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ASSOCIAZIONE ITALIANA CONTRO LE LEUCEMIE-LINFOMI E MIELOMA ONLUS

BITEs and DARTs in Hematological Malignancies

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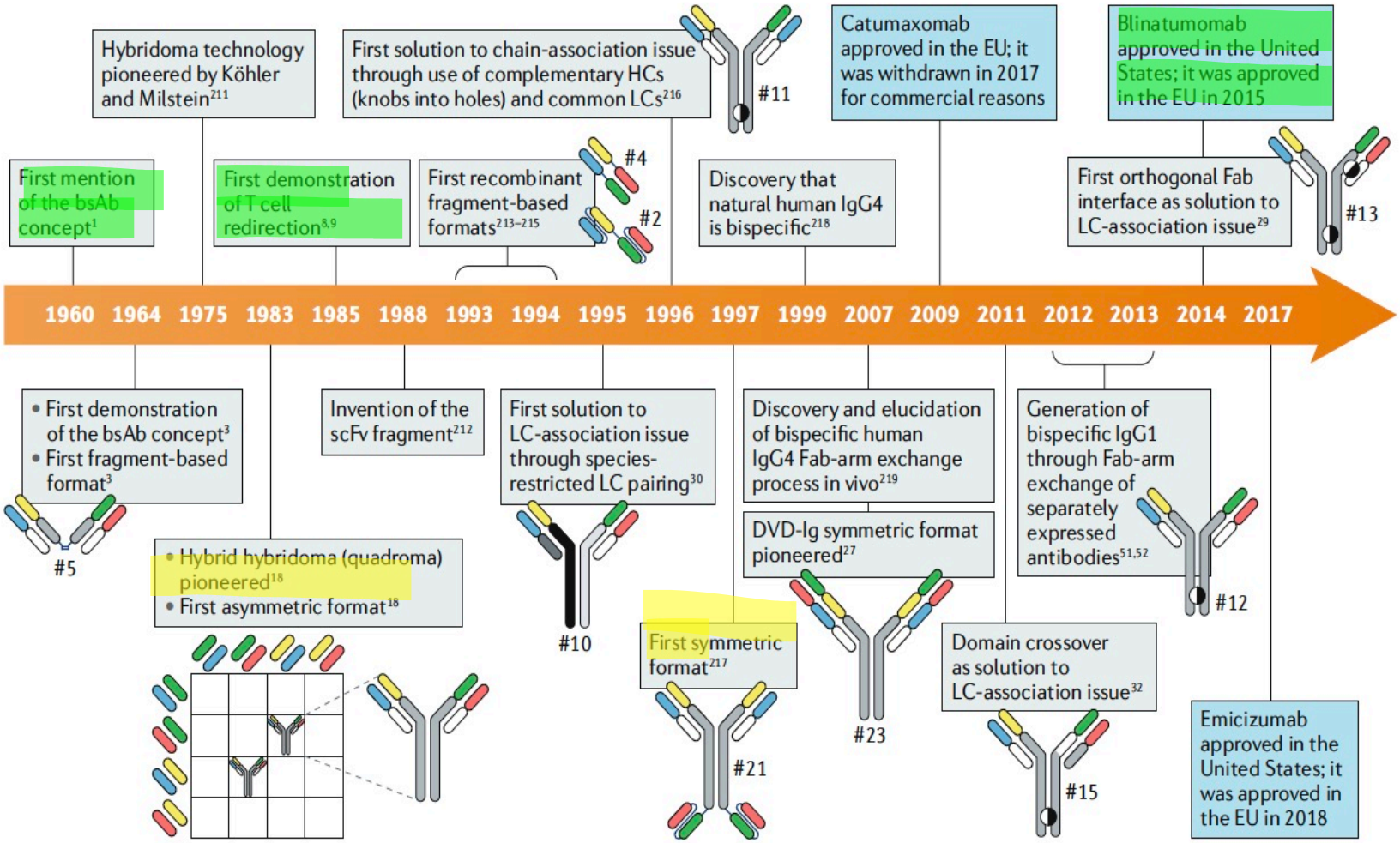
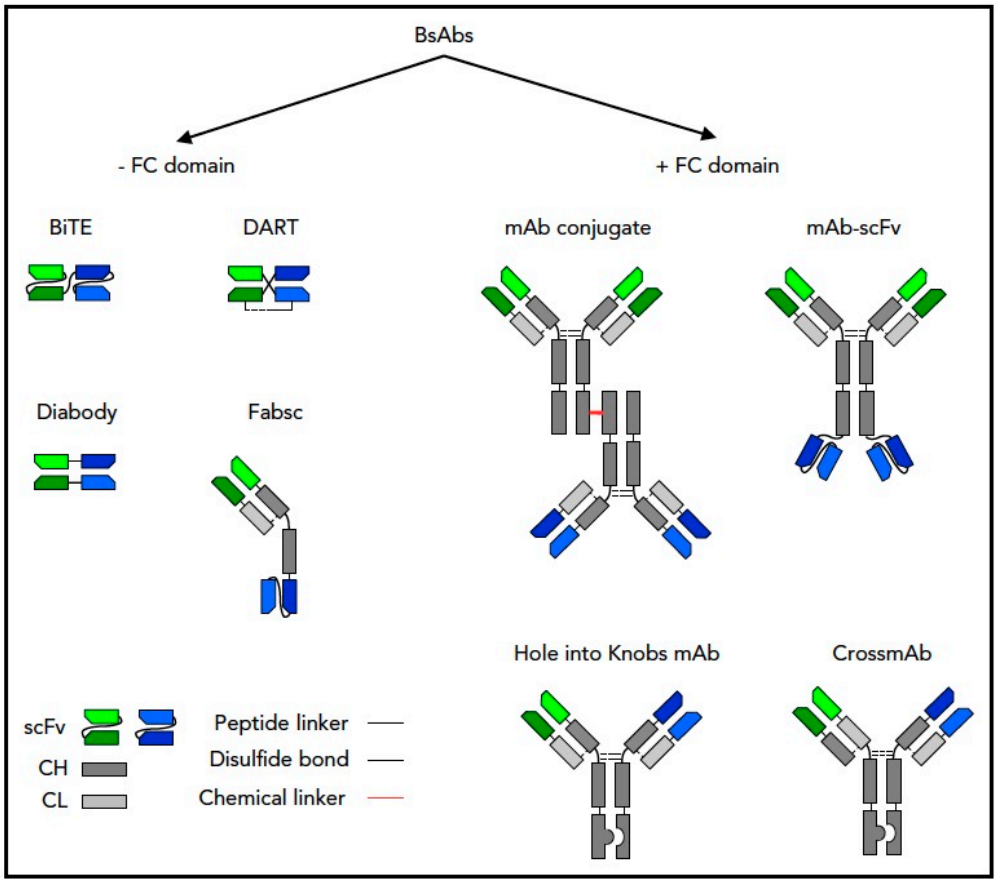
Development of Bispecific Antibodies



