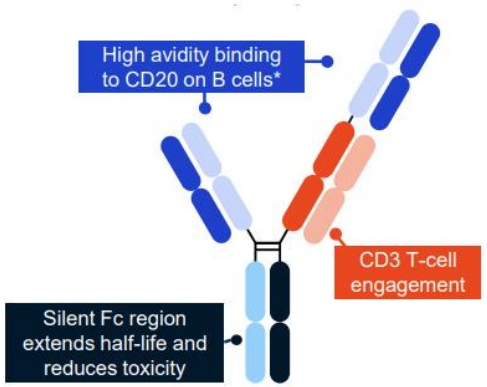
Thieblemont, JCO, 2022

Epcoritamab for R/R DLBCL

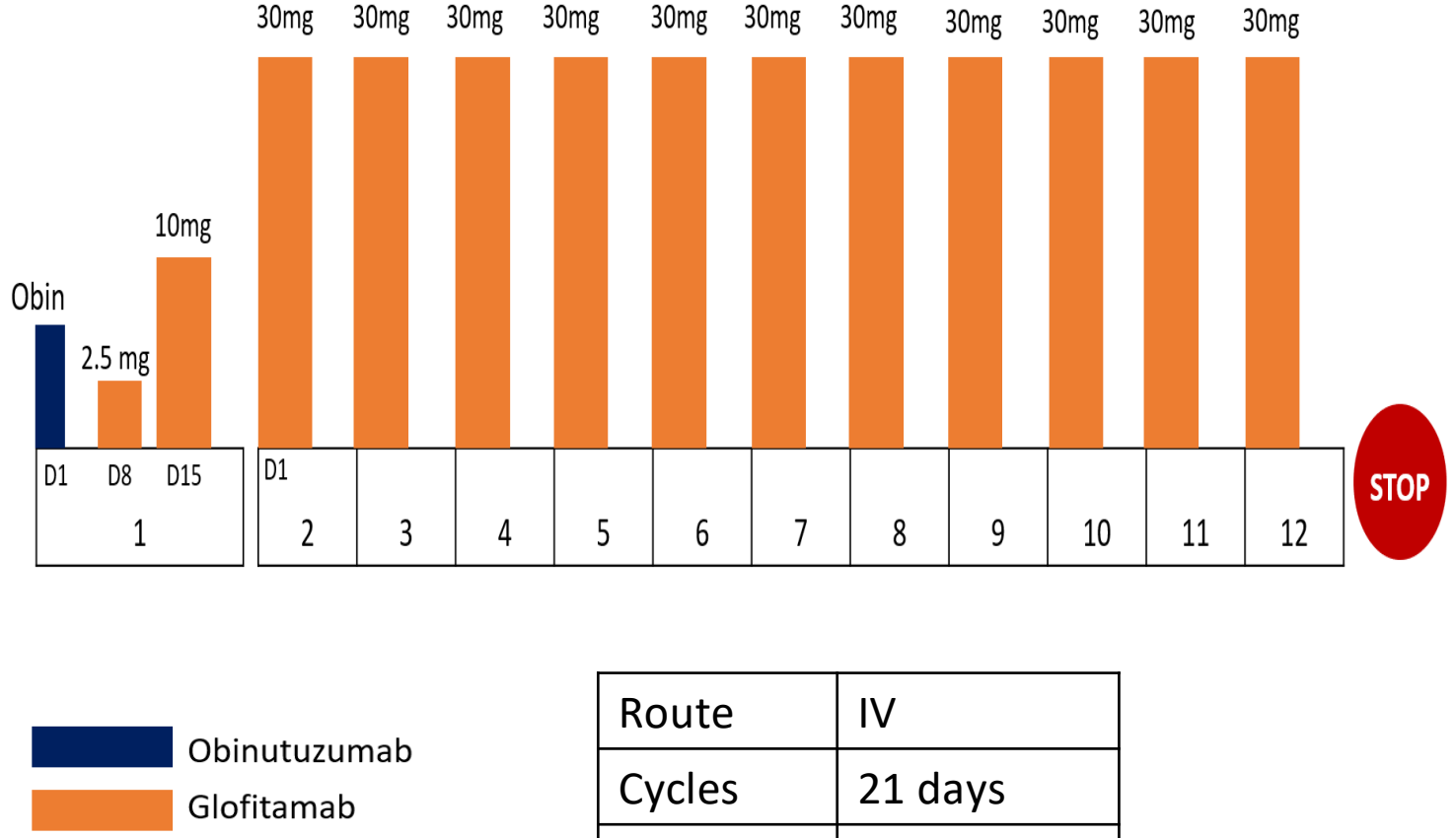
Neutropenia	21.7
Anemia	17.8
Thrombocytopenia	13.4
Sepsis	-
Infections (grade ¾)	14.6%
Febrile neutropenia	2.5%
Tumor flare	-
Tumor lysis syndrome	1.3
Grade 5	9 pts (5.7%)
COVID-19	2
ICANS	1
Myocardial infarction	1
hepatotoxicity	1
PML	1
loss of consciousness	1
General health deterioration	1
Pulmonary embolism	1

