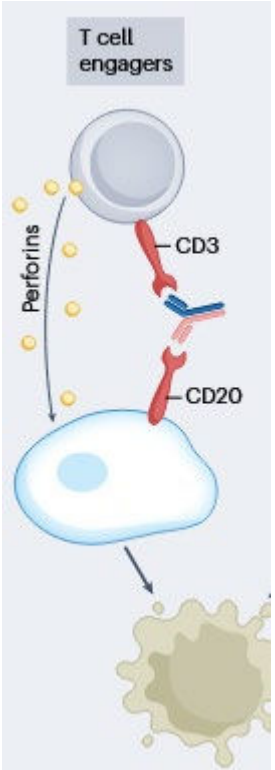
Disclosure Summary

Role	Relationship	Company/ies
Advisory Board	Advisor	Gilead-Kite, BMS-Juno, Miltenyi Biomedicine, Lilly Oncology, Incyte, Abbvie, Cargo, Beigene, Kite, Allogene, Astrazeneca, Genentech, Ipsen, and Galapagos
Research Funding	Researcher	Miltenyi Biotec, Lilly Oncology, Genentech
Scientific Advisory Board	Founder	Tundra Therapeutics

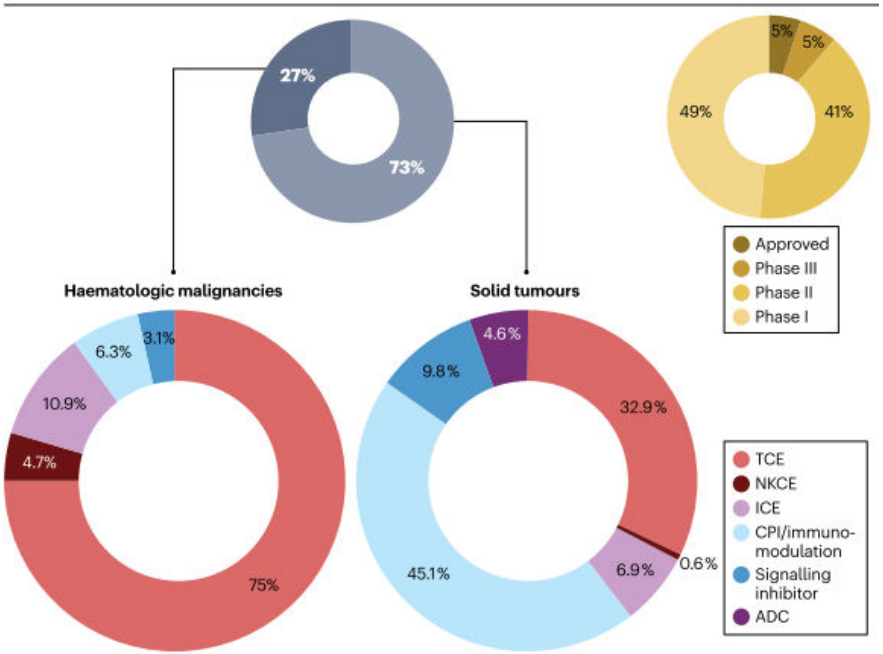
Bispecific antibodies: Ready or not here we come!

- T-cell engagers/bispecific antibodies bind two different antigens most commonly a cancer cell antigen and CD3 on T-cells
- Upon crosslinking, effector T cells kill target cancer cells and release cytokines with a risk profile similar to CAR-T cell therapy
- First approved T-cell engager was Blinatumomab in 2014 which has revolutionized the management of B-cell ALL



