3rd Cuneo City ImmunoTherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies 2023

CUNEO
May 18-20, 2023
Spazio incontri Fondazione CRC

Organized by Prof. Massimo Massaia, SC Ematologia AO S.Croce e Carle, Cuneo, Italy
and Centro Interdipartimentale di Ricerca in Biologia Molecolare (CIRBM), Torino, Italy

HUMANITAS UNIVERSITY

HUMANITAS CANCER CENTER

Curing r/r DLBCL with Bispecific Antibodies

Carmelo Carlo-Stella, MD

Department of Biomedical Sciences, Humanitas University, Milano, Italy

Department of Oncology and Hematology, Humanitas Research Hospital, Milano, Italy

3rd Cuneo City Immunotherapy Conference (CCITC) - May 18-20, 2023 - Cuneo

Disclosures

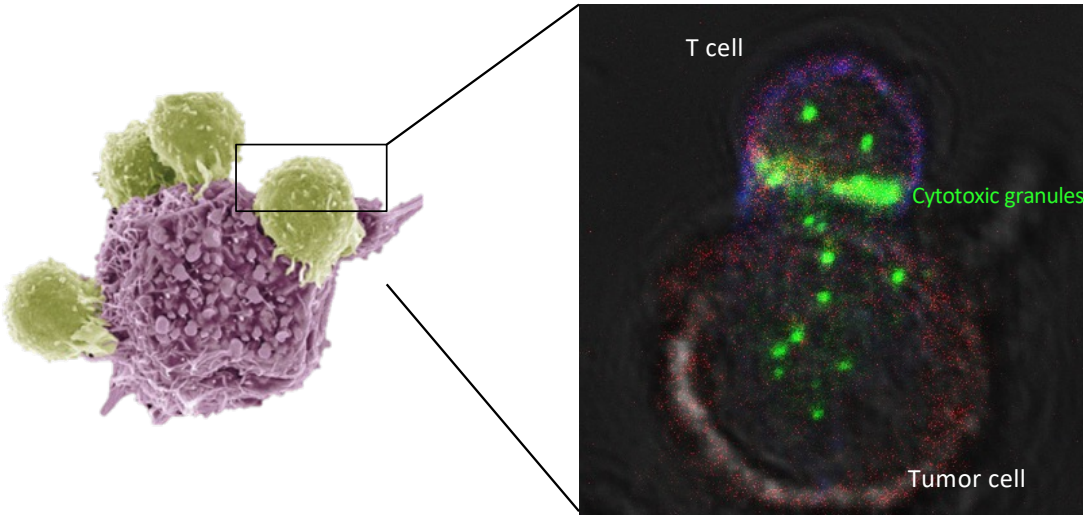
- Advisory Board
  - Sanofi, ADC Therapeutics, Bristol-Myers Squibb/Celgene, Roche, Karyopharm, Novartis, Scenic Biotech, Janssen Oncology, SOBI
- Consultancy
  - Sanofi, ADC Therapeutics
- Honoraria
  - Janssen Oncology, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Takeda, Roche, Incyte, ADC Therapeutics, Gilead
- Research Support
  - Sanofi, ADC Therapeutics, Roche

Features of T-cell Bispecific Antibodies

Simultaneous binding to

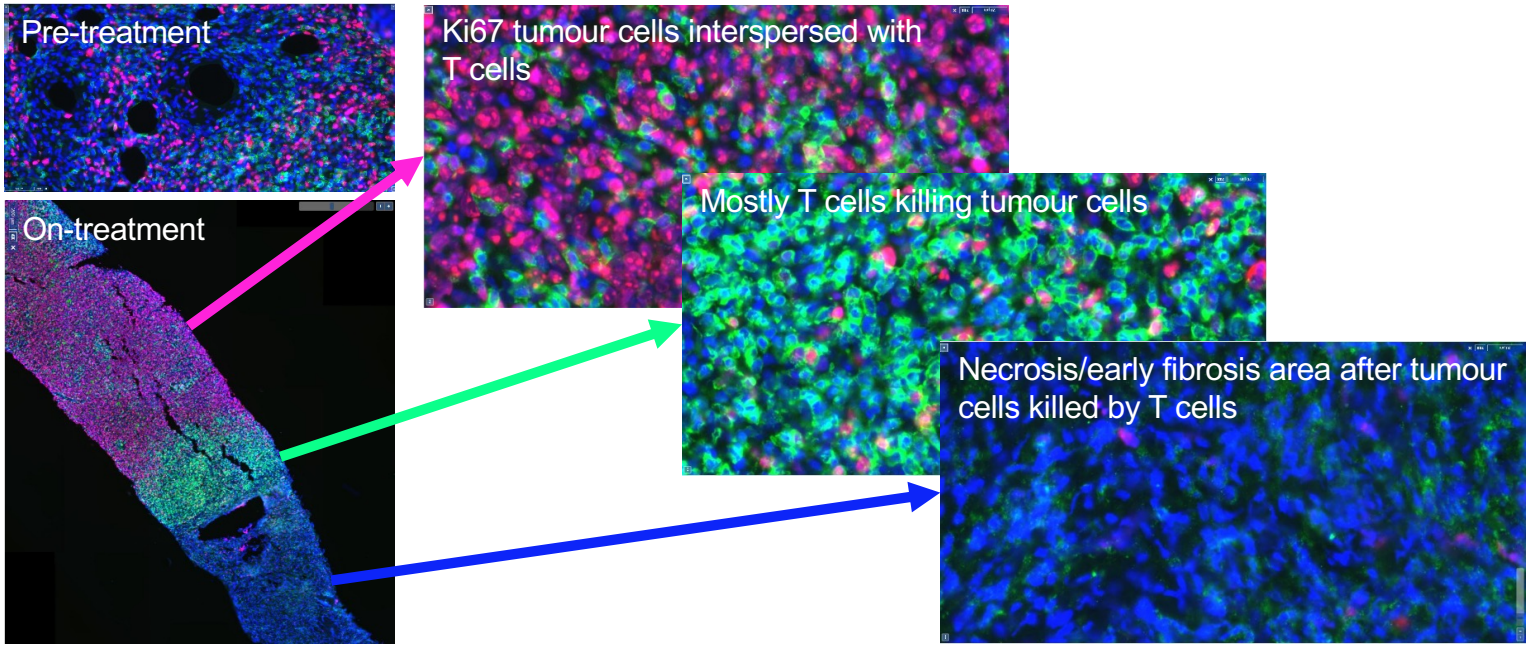
tumor antigen and CD3ε chain of TCR independent of peptide-MHC complex;