Thieblemont, JCO, 2022

Glofitamab for R/R DLBCL



N	154
Median age	66 (21-90)
Prior lines	3 (2-7)
Prior CAR-T	33%
Prior ASCT	18%
Primary refractory	58%
Refractory to previous treatment	90%

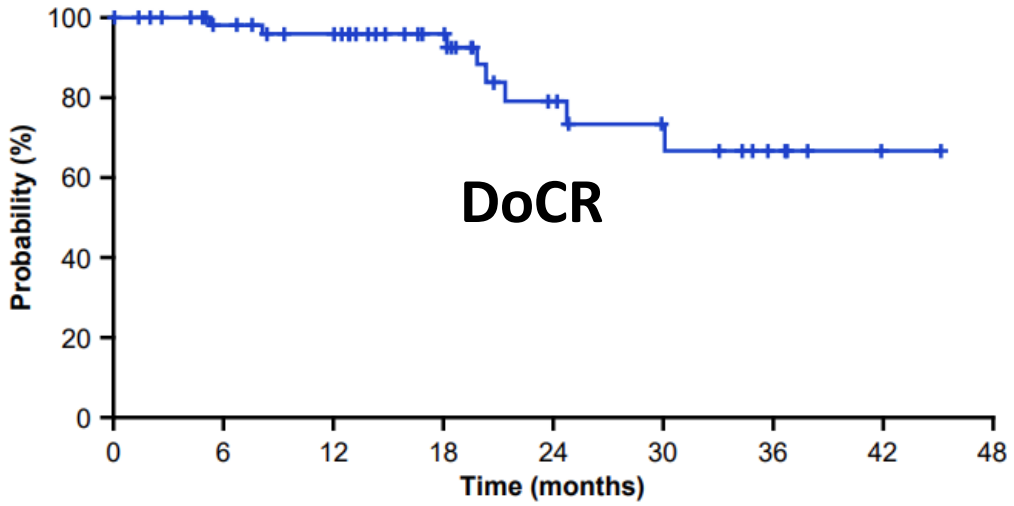


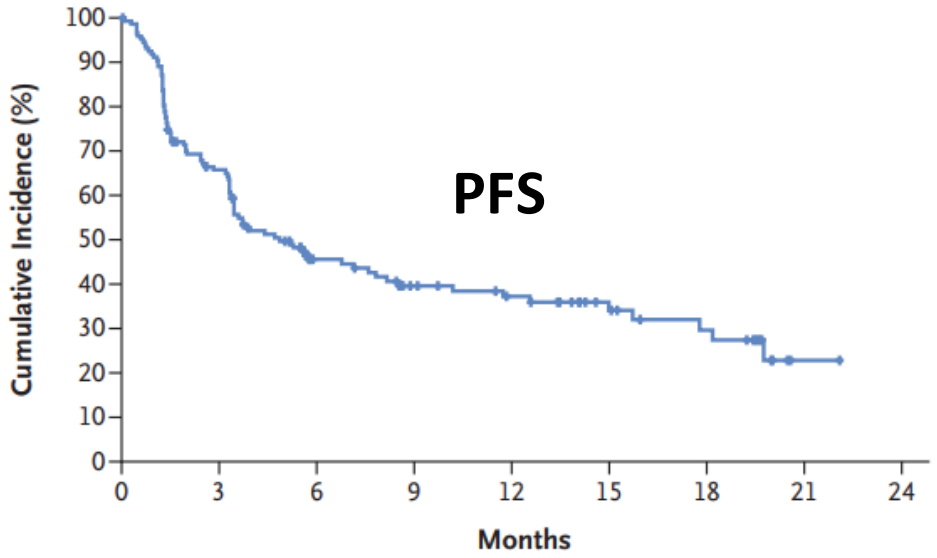
Route	IV
Cycles	21 days
Duration	12 cycles

Dickinson, NEJM, 2022

Glofitamab for R/R DLBCL

CR	39%
CR in pts with prior CAR-T	35%
DoCR	NR (30.1-NR)
CR at 24 months	79%
ORR	52%
DoOR	18.4 (13.7-NR)
OR at 12 months	64%
Median PFS (months)	4.9 (3.4-8.1)
12-month PFS	37%
Median OS (months)	11.5 (7.9-15.7)
12-month OS	50%
Median time to response	-
Median time to CR	1.4