Bispecific Antibodies

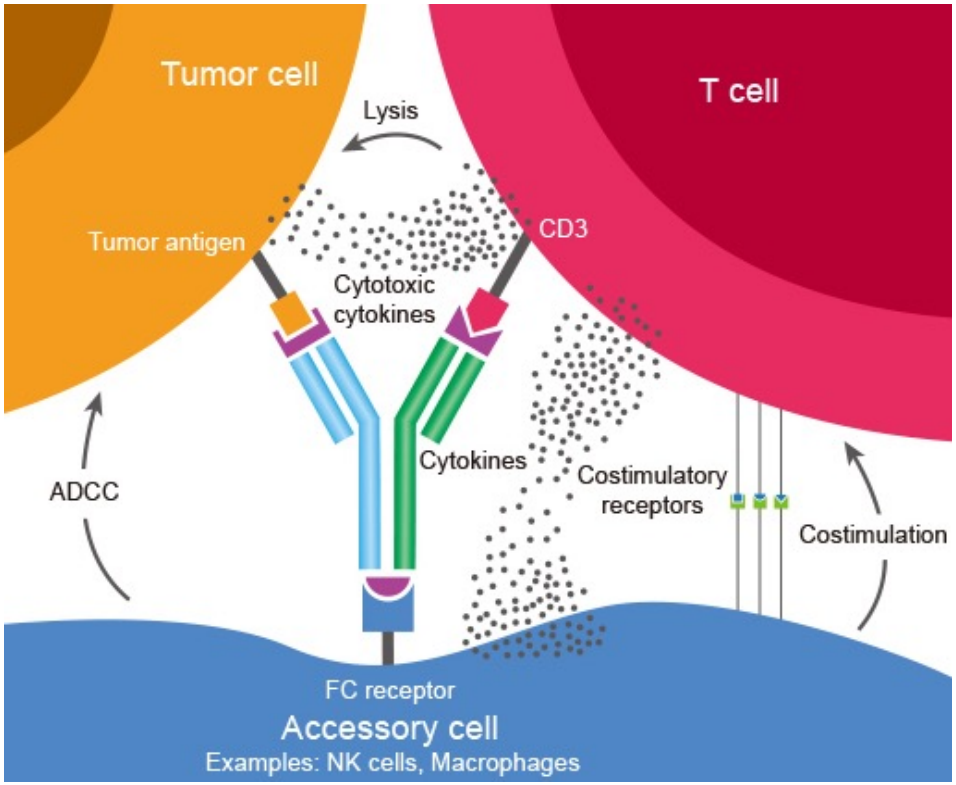


BITE = Bi-specific T-cell engager

DART = Dual-Affinity Re-Targeting Antibody

- By recombinant DNA methodologies a range of recombinant BsAbs with over 50 different formats are now being produced
- BsAbs are divided into two classes – those bearing an Fc region and those without an Fc region

Bispecific Antibodies



- BsAbs redirect immune effector cells in close proximity to malignant cells
- T cells undergo activation due to CD3 cross-linking, which is associated with cytokine release (IFN-g, TNF-a, IL-2, -6, -10) and cytotoxic granule release (granzyme B)
- T-cell activation is MHC-unrestricted and no longer depends on the native TCR specificity of the activated T cell

Bispecific Antibodies

- The Fc domain adds stability and increases the half-life of the molecule in vivo
- It induces ADCC by recruiting NK cells and/or macrophages, and mediates CDC by fixing complement
- Intricate interplay among Ab affinity, epitope location within the targeted antigen, and antigen density and mobility on the target cell surface, all of which contribute to optimal T-cell activation