Recruitment of endogenous T cells: 4 x 10^{11} in the circulation



- **T cell engagement, activation and killing** of tumor cells by cytotoxic granules
- **T cell proliferation** (expansion) at site of activation (blood? Lymph nodes)
- **Cytokine, chemokine release leading to recruitment of additional T-cells**
- Very high potency with EC_{50} values in the fM to pM range
- **Serial killing of tumor cells, activity at low effector-to-target (E:T) ratio**
- T cell killing independent of specificity, activation and differentiation status

Glofitamab – Mechanism of Action



CD8/Ki67 IF (green=CD8, pink=Ki67, blue=DAPI)

EPCORE NHL-1: LBCL Expansion Cohort

Dose escalation → **Dose expansion data cutoff: January 31, 2022**
Median follow-up: 10.7 mo

B-NHL:

- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

Key inclusion criteria:

- R/R CD20+ mature B-cell neoplasm
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T allowed

Step-up dosing[a]

Epcoritamab SC RP2D 48 mg
QW C1–3,
Q2W C4–9,
Q4W C10+

→ **Treatment until PD[b,c] or unacceptable toxicity**

→ **LBCL Cohort N=157**
DLBCL, HGBCL, PMBCL, and FL Gr3B

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 h in this part of the study
- **Primary endpoint:** ORR by independent review committee (IRC)
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, and safety/tolerability

[a]Step-up dosing (priming 0.16 mg and intermediate 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [b]Radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [c]Measurable disease with CT or MRI scan with involvement of ≥2 lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm (or 1 lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm) and FDG PET scan that demonstrates positive lesion(s) compatible with CT-defined (or MRI-defined) anatomical tumor sites for FDG-avid lymphomas. ClinicalTrials.gov: NCT03625037. EudraCT: 2017-001748-36.

Thieblemont C, et al. EHA 2022 oral presentation

Patients Were Challenging to Treat and Highly Refractory

Demographics	LBCL, N=157
Median age (range), y	64 (20–83)
<65 y, n (%)	80 (51)
65 to <75 y, n (%)	48 (31)
≥75 y, n (%)	29 (18)
ECOG PS, n (%)	
0	74 (47)
1	78 (50)
2	5 (3)
Disease Characteristics[a]	**LBCL, N=157**
Disease type, n (%)	
DLBCL	139 (89)
De novo	97/139 (70)
Transformed	40/139 (29)
Unknown	2/139 (1)
HGBCL	9 (6)
PMBCL	4 (3)
FL Gr3B	5 (3)

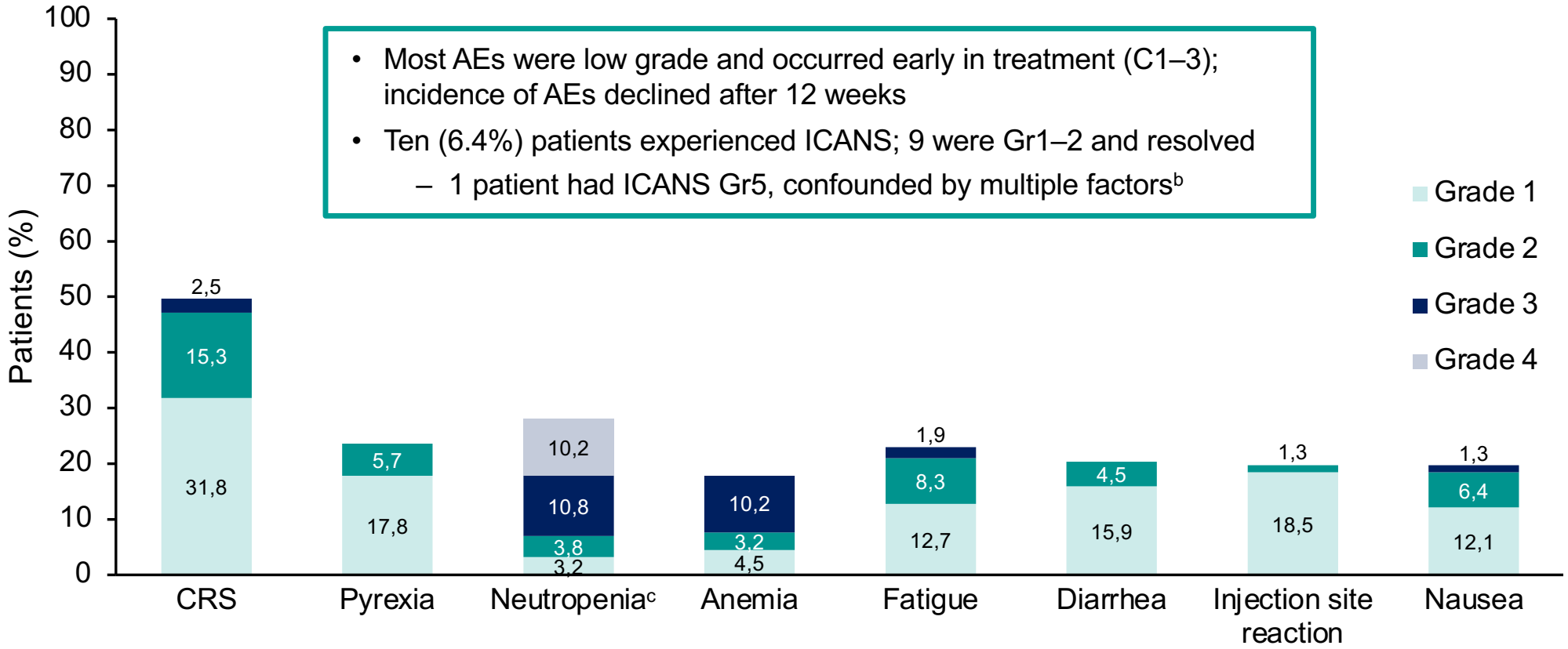
Prior Treatments	LBCL, N=157
Median time from initial diagnosis to first dose, y	1.6
Median time from end of last therapy to first dose, mo	2.4
Median prior lines of therapy (range)	3 (2–11)
≥3 Lines of therapy, n (%)	111 (71)
Primary refractory[b] disease, n (%)	96 (61)
Refractory[b] to last systemic therapy, n (%)	130 (83)
Refractory[b] to ≥2 consecutive lines of therapy, n (%)	119 (76)
Prior ASCT, n (%)	31 (20)
Prior CAR T therapy, n (%)	61 (39)
Progressed within 6 mo of CAR T therapy	46/61 (75)

[a]Double/triple-hit patients included, many with responses. [b]Refractory disease is defined as disease that either progressed during therapy or progressed within <6 months of completion of therapy.