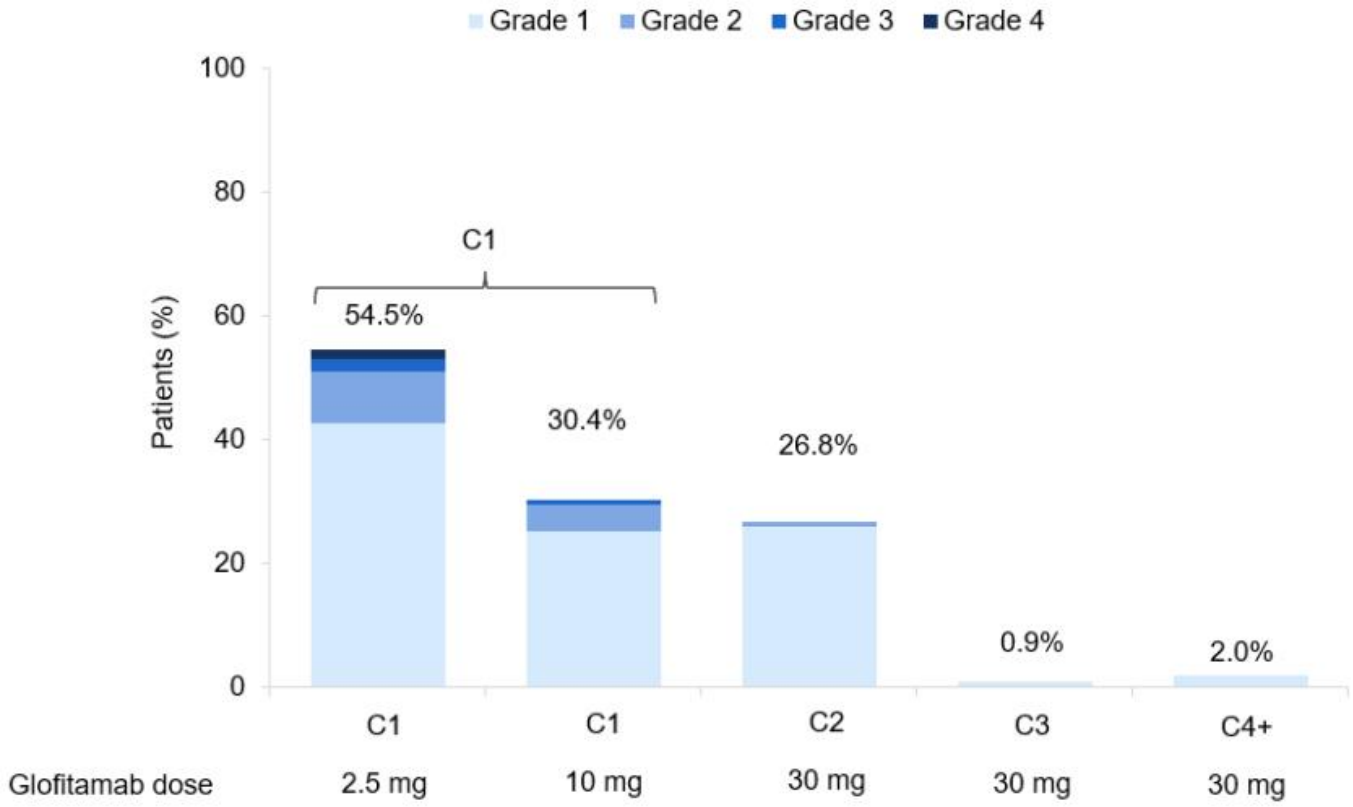


median follow-up of 12.6 months

ɔn, NEJM, 2022; Hutchings, ASH, 2022

Glofitamab for R/R DLBCL

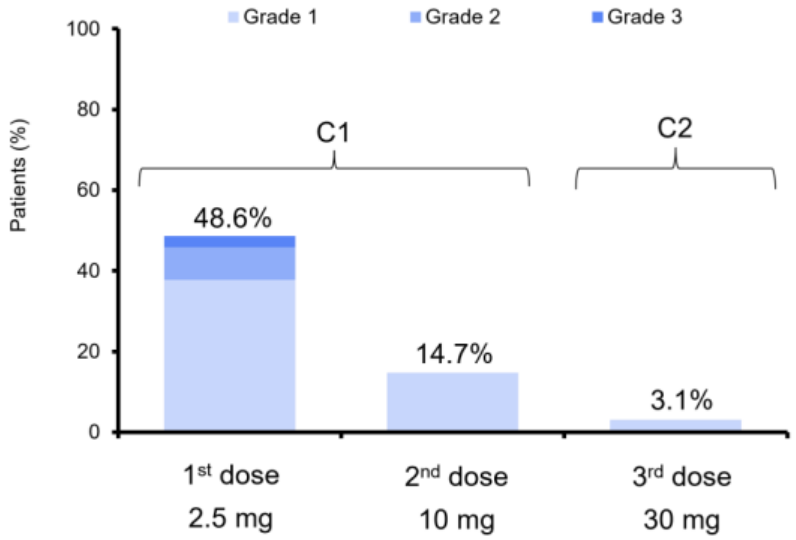
CRS (ASTCT)	**63%**	
G1		**47%**
G2		**12%**
G3		**3%**
G4		**1%**
ICANS	**8%**	
G1		
G2	**5%**	
G3	**3%**	
G4		