Paul et al. Nature Reviews Cancer, 2024

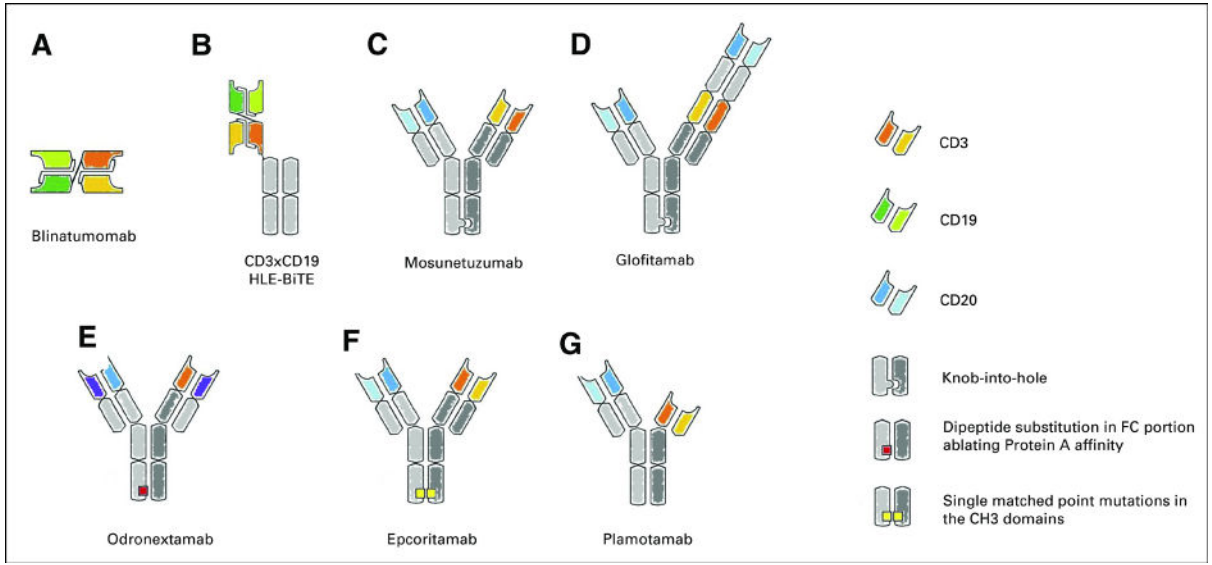
Clinical Development



>200 bispecific antibody treatments under development with the majority being for solid malignancies while to date most approval are in hematological malignancies

Klein et al. Nature Reviews Cancer, 2024

T cell Engagers in B-cell NHL



- TCE in lymphoma dominated by CD20xCD3 bispecific antibodies
- Powerful immunotherapeutic agents even in relapsed, refractory setting.
- Offers an immunotherapeutic approach similar to CAR-T without gene modification

Lussana, F. et al. *J Clin Oncol, 2021. 39(5): p. 444-455.*

From Third Line → First Line

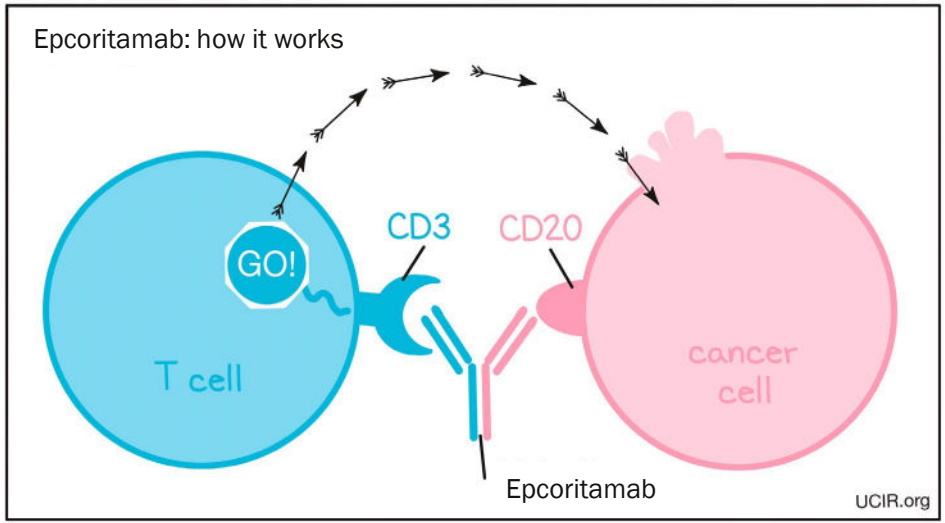
- Epcoritamab, Glofitimab approved in Third Line DLBCL
- Mosunetuzumab, Epcoritamab approved in Third line FL
- Ondronextamab approved in Europe for FL and DLBCL in third-line setting