Thieblemont C, et al. EHA 2022 oral presentation

Adverse Events Were Primarily Low Grade

Treatment-Emergent Adverse Events[a] (≥15%) by Grade



[a]COVID incidence 4.5%. [b]Patient experienced ICANS after intermediate dose with multiple confounders, including extensive opioid use for Gr3 pancreatitis, hyperammonemia, multifocal cerebral infarcts in setting of possible microangiopathy, and tocilizumab administration. [c]Combined term includes neutropenia and decreased neutrophil count.

Thieblemont C, et al. EHA 2022 oral presentation

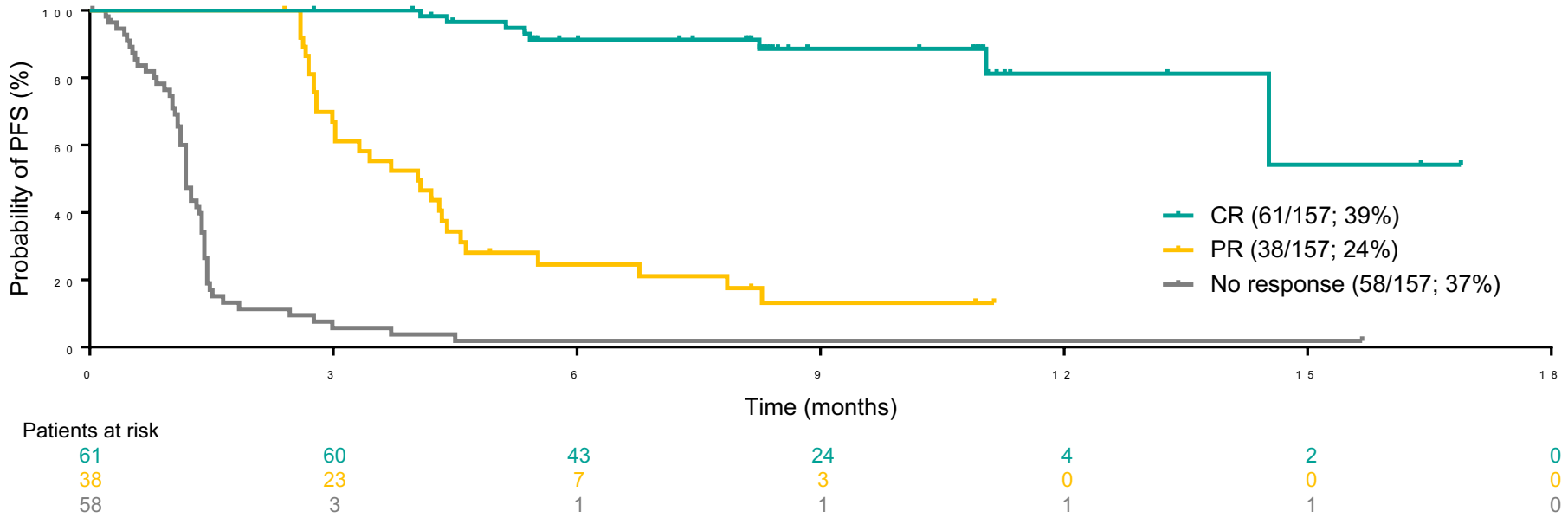
High Response Rates Observed

Best Overall Response by IRC, n (%)[a]	LBCL N=157
Overall response	**99 (63)** [95% CI: 55–71]
Complete response	**61 (39)** [95% CI: 31–47]
Partial response	38 (24)
Stable disease	5 (3)
Progressive disease	37 (24)

[a]Based on Lugano criteria.

Thieblemont C, et al. EHA 2022 oral presentation

PFS by Best Response per IRC



Patients at risk

61	60	43	24	4	2	0
38	23	7	3	0	0	0
58	3	1	1	1	1	0

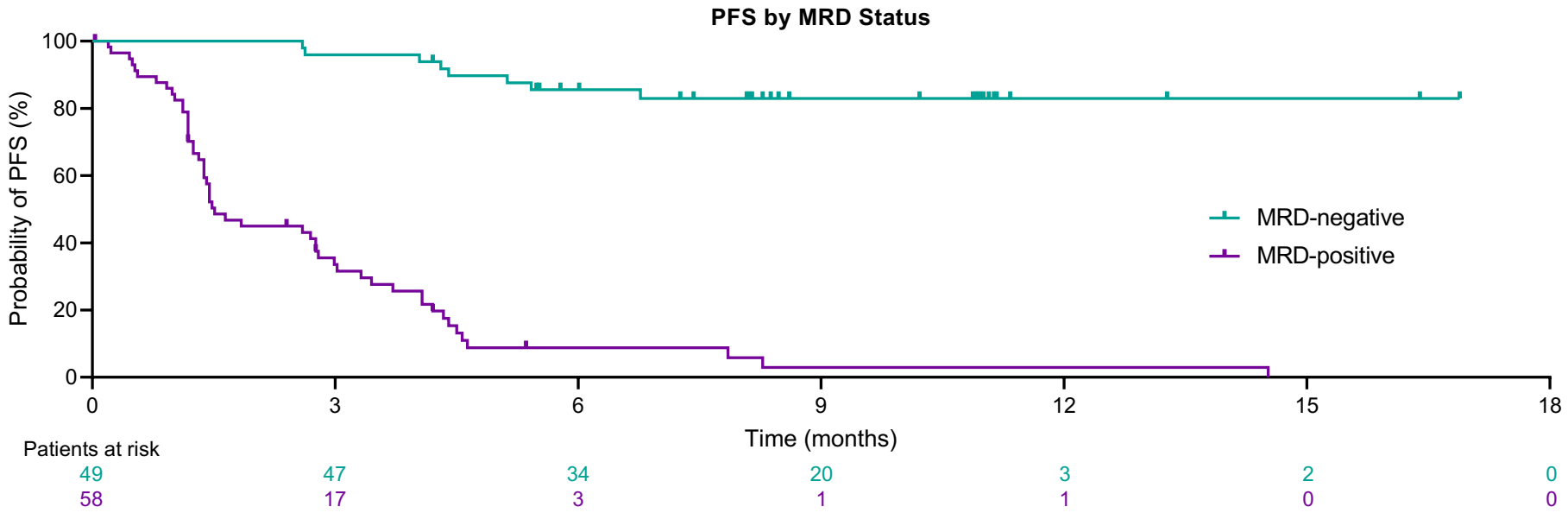
Kaplan–Meier Estimate	
Median PFS for complete responders	**Not reached**
Complete responders remaining in complete response at 9 mo	**89%**
Median PFS, mo (95% CI)	4.4 (3.0–7.9)
PFS at 6 mo, % (95% CI)	43.9 (35.7–51.7)