Dickinson, NEJM, 2022

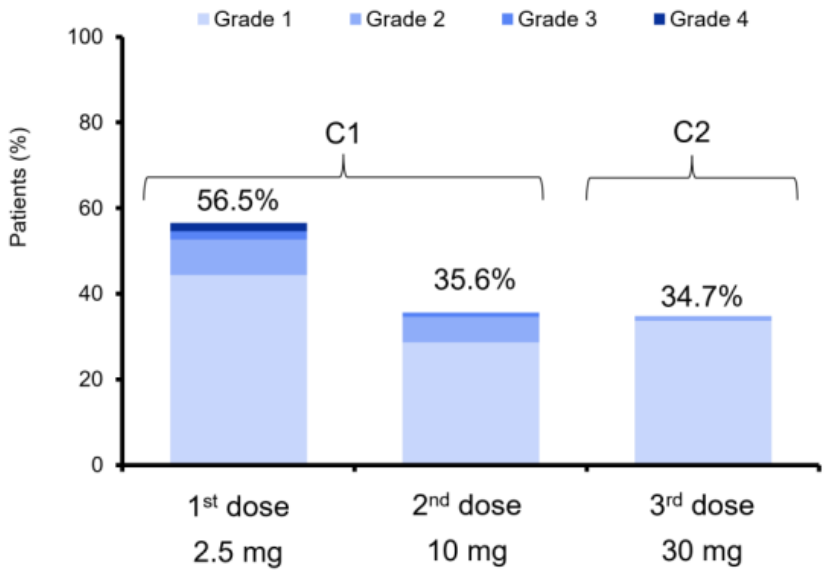
Glofitamab for R/R DLBCL

Mandatory Dexamethasone



Any grade CRS: 48%

Any Corticosteroids



Any grade CRS: 68%

- CRS of grade 2 or higher (in 10% of patients) occurred just after the first infusion in this cohort; no events of CRS of grade 2 or higher were observed in patients after the second or subsequent doses of glofitamab