Second line Clinical Trials

- STARGLO
- ECPOR NHL-2 Trial

Epcoritamab

- Phase I/II trial in R/R DLBCL
- Failed minimum two prior lines of therapy
  - prior CAR T-cell exposure=39%
  - Median 3 prior lines, range 2-11
- Step-up dosing, given subcutaneously.
- Safety
  - CRS Grade 1-2 ~50%, Grade 3+ 2.5%
  - ICANS Grade 1-2 6.5%, Grade 3+ 0.6%

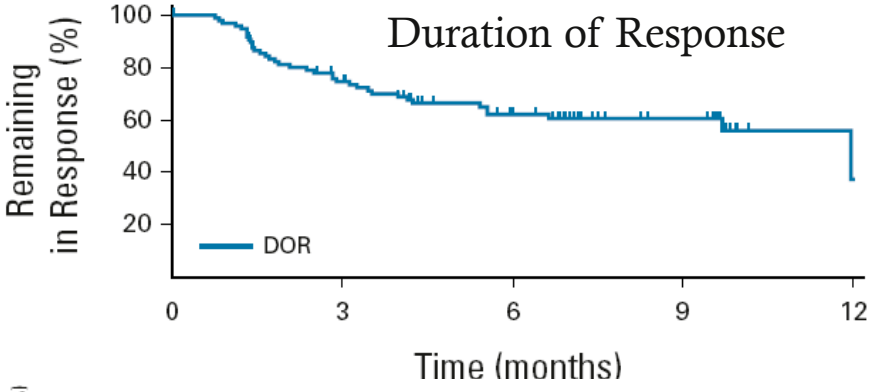


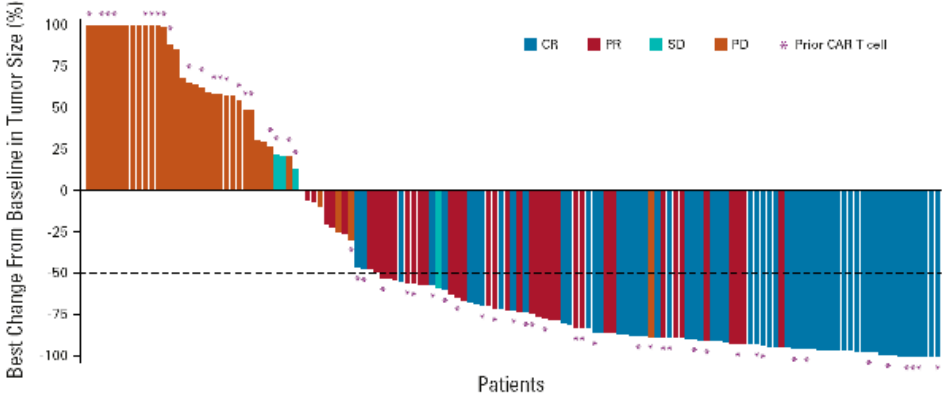
Thieblemont et al. JCO 2022
https://www.ucir.org/immunotherapy-drugs/epcoritamab-bysp

Outcomes

ORR=63%, CR=39%

- ORR for Prior CAR-T=54%
- ORR for CAR naïve=69%
- Limited follow-up, median DOR=12 months
- DOR of CR patients not reached
- ? Is this curative