A correlation between depth of response and PFS was observed

Thieblemont C, et al. EHA 2022 oral presentation

MRD Negativity Correlated With Improved PFS

- **Exploratory ctDNA analysis shows that MRD-negative responses were durable and correlated with PFS**



MRD Results per ctDNA Assay	All LBCL n=107
MRD-negative rate, n (%)	49 (45.8) [95% CI: 36.1–55.7]

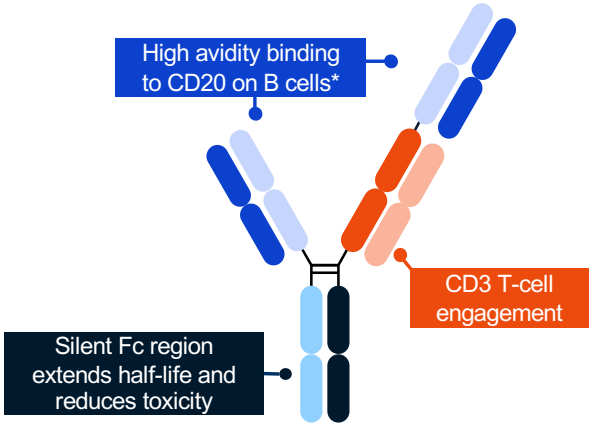
Based on MRD-negative evaluable set, which included patients with ≥1 postbaseline MRD sample/evaluation who had detectable disease (n=104) or were not evaluated (n=3) at baseline. MRD negativity was defined as the absence of detectable clone sequences in plasma at any on-treatment time point (clonoSEQ).

Thieblemont C, et al. EHA 2022 oral presentation

Glofitamab phase 2 DLBCL expansion cohort – study design and patients

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - anti-CD20 antibody
  - anthracycline



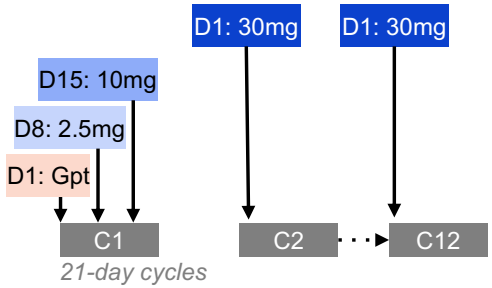
Glofitamab IV administration

Fixed-duration treatment

- max. 12 cycles

CRS mitigation:

- obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- monitoring after first dose (2.5mg)



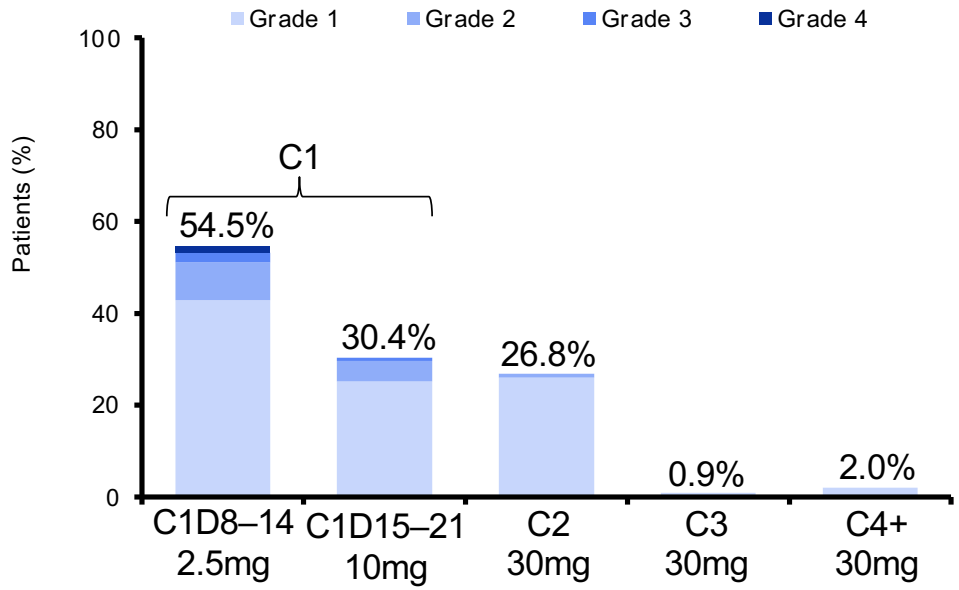
n (%)*	N=154
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	62 (40.3)
≥3 prior lines	92 (59.7)
Prior anti-CD20 Ab	154 (100.0)
Prior anthracycline	149 (96.8)
Prior CAR-T	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to any prior therapy	139 (90.3)
Refractory to last prior therapy	132 (85.7)
Primary refractory	90 (58.4)
Refractory to prior CAR-T	46 (29.9)
Refractory to any prior anti-CD20	128 (83.1)

Dickinson M, et al. N Engl J Med. 2022 Dec 15;387(24):2220-2231.

Gloftitamab phase 2 DLBCL expansion cohort – cytokine release syndrome

n (%)	N=154
CRS (any grade)*	97 (63.0)
Grade 1 (fever)	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS onset from C1D8 dose, hours (range)	13.6 (6.2–51.8)
Corticosteroids for CRS management	27/97 (27.8)
Tocilizumab for CRS management	31/97 (32.0)

CRS by cycle and grade†

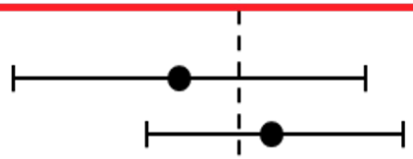


CRS was mostly low grade, time of onset was predictable, and most events occurred during C1