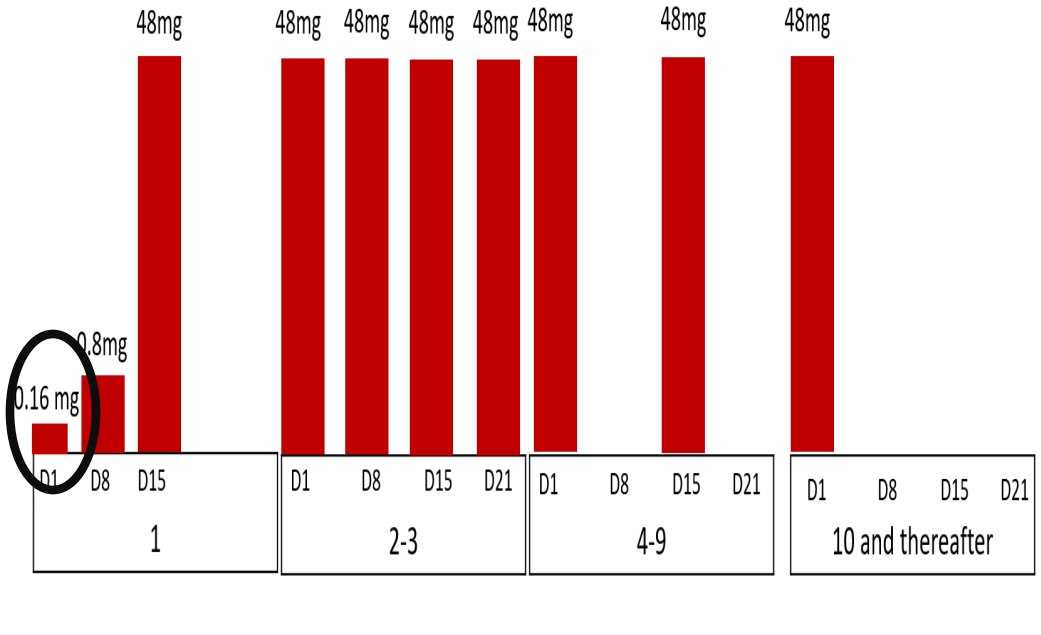
Dickinson, NEJM, 2022

Glofitamab for R/R DLBCL

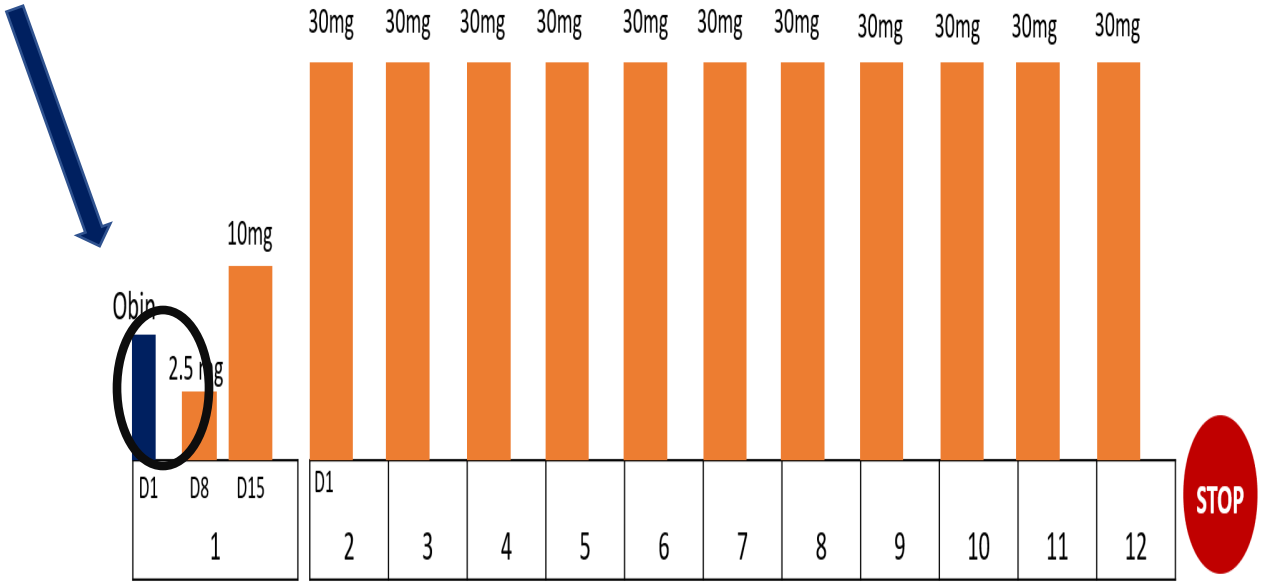
Neutropenia	**27%**
Anemia	6%
Thrombocytopenia	8%
Sepsis	4%
Infections (grade ¾)	15%
Febrile neutropenia	**3%**
Tumor flare (g more than 3)	**3**
Tumor lysis syndrome (G more than 3)	**1**
Grade 5	8 pts (5%)
COVID-19	5
Sepsis	2
Delirium	1