BsAbs in Clinical Development

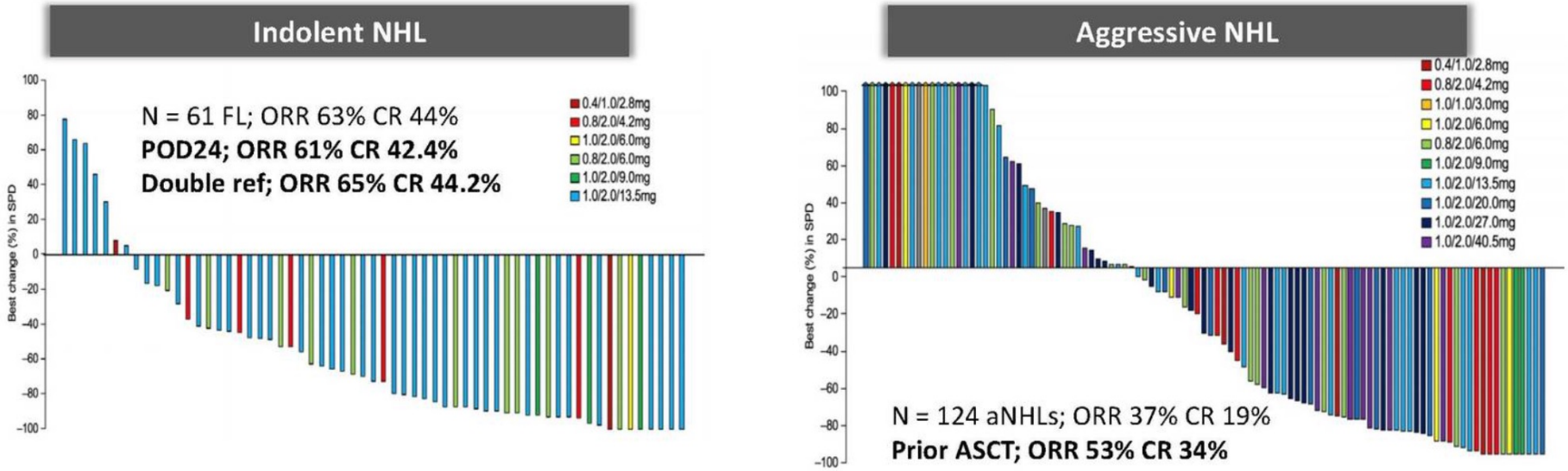
Bispecifics	Indications	Lymphoma type	ORR	CR	CRS	CRS Gd 3-4
Mosunetuzumab[1]	r/r NHLs	iNHL aNHL	63% (42/67) 37% (46/124)	44% 19%	29%	1%
Odranextamab[2]	r/r NHLs	FL DLBCL	96% 58%	77% 42%	59%	6.4%
Glofitamab*[3]	r/r NHLs	iNHL aNHL	67% (12/18) 49% (42/85)	52% 31%	56.4%	3.2%
Epocritamab[4]	r/r NHLs	FL DLBCL	100% (6/6) 56% (5/9)	0% 44%	59%	0%
Plamotamab[5]	r/r NHLs	FL DLBCL	75% 57%	38% 38%	55%	5%

* Pretreatment with Obinutuzumab 7 days prior to Glofitamab to debulk and mitigate CRS

[1]Schuster *et al*, ASH 2019; abstr 6; [2]Bannerji *et al*, ASH 2019; abstr 762; [3]Dickinson et al, EHA 2020, abstr 241; [4]Hutchings et al, EHA 2020, abstr 1218; [5]Patel et al, ASH 2019, abstr 4079

Mosunetuzumab

- Phase 1: 270 patients with R/R NHLs (66.7% aNHL, 31.5% iNHL) incl. 30 prior CAR T-cell



- 29% experienced CRS (only 1% Gd 3-4); and 44% experienced neuro AEs (10% Gd 3-4)

Schuster aet al., ASH 2019, Abs 6

Epcoritamab (sc)

Table: Antitumor activity of epcoritamab in evaluable patients with R/R B-NHL

	DLBCL		FL	
	≥12 mg	≥48 mg	≥0.76 mg	≥12 mg
Evaluable patients	18[a]	7	8	3
Overall response rate, %	66.7	100	100	100
Complete response, n (%)	6 (33.3)	2 (28.6)	2 (25.0)	2 (66.7)
Partial response, n (%)	6 (33.3)	5 (71.4)	6 (75.0)[b]	1 (33.3)
Stable disease, n (%)	1 (5.6)	0	0	0
Progressive disease, n (%)	5 (27.8)	0	0	0

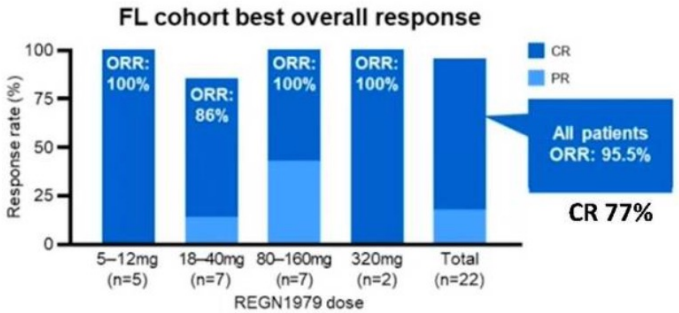
Based on data snapshot taken on July 6, 2020. Response assessments were based on Lugano 2014 response criteria by investigator assessment (modified response evaluable population).

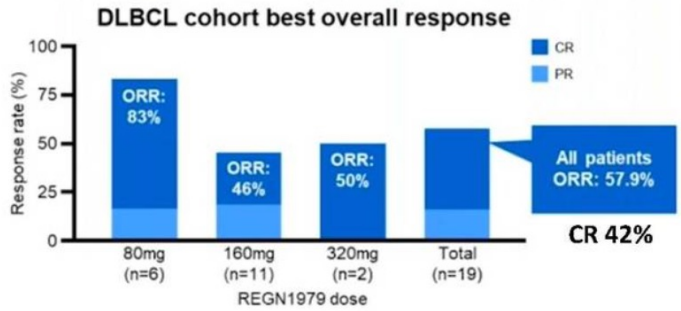
[a]Excludes 1 patient who discontinued before first assessment due to COVID-19.

[b]4/6 patients with partial response did not have PET scans (not mandatory until recent protocol amendment).

M Hutchings, ASH, 2020

Odronextamab





SAFETY PROFILE and ADVERSE EVENTS

- **CRS 59.1%; Gr 3-4 CRS 6.4%**
- Other Gr 3-4 TEAEs:
  - Anaemia (21.8%)
  - Hypophosphataemia (19.1%)
  - Neutropenia (19.1%)
  - Lymphopenia (19.1%)
  - Thrombocytopenia (13.6%)
- 11 patients died on study