Dickinson M, et al. EHA 2022 oral presentation

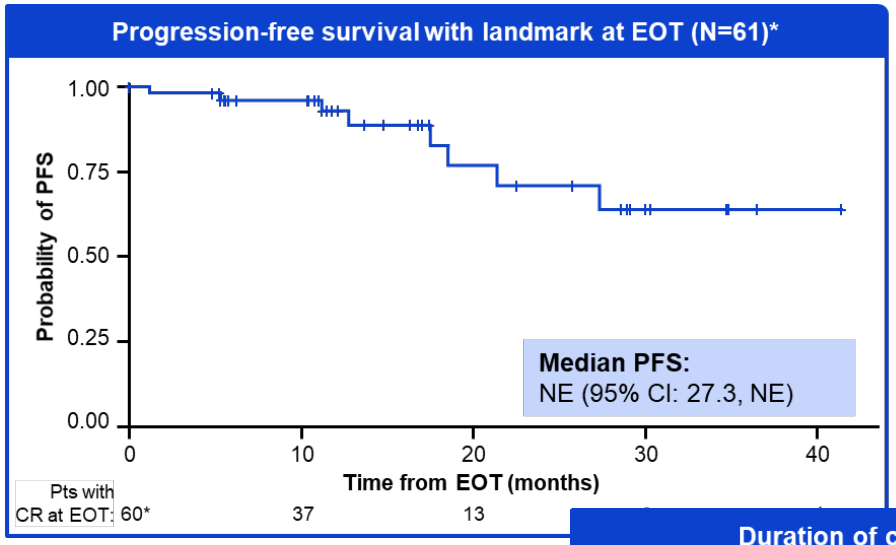
NP30179 phase 2 DLBCL expansion: Response rates at RP2D

Efficacy endpoint[1]	Glofitamab 2.5/10/30mg (n=155)
CR rate*	**61 (39.4%)** [95% CI: 31.6%, 47.5%]
ORR*	**80 (51.6%)** [95% CI: 43.5%, 59.7%]

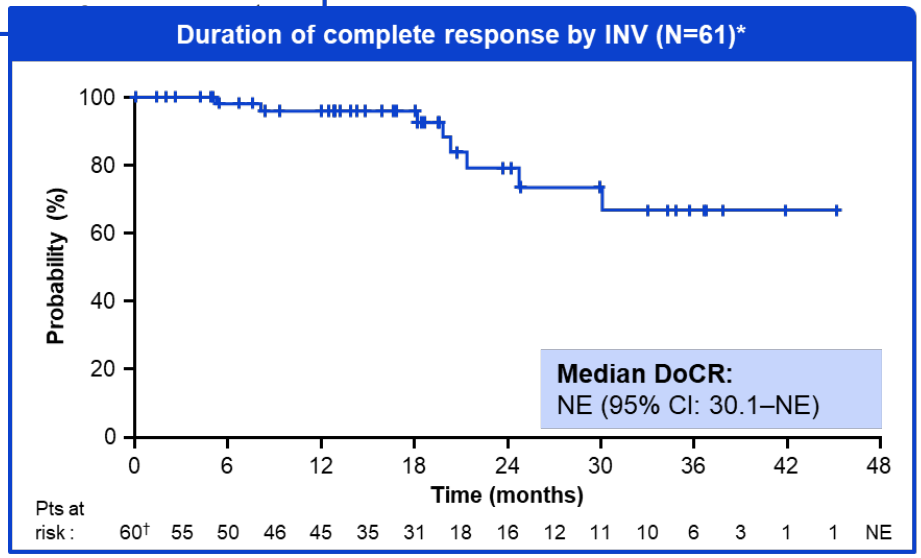
Prior CAR-T therapy			
Yes	52 (34%)	35% (22%, 49%)	
No	103 (66%)	42% (32%, 52%)	

Dickinson M, et al. N Engl J Med. 2022 Dec 15;387(24):2220-2231.

Gloftitamab phase 2 DLBCL expansion cohort – duration of response



	N=61
Median PFS follow-up from EOT, months (95% CI)	11.5 (10.5–16.4)
Median PFS, months (95% CI)	NE (27.3–NE)
12-month PFS, % (95% CI)	92.6 (84.3–100.0)

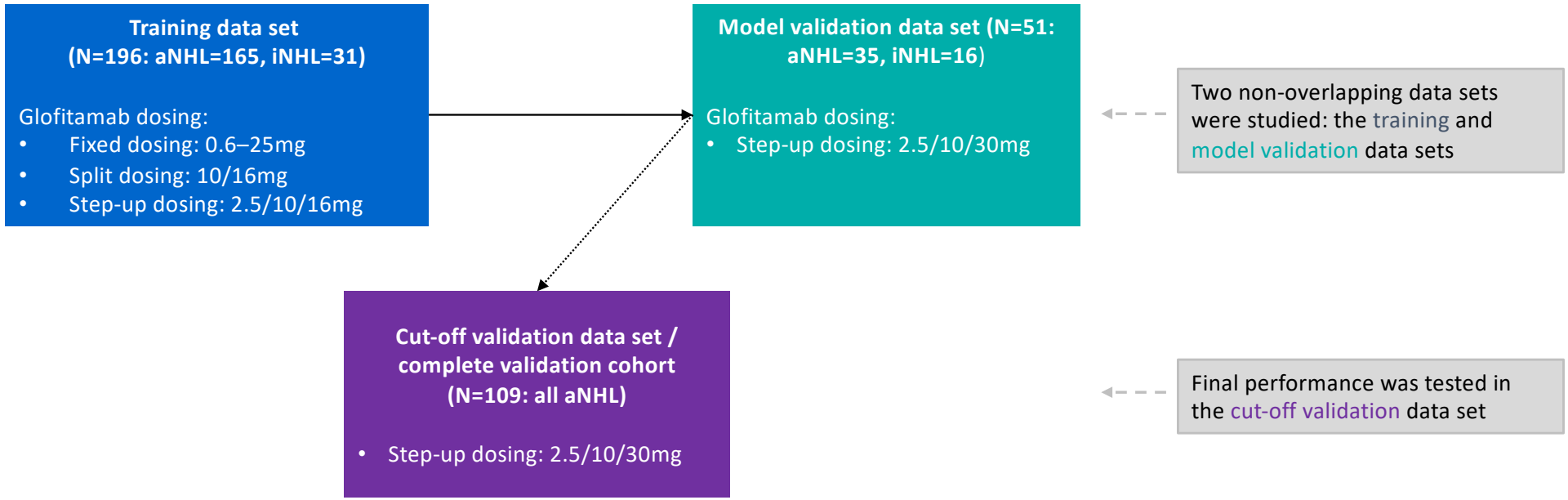


	N=61
Median DoCR follow-up from first CR, months (95% CI)	18.1 (14.8–20.7)
Median DoCR follow-up from EOT, months (95% CI)	11.5 (10.5–16.4)
Median DoCR, months (95% CI)	NE (30.1–NE)
24-months DoCR, % (95% CI)	79.1 (63.3–95.0)
CRs ongoing at CCOD, n (%)	52 (85.2)