Dickinson, NEJM, 2022

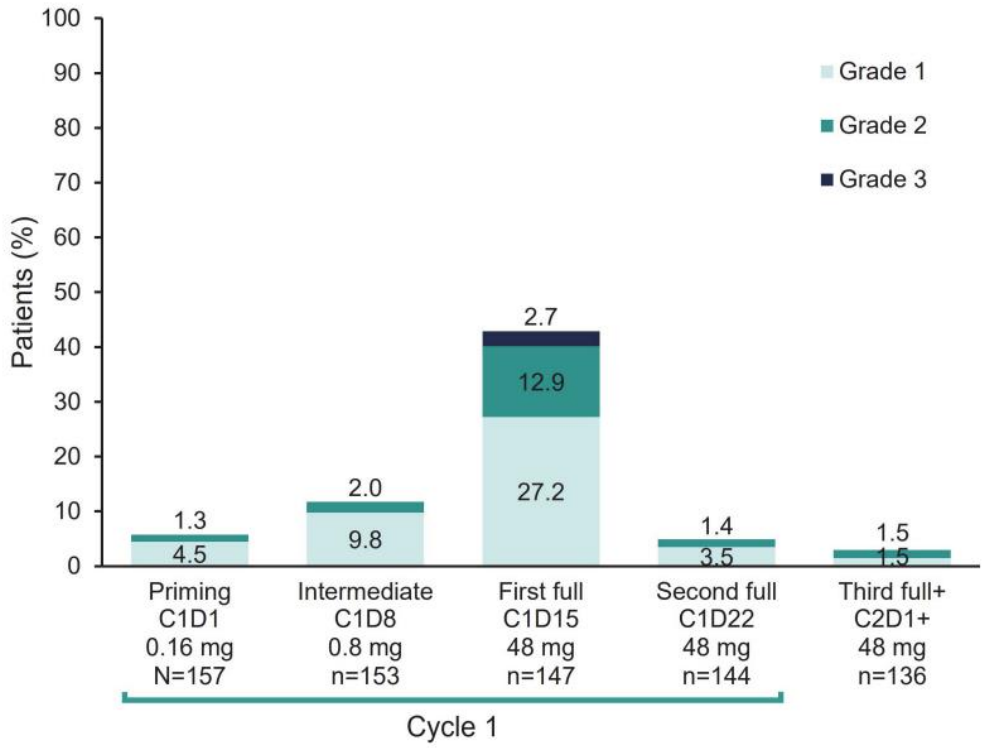
Epcoritamab



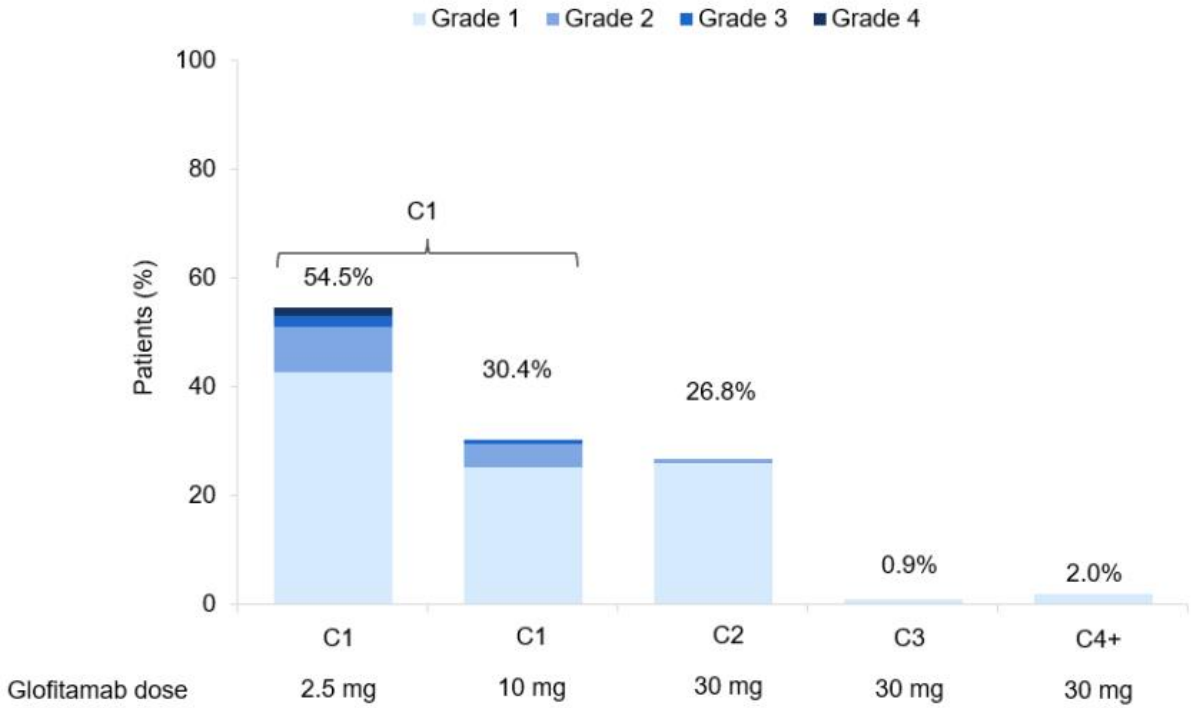
Glofitamab



Epcoritamab



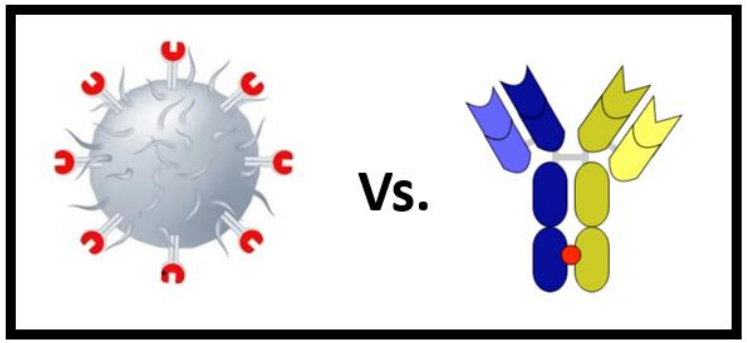
Glofitamab



Thieblemont, JCO, 2022; Dickinson, NEJM, 2022

	Epcoritamab	Glofitamab
	Median follow-up 10.7 months	Median follow-up 12.6 months
CR	38.9%	39%
CR in pts with prior CAR-T	34.4%	35%
DoCR months	12 (9.7-NR)	NR (30.1-NR)
CR at 12 months	-	79%
ORR	63%	52%
DoOR	12 (6.6-NR)	18.4 (13.7-NR)
OR at 12 months	-	64%
Median PFS (months)	4.4 (3.0-7.9)	4.9 (3.4-8.1)
12-month PFS	-	37%
Median OS (months)	NR (11.3-NR)	11.5 (7.9-15.7)
12-month OS	-	50%
Median time to response	1.4 months	-
Median time to CR	2.7 months	1.4 months