Bannerji et al, *ASH* 2019; abstr 762

Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial

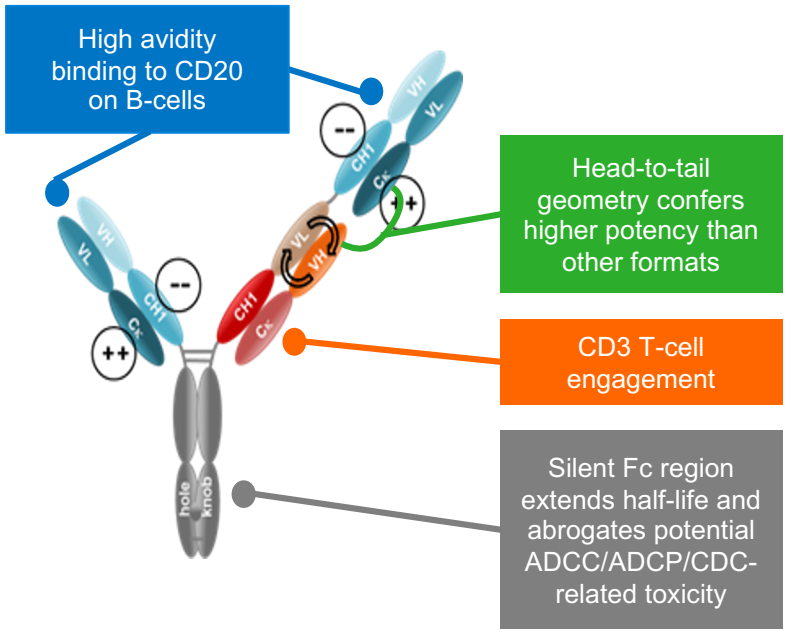
Martin Hutchings, PhD[1]; Franck Morschhauser, MD, PhD[2]; Gloria Iacoboni, MD[3,4]; Carmelo Carlo-Stella, MD[5]; Fritz C. Offner, MD, PhD[6]; Anna Sureda, MD, PhD[7]; Gilles Salles, MD[8]; Joaquín Martínez-Lopez, MD, PhD, MBA[9]; Michael Crump, MD[10]; Denise N. Thomas, MSc[11]; Peter N. Morcos, PharmD[11]; Cristiano Ferlini, MD[11]; Ann-Marie E. Bröske, PhD[12]; Anton Belousov, PhD[13]; Marina Bacac, PhD[13]; Natalie Dimier, PhD[14]; David J. Carlile, PhD[14]; Linda Lundberg, PhD[15]; David Perez-Callejo, MD, PhD[15]; Pablo Umaña, PhD[13]; Tom Moore, MD[12]; Martin Weisser, MD[12]; and Michael J. Dickinson, MBBS, DMedSci[16]

J Clin Oncol 00. © 2021

Glofitamab (CD20-TCB, RG6026, RO7082859) is a novel T-cell-engaging bispecific full-length antibody with a unique 2:1 molecular configuration

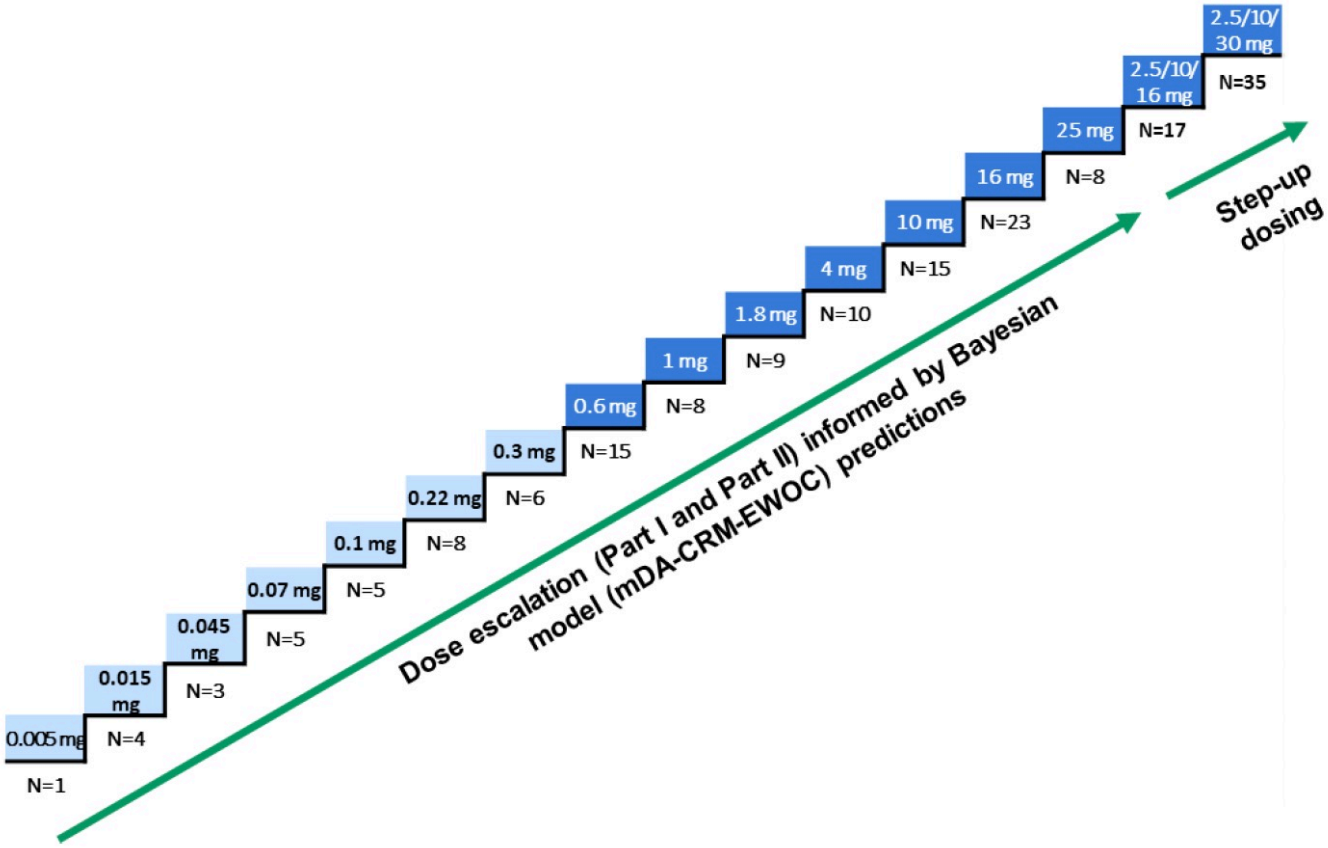
Glofitamab's molecular configuration is associated with superior potency under experimental conditions vs other CD20-CD3 bispecific antibodies with a 1:1 format, enabling concomitant treatment with other CD20 directed antibodies[3,4]