Martin Hutchings, et al.,
Presented at ASH 2022; No. 441

Prediction and mitigation of CRS

CRS after glofitamab: predictive model



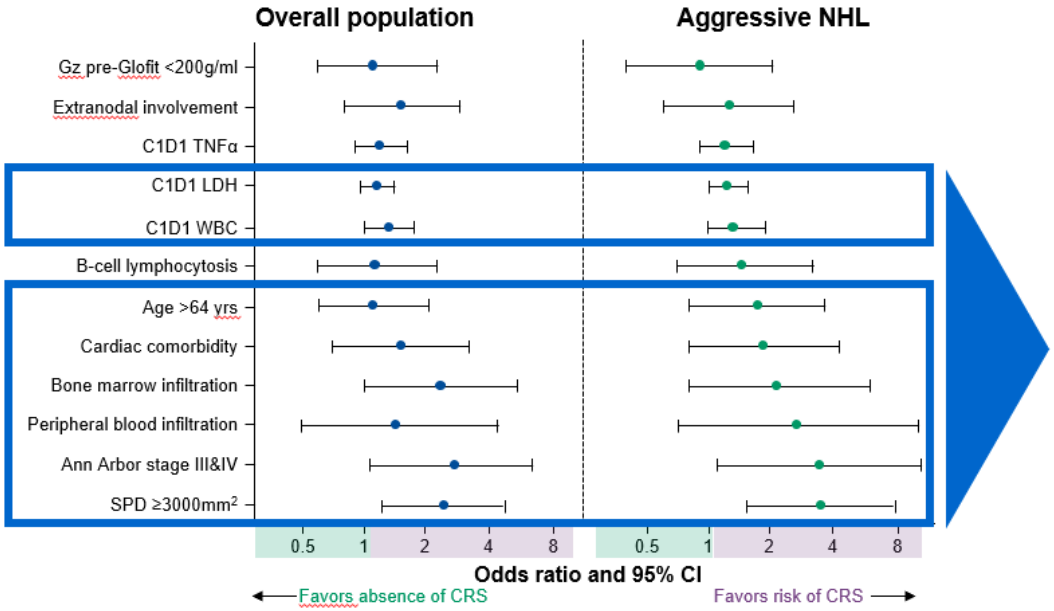
- Primary outcome was Grade ≥2 CRS in the week after first glofitamab dose, and included 65 CRS events (n=58/196 training, n=7/51 model validation)
- Training data set: associations validated between glofitamab dose, putative risk factors (i.e. demographics, clinical characteristics) and occurrence of CRS

Komanduri KV, et al. ASH annual meeting 2021. Doi: https://doi.org/10.1182/blood-2021-147303

Risk factors for development of CRS after glofitamab

- Glofitamab dose and eight factors were selected for inclusion in the CRS Grade ≥2 model
- CRS risk score is a weighted combination of the baseline values of risk factors

Training cohort (fixed, split dose 2.5/10/16mg, N=196) results adjusted for the initial glofitamab dose

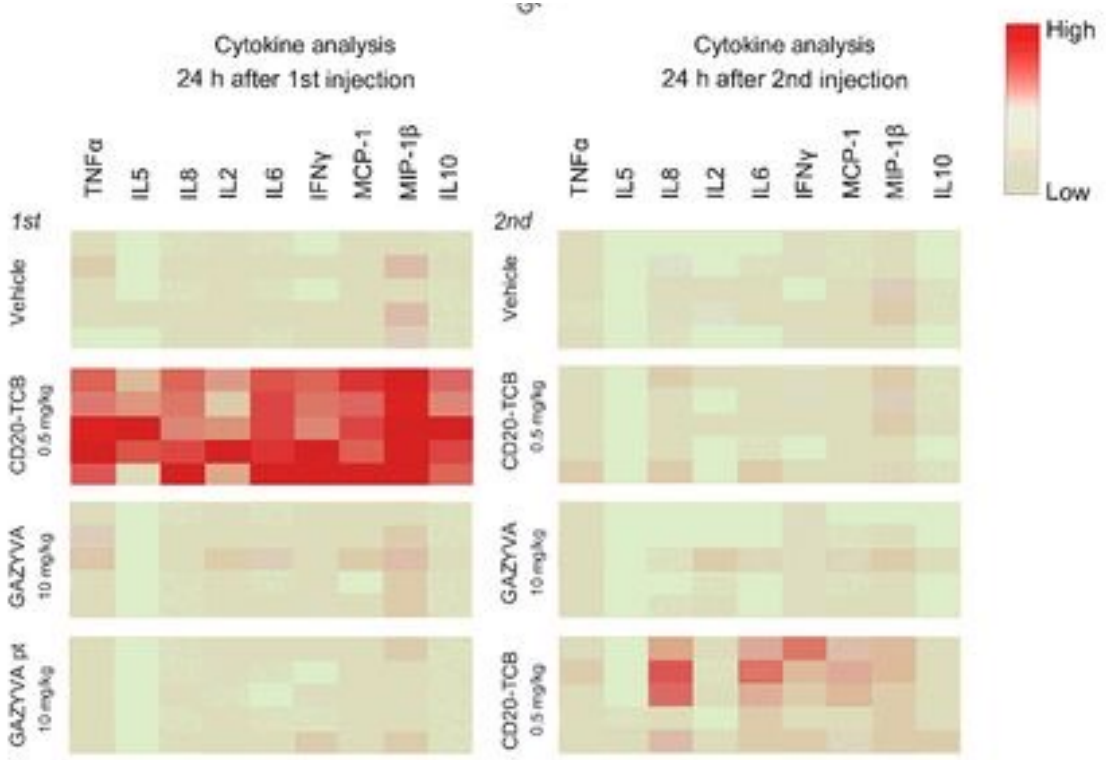


Parameter and cut-off	Weight
Ann Arbor Stage III or IV	2
SPD ≥3000mm^2	2
Bone marrow infiltration	1
Atypical cells in PB	1
Age >64 yrs	1
LDH >280U/l	0.5
WBC >4.5*10^9 cells/l	0.5
Cardiac comorbidity	0.5

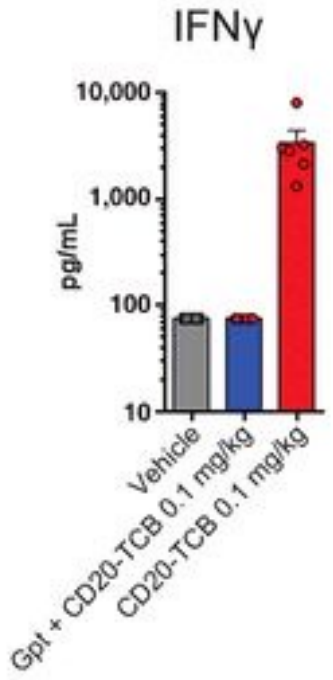
CRS risk score = weighted sum of (Weight * Parameter value at baseline), [0, 8.5].