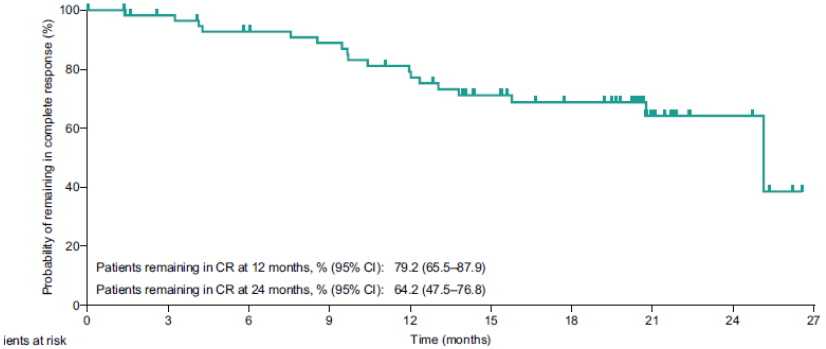


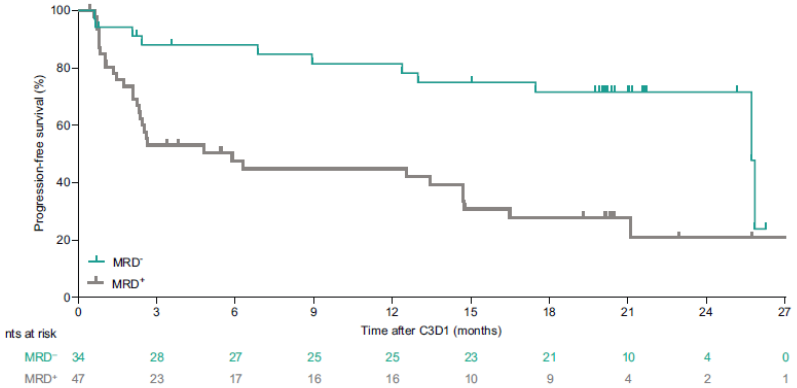


Thieblemont et al. JCO 2022

Long-term Outcomes

- 24-month PFS for Epcoritamab is 27.8% and OS is 44.6% for the entire population
- Of the 40.1% of patients who achieved a CR to epcoritamab; ~65% remained in CR at 24 months
- 119 patients were MRD evaluable, 45% were MRD negative which correlated with improved PFS

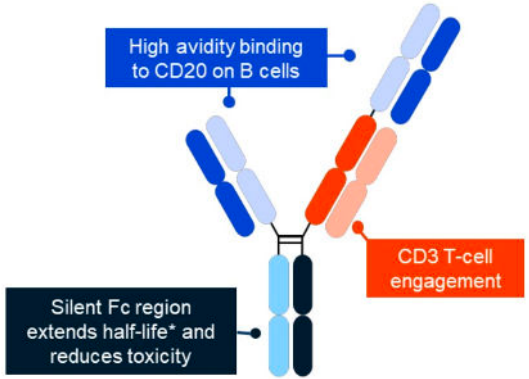




Thieblemont et al. *Leukemia* **38**, 2653–2662 (2024).

Glofitamab

- Glofitamab is a CD20xCD3 bispecific T-cell engage with a 2:1 configuration enabling bivalent binding to CD20 improving target-effector cell binding.
- Obinutuzumab 1000 mg given 7 days prior to deplete peripheral and tissue-based B-cells to mitigate severe CRS



Dickinson et al. NEJM 2022

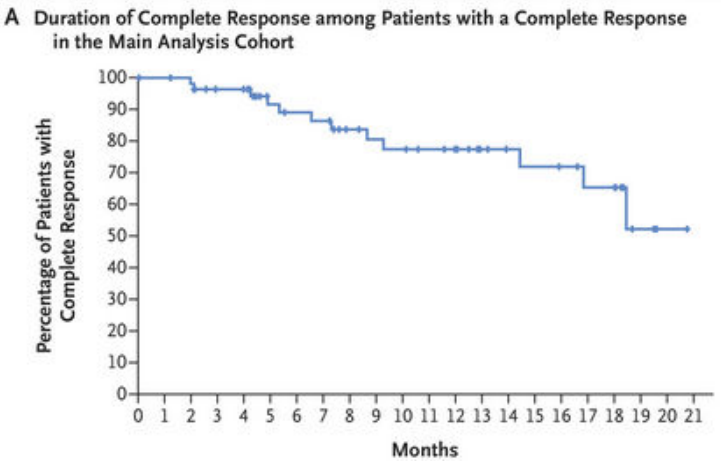
Glofitamab Outcomes

154 pts treated, median age 66, median 3 prior lines of therapy

- 33% received prior CAR T-cell therapy
- ORR=52%, CR=39% for all patients
- Among complete responders, 78% remained in CR at month 12
- Prior CAR-T CR rate 35% vs 42% no prior CAR)