Induces rapid T-cell activation, proliferation and cytokine release, leading to target cell lysis



CH1, constant heavy 1; CK, kappa light chain; Fc, fragment crystallisable; VH, variable heavy; VL, variable light

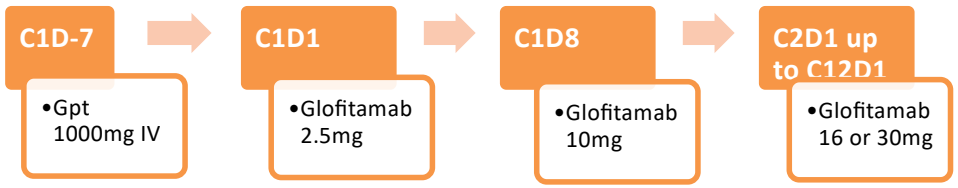
Treatment Schedule



Treatment Schedule & Key Inclusion Criteria

Treatment schedule

- 1000mg Gpt 7 days prior to glofitamab administration
- Glofitamab IV step-up doses on C1D1 and D8 and at target dose from C2D1 (2.5/10/16mg or 2.5/10/30mg)
- Cycle 1 was 14-days long; glofitamab was given Q3W thereafter for up to 12 cycles



Key inclusion criteria

- Age ≥18 years
- CD20+ B-cell R/R NHL
- ≥1 prior therapy
- ≥1 measurable lesion
- Adequate haematological and liver function
- ECOG PS ≤1

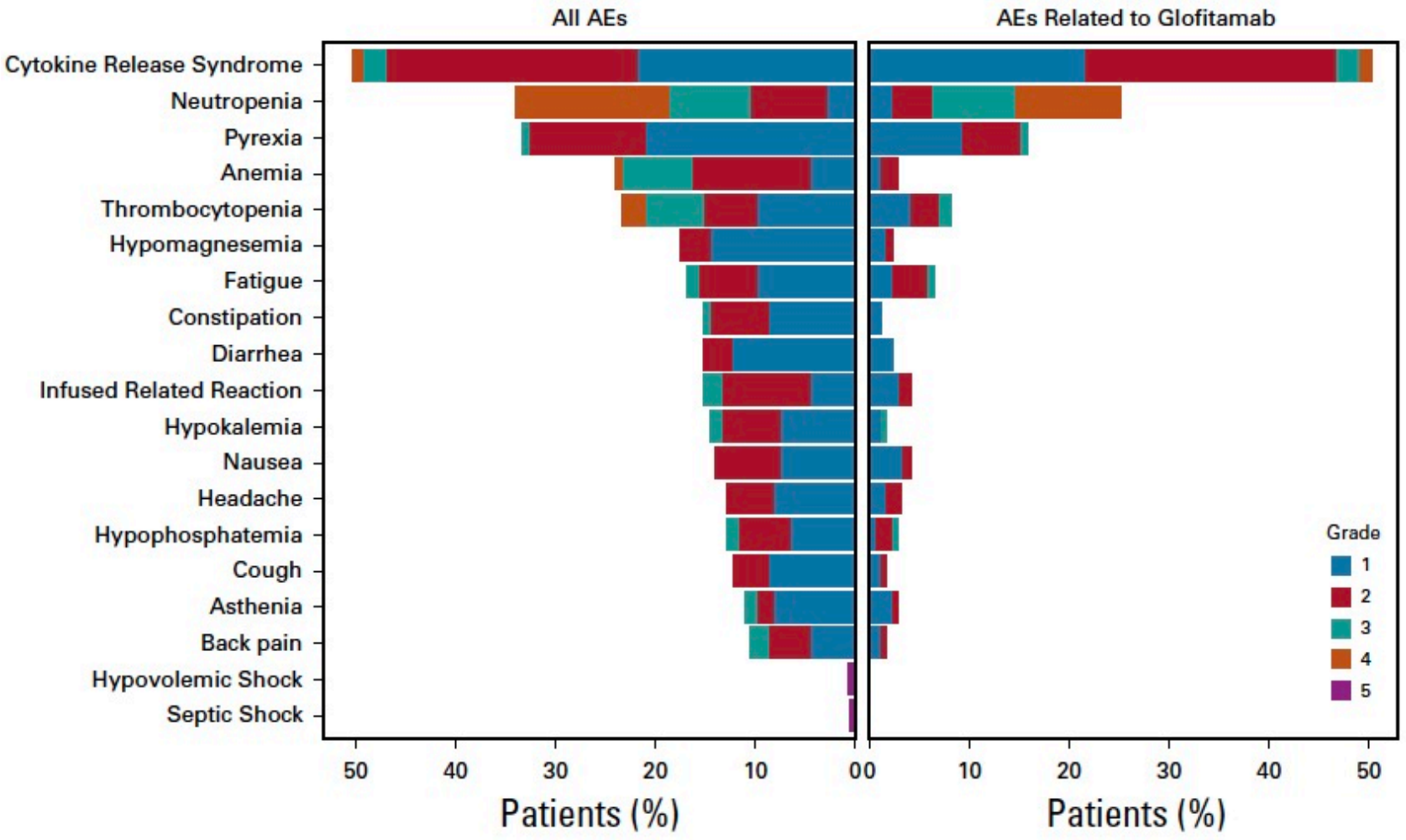
Primary objectives

- Evaluate safety, tolerability, PK, and anti-tumor efficacy (Lugano criteria)[1]
- Determine MTD/OBD and RP2D