Komanduri KV, et al. ASH annual meeting 2021.

Obinutuzumab (anti-CD20) pre-treatment to mitigate CRS



Cytokines released in peripheral blood among the different treatment groups 24 hours after the first and second treatments



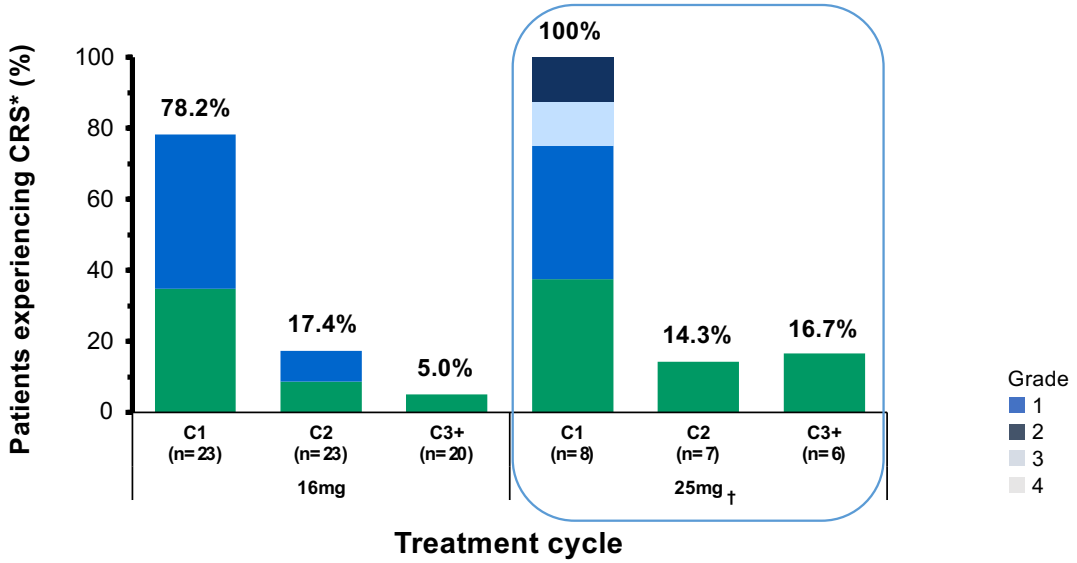
Toxicology study in cynomolgus monkey with administration of vehicle or obinutuzumab (50 mg/kg i.v.) at day 1 to reduce B-cell load

Bacac M, et al. Clin Cancer Res (2018) 24 (19): 4785–4797.

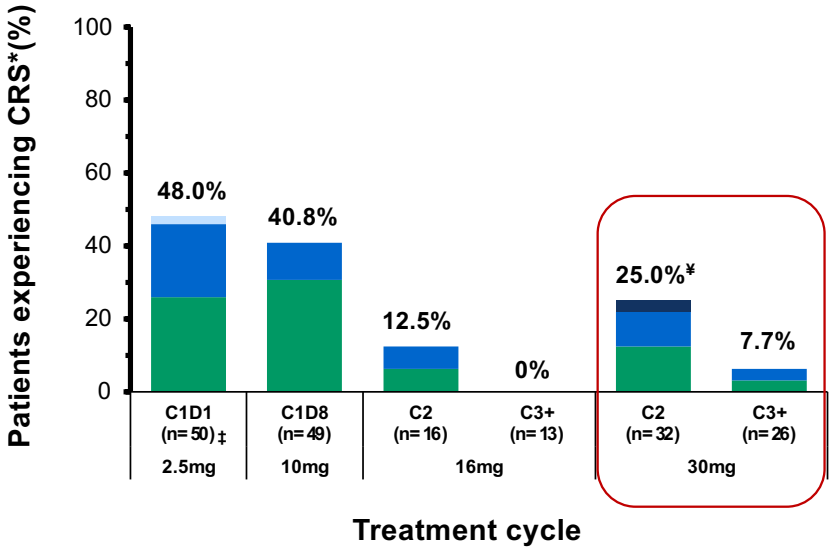
CRS frequency/severity: step-up dosing is necessary to reach the optimal dose of glofitamab

- **While the overall CRS rates were similar between the fixed-dosing and step-up dosing cohorts, step-up dosing reduced the frequency of high-grade CRS (Grade ≥2; 36.3% in the ≥10mg fixed-dosing versus 30.7% in the step-up dosing cohort)**

Glofitamab ≥10mg fixed dosing (10, 16, 25, 10/16mg)[1]



Glofitamab step-up dosing 2.5/10/16mg or 2.5/10/30mg[2]



1. Dickinson M, et al. EHA 2020, abstract #241
2. Hutchings M, et al. ASH 2020. Abstract 403

CRS mitigation: dexamethasone as the corticosteroid of choice?

"Any corticosteroid"*

Glofitamab 2.5/10/30mg, D2 sub.2 + D3 cohort (N=114)

	Cycle 1		Cycle 2
	1st dose	2nd dose	3rd dose
	2.5 mg (N=108)	10 mg (N=101)	30 mg (N=95)
Any grade	61 (56.5%)	40 (39.6%)	33 (34.7%)
Grade 1	47 (43.5%)	33 (32.7%)	32 (33.7%)
Grade 2	10 (9.3%)	6 (5.9%)	1 (1.1%)
Grade 3	2 (1.9%)	1 (1.0%)	0
Grade 4	2 (1.9%)	0	0

Mandatory Dexamethasone**

Glofitamab 2.5/10/30mg, Cohort D5 (N=40)

	Cycle 1		Cycle 2
	1st dose	2nd dose	3rd dose
	2.5 mg (N=37)	10 mg (N=34)	30 mg (N=32)
Any grade	18 (48.6%)	5 (14.7%)	1 (3.1%)
Grade 1	14 (37.8%)	5 (14.7%)	1 (3.1%)
Grade 2	3 (8.1%)	0	0
Grade 3	1 (2.7%)	0	0
Grade 4	0	0	0

**Any corticosteroid - investigator could choose one of methylprednisolone, prednisone or dexamethasone; CRS grade by ASTCT criteria; ** D5 cohort had mandatory dexamethasone*

CRS, cytokine release syndrome; ASTCT, American Society for Transplantation and Cellular Therapy

Mandatory dexamethasone demonstrates a trend in the reduction in the incidence of all grade and high grade CRS with each step-up dose

Dickinson M, et al. N Engl J Med. 2022 Dec 15;387(24):2220-2231.