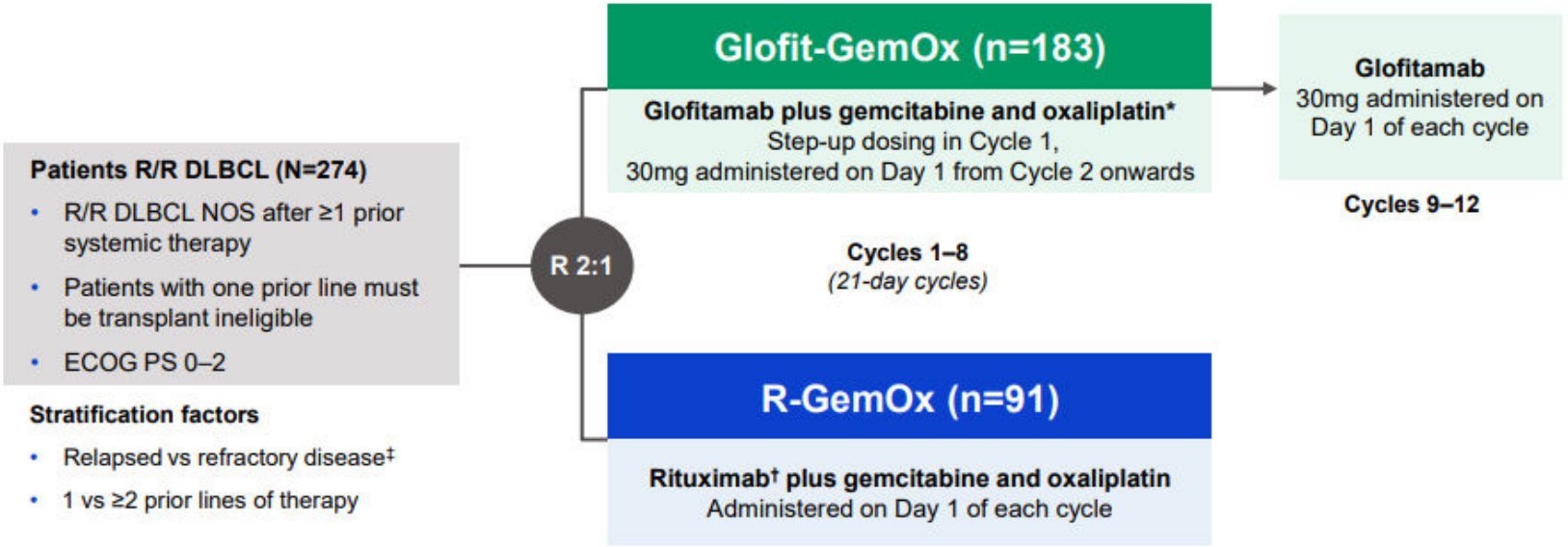
Safety

- CRS=97%, almost all grade 1-2
- ICANS=8%, again mostly grade 1-2
- Eight grade 5 events, mostly due to infections