Thieblemont, JCO, 2022; Dickinson, NEJM, 2022



3rd line

BsAb=bispecific antibody

CAR-T vs. Bispecific antibodies

phase 2 studies in DLBCL 2+ Prior lines

	Phase 2 CAR-T trials			Phase 2 Bispecific trials	
	ZUMA-1 (Axi-cel)	JULIET (Tisa-cel)	TRANSCEND (Liso-cel)	Epcoritamab	Glofitamab
Median age	58	56	63	68	66
ORR/CRR	82%/58%	52%/40%	73%/53%	63%/39%	52%/39%
12-month PFS	44%	NR	44%	NA	37%
Any grade CRS// ≥grade 3	93%/13%	58%/22 %	42%/2%	50%/2.5%	63%/4%
Any grade ICANS/ ≥grade 3	64%/28%	21%/12%	30%/10%	6%/0.6%	8%/3%
NRM	3%	0%	NA	0.6%	0%
Median f/u (months)	27 months	40.3 months	18 months	10.7	12.6

5-year DFS : 51%

2-year PFS : 40.6%

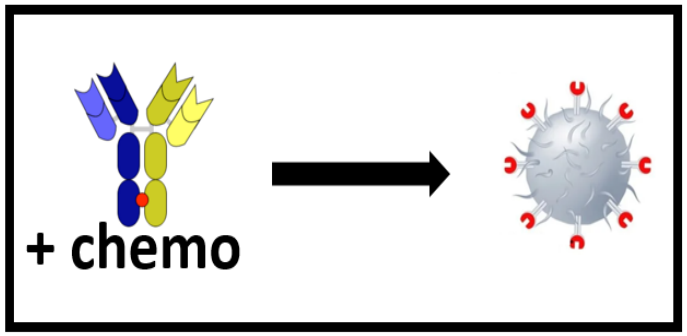
Gurumurthi, Blood Adv, 2023 (modified) ; Neelapu, Blood, 2023; Abramson, ASH, 2021

Glofitamab

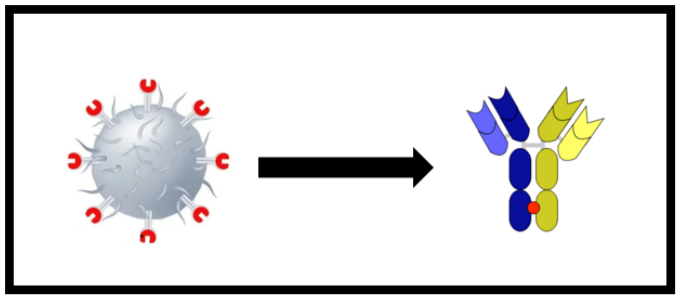
- NCT04077723: Phase 1b Glofit + CD19-41BB R/R B-Cell NHL
- Phase 1 Glofit SQ
- Phase I Glofit+CD28 in R/R DLBCL
- NCT04408638: Phase III Glofit+Gem/Ox vs R+Gem/Ox R/R DLBCL
- NCT04980222: Phase 2 Glofit + RCHOP in 1L DLBCL guided by ctDNA
- NCT03533283: Phase IB Glofit+Atezo or Pola, (Single Dose G) R/R Bcell NHL
- NCT03467373: Phase Ib Glofit+R or GCHOP R/R B-cell NHL
- NCT05364424: Phase 1b Glofit+RICE in R/R BMT eligible DLBCL
- NCT05169515: Glofit + CellMods
- 1L DLBCL Glofit+PolaRCHP vs. PolaRCHP