CD20:CD3 bi-specific antibody therapy – *other toxicities*

- **Neurological toxicity**
  - Difficult to interpret significance/relatedness in some datasets
  - CTCAE-defined neurologic AEs consistent with ICANS are uncommon and mostly mild e.g. Gd≥3 in 3% of patients with Glofitamab

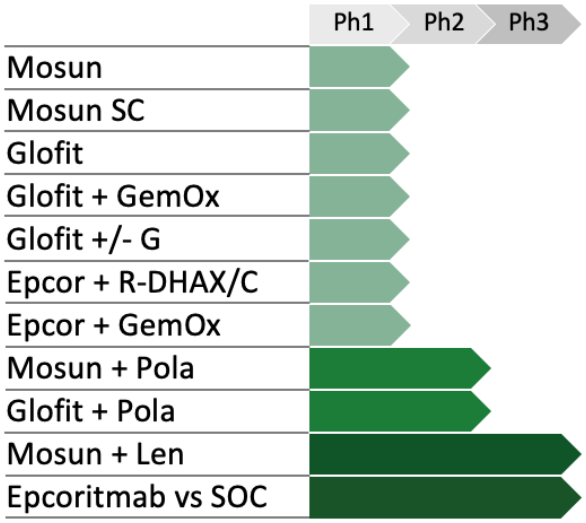
- **Cytopenias and infections**
  - Neutropenia common but febrile neutropenia rare; typically G-CSF responsive
  - No good data on hypogammaglobulinaemia, but this is observed very frequently
  - COVID-19 deaths reported in pivotal studies and anecdotally in practice

- **Tumour flare**
  - Rare but warrants consideration in bulky sites with compartmental risk

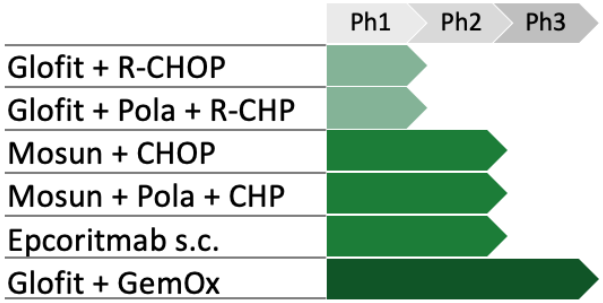
Combination studies

Ongoing combination studies with bispecific CD3:CD20 antibodies in DLBCL

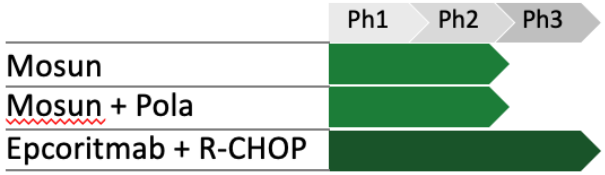
R/R DLBCL



1st Line DLBCL

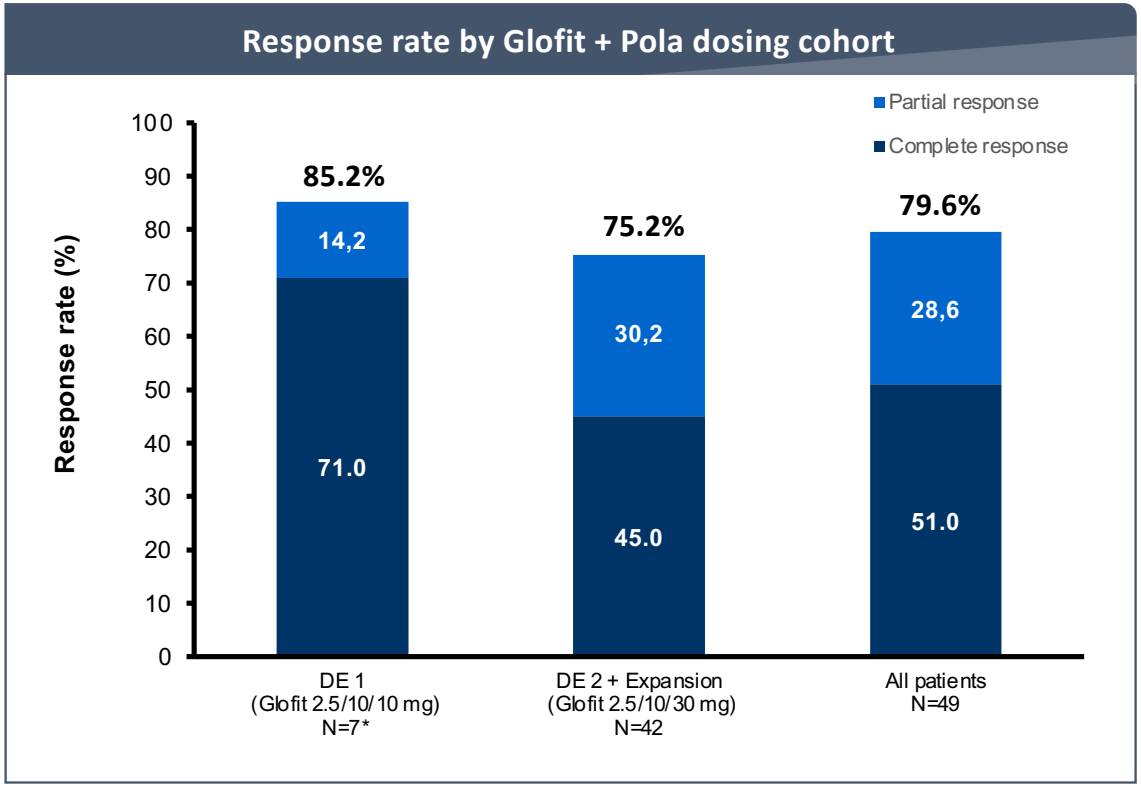


Elderly/Unfit DLBCL



Slide borrowed from Marion Subklewe

NP39488: Glofitamab and Polatuzumab vedotin in DLBCL



- **49/59 patients were evaluable for interim response**
- **7/49 (14.3%) patients had PD as best response and discontinued study treatment**
- **Encouraging ORR and CR rates in patients with:**
  - trFL: ORR, 8/11 and CR, 7/11
  - HGBCL: ORR, 5/8 and CR, 4/8

- **Glofit + Pola combination resulted in high response rates**

Hutchings M, et al. ASH 2021. Abstract 525.

Conclusions

- Recent data from DLBCL phase 2 expansion cohort

- The toxicity profile is favourable:
  - Very little CRS > grade 2
  - Little or no treatment-related CNS toxicity

- The toxicity profile and mechanism of action make the bispecifics ideal for combination strategies
  - Dose-escalation and combination studies with Obinutuzumab, R-chemo, Polatuzumab vedotin, and targeted immune agonists are ongoing