Dickinson et al. NEJM 2022

STAR-GLO STUDY

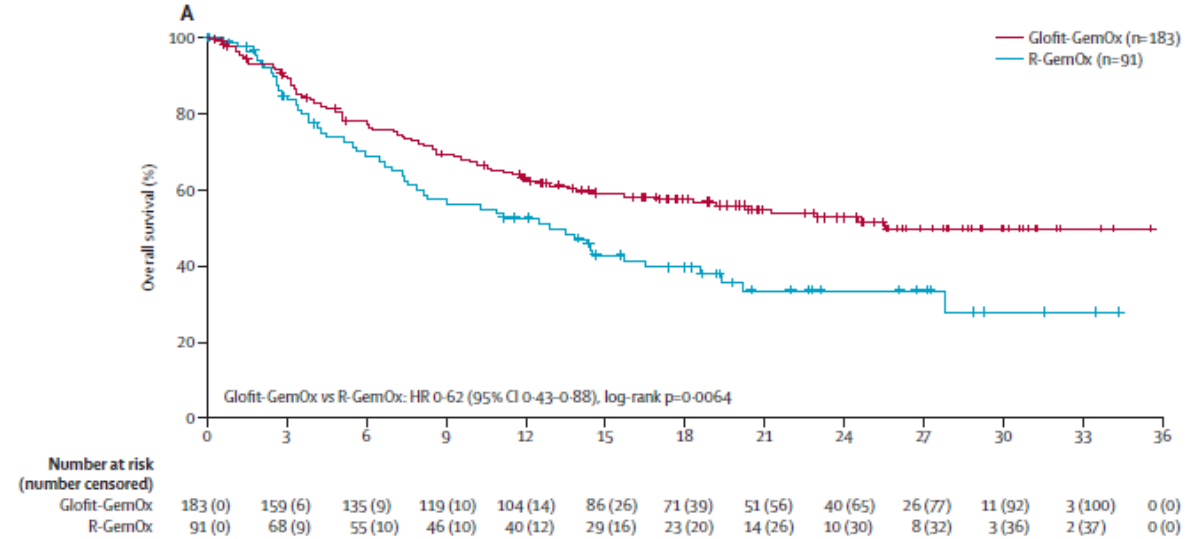


63% in both arms had 1 prior line of therapy
51% in R-GemOx, 58% Glofit-GemOx arms were primary refractory disease
<10% of patients with prior CAR T

Overall Survival Benefit

Median overall survival was significantly improved NR versus 9 months with 11.3 months follow-up

Most common reason for discontinuation in both groups was disease progression



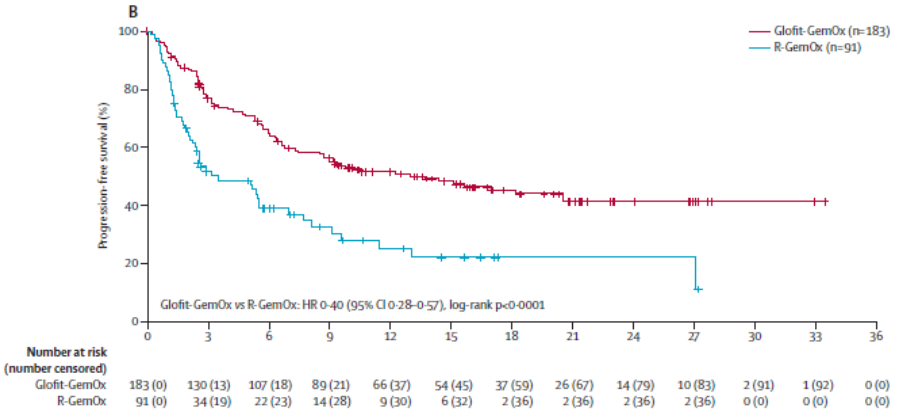
Abramson et al. Lancet 2024

PFS and Toxicities

Median PFS of 13.8 months versus 3.6 months with R-GemOx

Toxicities

- Grade 3+ CRS in 2% of patients
- Grade 2+ Neurologic events in 31% of patients
- Non-relapse mortality of 8% in Glofit arm versus 5%, largely driven by infectious complications



Abramson et al. Lancet 2024

EPCORE-NHL

- Epcoritamab + Gem/Ox for second-line and ASCT ineligible patients
- R/R large cell lymphoma ≥ 1 line of therapy
- Gem/Ox x 8 cycles with Epcoritamab on Days 1, 8 (step-up) and full dose on day 15

Treatment regimen: Epcoritamab SC 48 mg + GemOx IV						
Agent	C1	C2	C3	C4	C5–9	C10+
Epcoritamab	QW	QW	QW	Q2W	Q2W	Q4W
Gemcitabine	Q2W					
Oxaliplatin						

Key Demographics
Median age 72 (20-87)
Primary Refractory 52%
Prior CAR-T 28%
Prior ASCT 10%