Epcoritamab

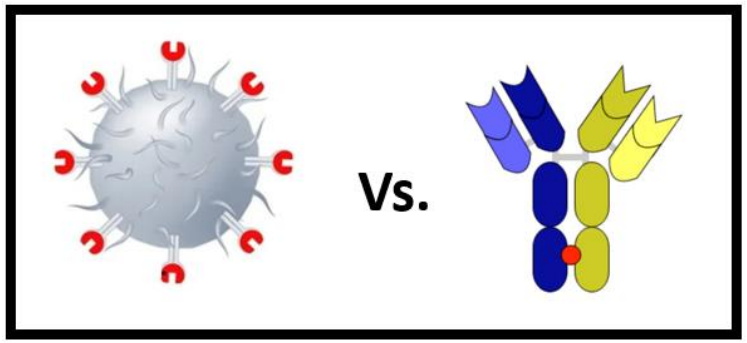
- NCT05283720: Phase 2 Epco + len or Epco ibrutinib for R/R DLBCL and Epco-Pola-RCHP for TN DLBCL
- NCT04663347: Phase 1b/2: Epco+R-CHOP and Epco+R-miniCHOP for TN DLBCL, Epco+R-DHAX/C, Epco+GemOx for R/R DLBCL
- NCT04542824: Phase 1/2 Epco+ R2, Epco + GemOx, Epco+RCHOP
- NCT05201248: Phase 1b/2 Epco+ R2, Epco+RCHOP
- NCT04628494: Phase 3: Epco vs. R-GemOx or BR in R/R DLBCL



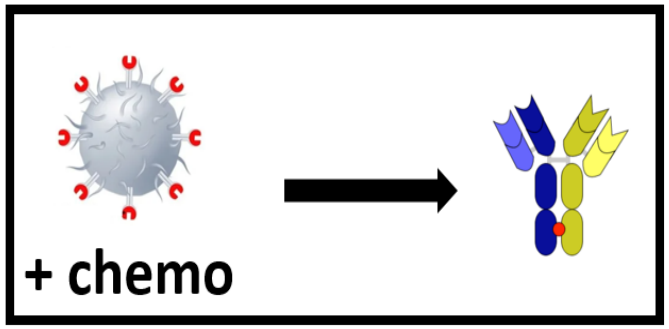
BsAb in 1st line



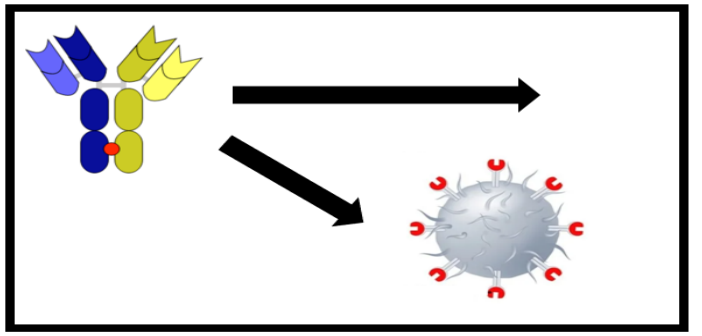
Post-CAR-T relapse



3rd line



CAR-T in 1st line



BsAb as a bridge vs. destination

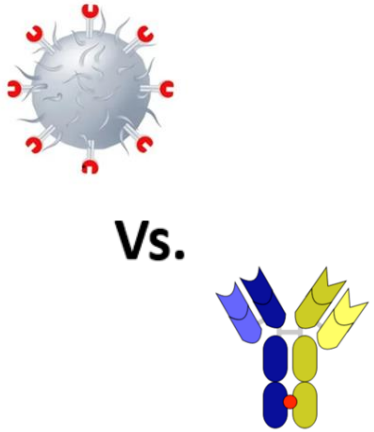
BsAb=bispecific antibody

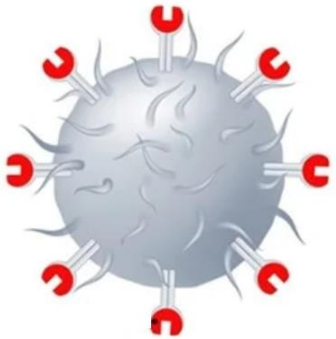
Frist line

Second line

Third line

Forth line



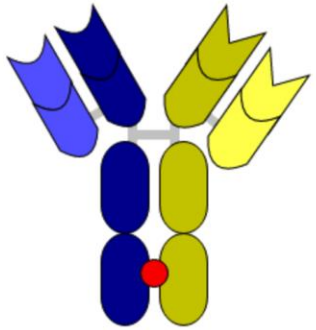


- Data: N of studies, follow-up, RWE
- One time treatment!
- Established in second line (OS benefit)

- Intent-to-treat results?
- Logistical challenges
  - Healthcare related
  - Patient related

- Off-the-shelf
- Patient convenience
- High potential for combination
- Retreatment potential

- Shorter follow-up
- Long-term AEs (infections, cytopenia, etc.)
- Physicians' comfort level?
- Approval in earlier lines?



Right treatment? Vs. Right sequence?

Fred Hutch
Cancer Center

Thank you

@mshadman

mshadman@fredhutch.org



UW Medicine