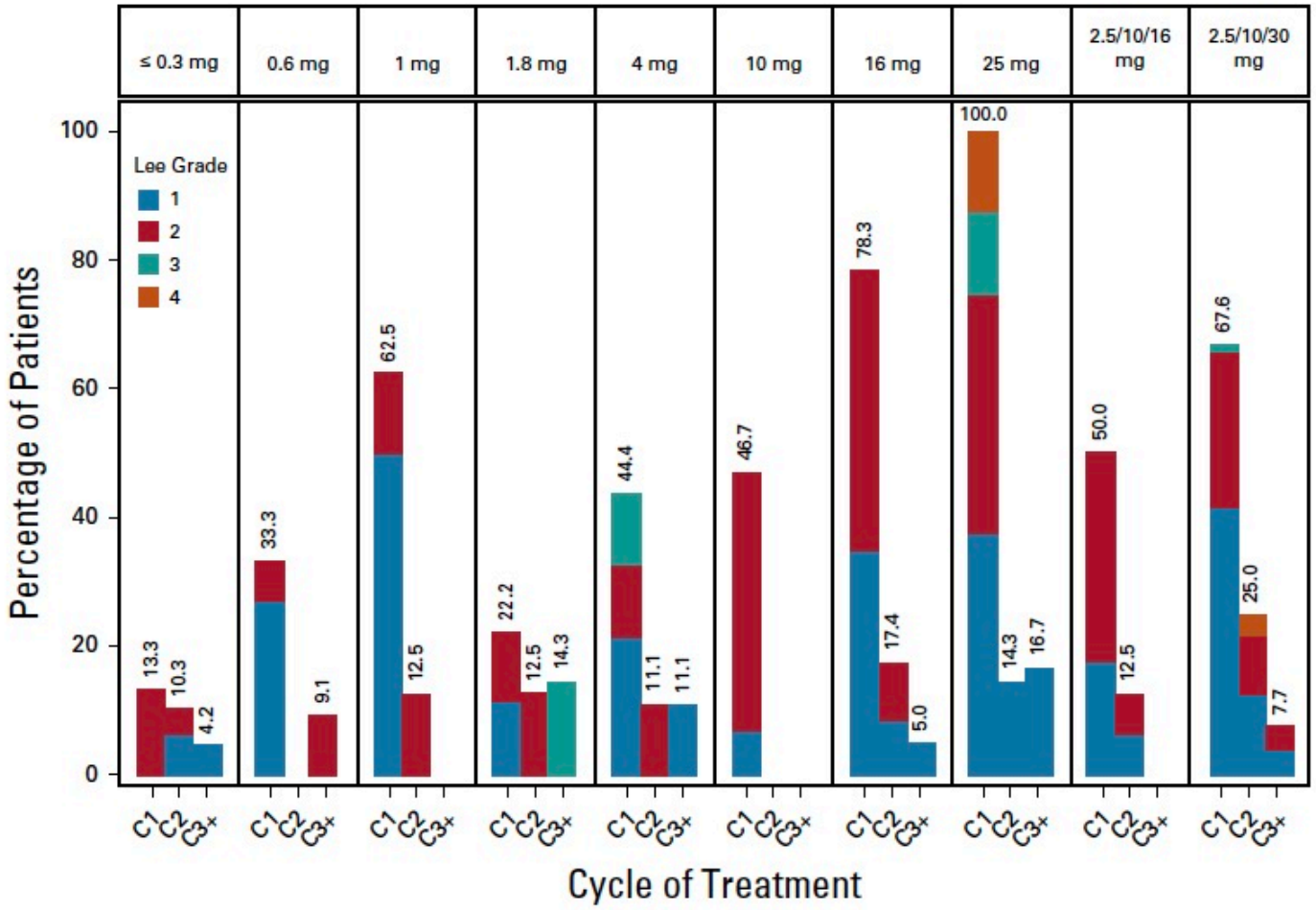
Patient Characteristics

Characteristic	All Glofitamab Cohorts (N = 171)	RP2D Glofitamab Cohort 2.5/10/30 mg (n = 35)
Age, years		
Median	64	66
Histology subtype, No. (%)		
DLBCL	73 (42.7)	5 (14.3)
FL grades 1-3A	44 (25.7)	21 (60.0)
DLBCL arising from FL	29 (17.0)	3 (8.6)
Richter's transformation	10 (5.8)	2 (5.7)
PMBCL	3 (1.8)	0
Others[b]	12 (7.0)	4 (11.4)
Prior autologous stem-cell transplant, No. (%)	41 (24.0)	9 (25.7)
Prior CAR-T therapy, No. (%)	3 (1.8)	1 (2.9)
Prior lines of therapy, No.		
Median	3	3
Range	1-13	1-12
Refractory to any prior therapy, No. (%)		
Refractory	155 (90.6)	29 (82.9)
Relapsed	16 (9.4)	6 (17.1)