Brody et al. Blood 2025 in press

Outcomes

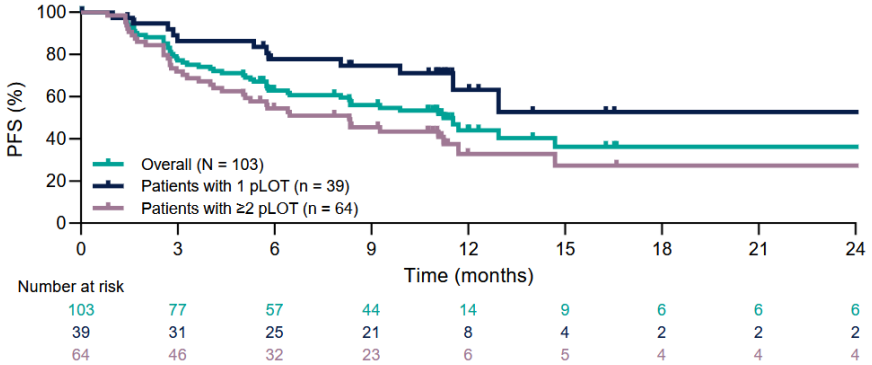
ORR of 85%

CR rate of 61%

Median time to response was 1.5 months

Median PFS was 11.2 months for all patients and 26.7 months for patients who achieved a CR

Median OS was 21.6 months



	IRC assessment N = 103	Investigator assessment N = 103
Overall response rate, n (%)	88 (85.4)	82 (79.6)
CR	63 (61.2)	60 (58.3)
PR	25 (24.3)	22 (21.4)
Stable disease, n (%)	3 (2.9)	7 (6.8)
Progressive disease, n (%)	8 (7.8)	9 (8.7)
Not evaluable, n (%)	4 (3.9)	5 (4.9)
Time to response, months, median (range)	1.5 (0.9–3.0)	1.5 (0.9–11.1)
Time to CR, months, median (range)	2.6 (1.3–22.1)	1.7 (1.3–10.7)

Brody et al. Blood 2025 in press

Toxicities

- CRS in 52% (all low grade), 1 patient with high grade CRS.
- Tocilizumab administered in 23% of patients
- Grade 3+ Infectious complications in 29% of patients, largely driven by COVID19 complications

Brody et al. Blood 2025 in press

Front-Line Studies

SKYGLO

- Pola-R-CHP vs Glofit-Pola-R-CHP

EPCORE

- R-CHOP vs Epcor-R-CHOP

Olympia

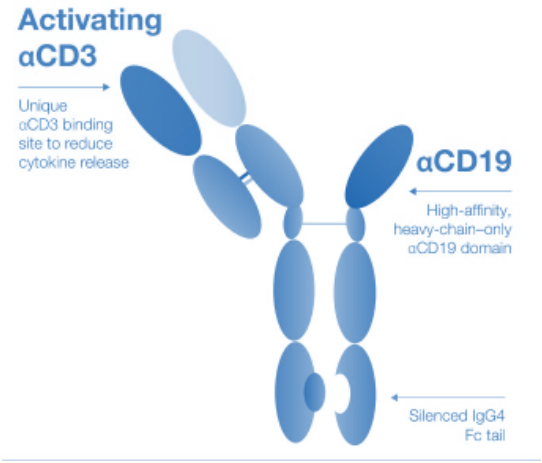
- R-CHOP vs Ondronextamab+CHOP

Results of these frontline studies may establish a new standard of care in DLBCL

Coming soon to a hospital near you!

AZD0486 is a novel IgG4 fully-human CD19xCD3 T cell engager currently being evaluated in clinical trials

- Administered with step-up dosing protocol
- 60% of patients had prior CAR-T
- Among 40 patients who received doses≥2.4 mg, the ORR was 47% with CR rate of 42%



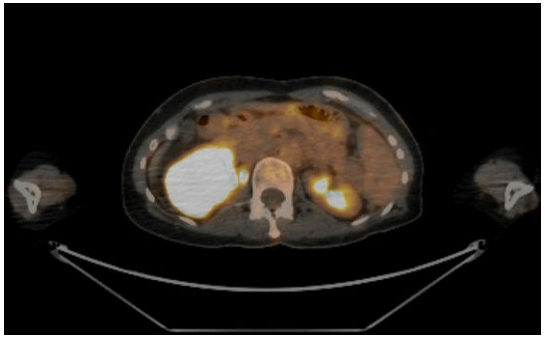
Gaballa et al. ASH 2024

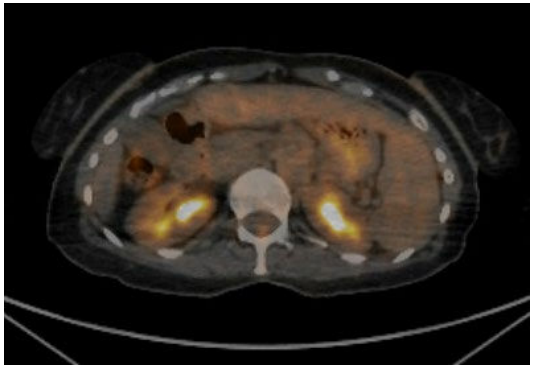
Case Study

55-year-old female with DLBCL, non-GCB phenotype

Treatment History:

- DA-EPOCH x 6 (April-August 2020), PR
- R-GDP x 2 (Dec 2020- Jan 2021), PD
- Polatuzumab-Rituximab x1 (Feb 2021), PD
- Tisagenlecleucel (CART) after Bendamustine LD, Progression
- Pembrolizumab x 3 (April-June 2021), mixed response
- EBRT 50.4 Gy in 28 fractions to mediastinal and neck disease, July-Aug 2021, CR-> PD within 4 months
- PET/CT (upper image): New renal mass, biopsy proven DLBCL
- Started AZD0486; achieved MRD negative CR (lower image), proceeded with allogeneic stem cell transplant, no relapse +3 years

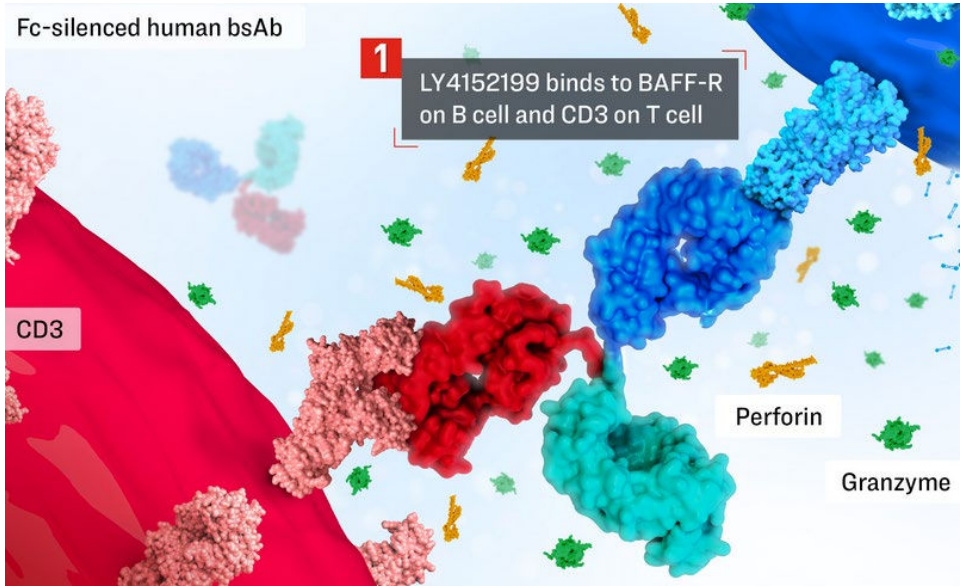




BAFF Bispecific Antibody

LY4152199 BAFF redirected bispecific antibody under development

No data to date, but BAFF CAR-T has shown efficacy in early phase clinical trils



Conclusions

- T-cell engagers have revolutionized the management of B-cell malignancies and are currently utilized in the 3+ line of therapy
- Second line approvals are pending, and frontline studies are ongoing and may change our upfront approach
- New targets, CD19, BAFF, CD22 are under investigation and will offer more therapeutic options for our patients

Thanks!

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