Adverse Events ≥10%



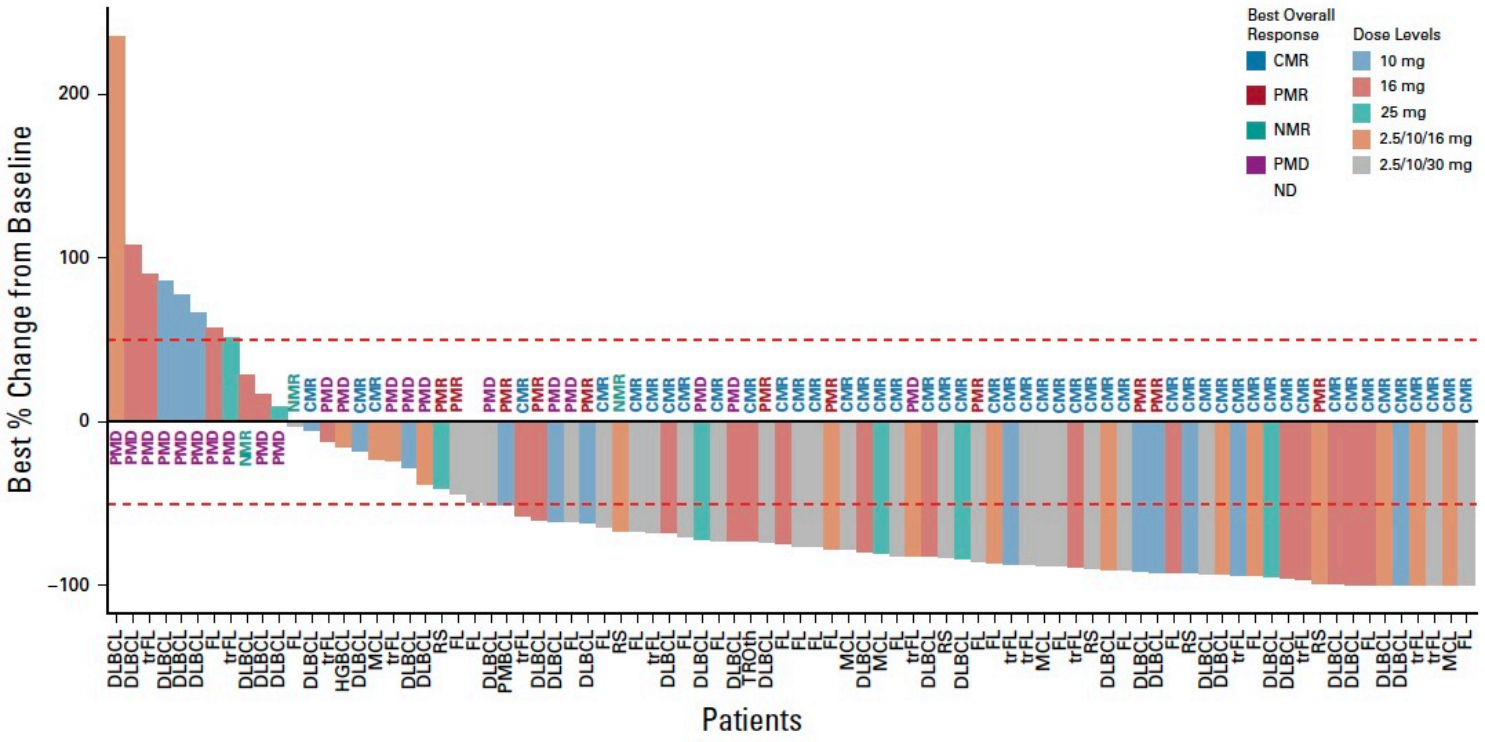
Incidence of CRS by Cycle and Dose



CRS was predominantly confined to cycles 1 and 2

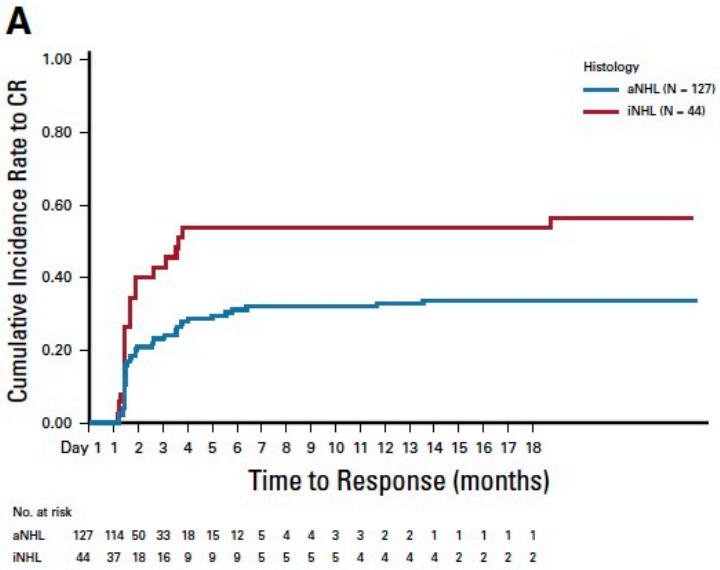
Step-Up Dosing allowed the administration of a high target dose (30 mg)

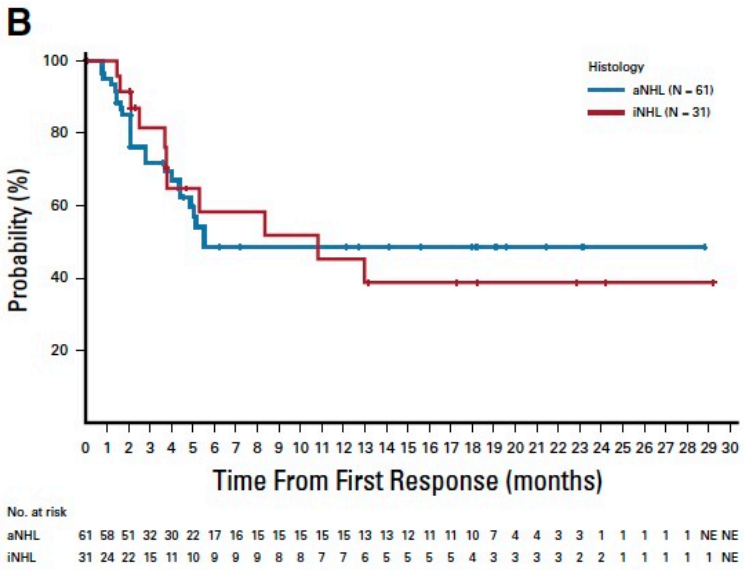
Waterfall Plot of the BOR



- Aggressive B-NHL
  - All cohorts, ORR and CR were 48.0% and 33.1%, respectively
  - RP2D, ORR and CR were 71.4% and 64.3%, respectively

Time to CR & DOR

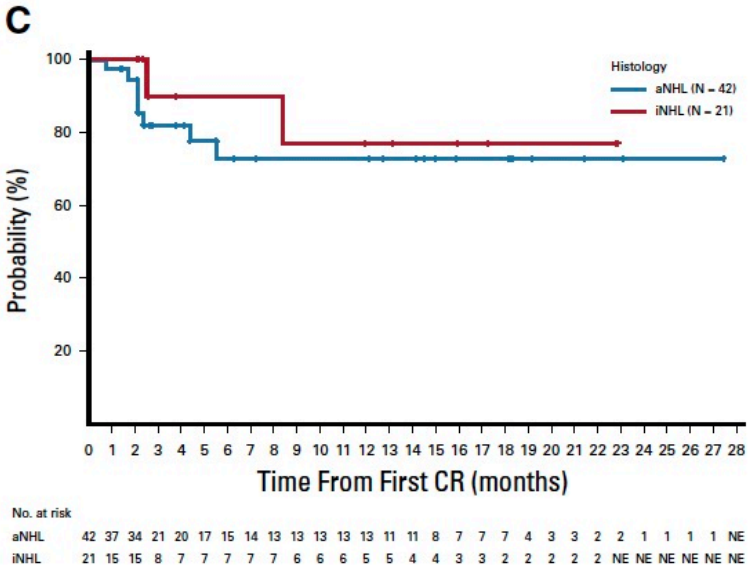


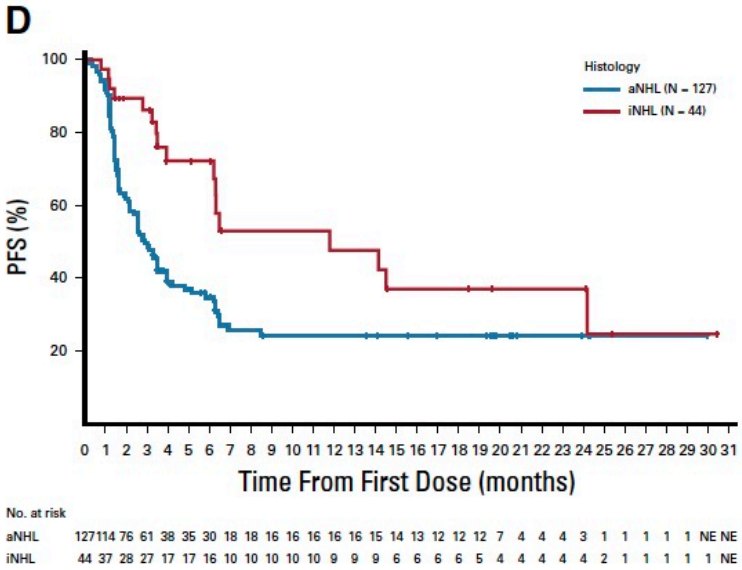


Time to CR was short, with the majority occurring by cycle 3

In aggressive NHL, the mDOR was 5.5 months

Duration of CR and PFS

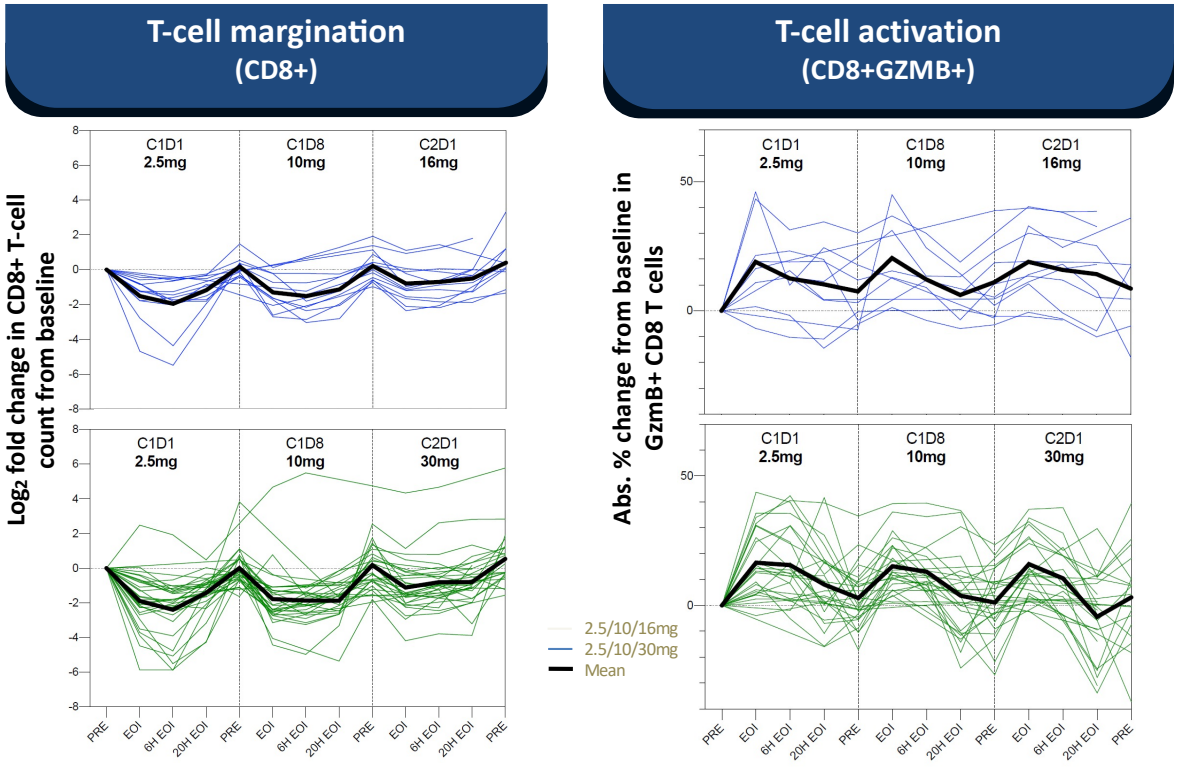




Median DOCR not reached
Of 63 patients with CR
53 (84.1%) ongoing CR with a maximum observation of 27.4 mos

The median PFS was 2.9 months, with a plateau of approximately 24% from 8 months onward

Pharmacodynamic effects are observed at all doses of glofitamab



- **A transient reduction in peripheral T cells* was observed after each glofitamab infusion**
  - strongest effects after first glofitamab infusion
  - consistent with T-cell margination described with other CD3 bispecifics
- **T-cell activation (granzyme B+ T cells*) was observed with each glofitamab infusion**
  - Increased activation with 30mg vs 16mg dose