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Aggressive Lymphoma Workshop

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Bispecific antibodies - Glofitamab

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Disclosures

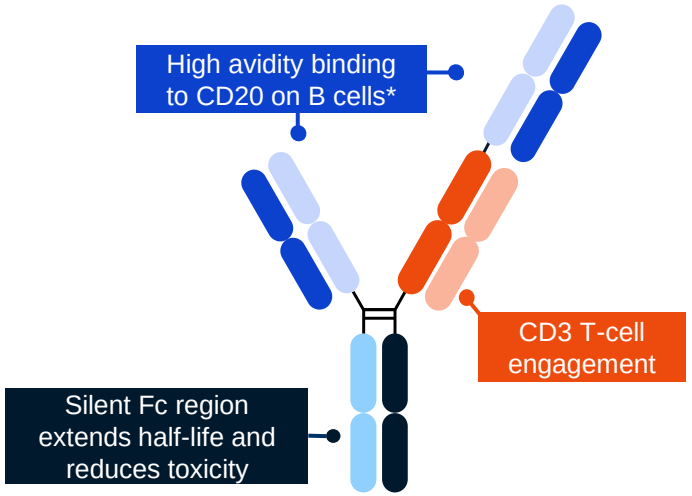
- **Scientific advisory boards:**
  - AbbVie, AstraZeneca, Celgene, Genmab, Janssen, Merck, Roche, Takeda
- **Research support (institution):**
  - AbbVie, AstraZeneca, Bristol Myers-Squibb, Celgene, Genentech, Genmab, Incyte, Janssen, Merck, Novartis, Roche, Takeda

Recent data from the DLBCL phase 2 expansion cohort

Gloftitamab 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



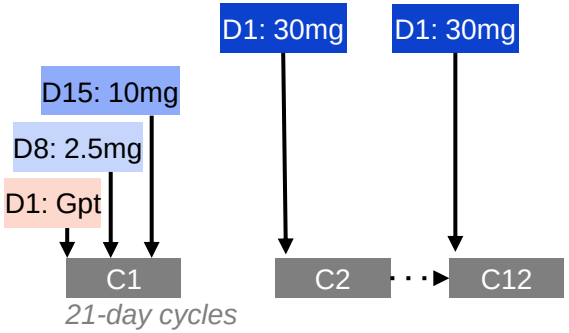
Glofitamab IV administration

Fixed-duration treatment

- max. 12 cycles

CRS mitigation:

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



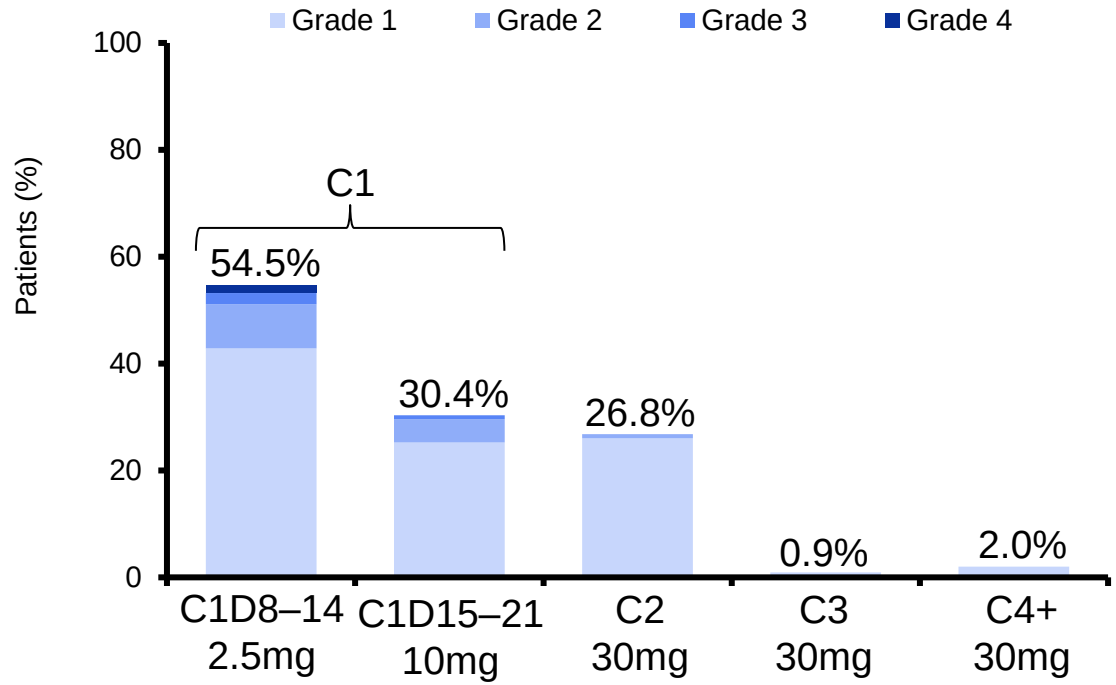
n (%)*	N=154
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	62 (40.3)
≥3 prior lines	92 (59.7)
Prior anti-CD20 Ab	154 (100.0)
Prior anthracycline	149 (96.8)
Prior CAR-T	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to any prior therapy	139 (90.3)
Refractory to last prior therapy	132 (85.7)
Primary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

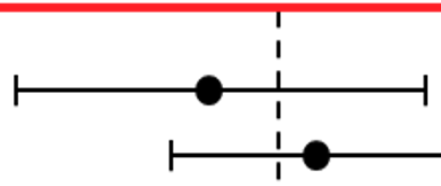


CRS was mostly low grade, time of onset was predictable, and most events occurred during C1

Dickinson M, et al. EHA 2022 oral presentation

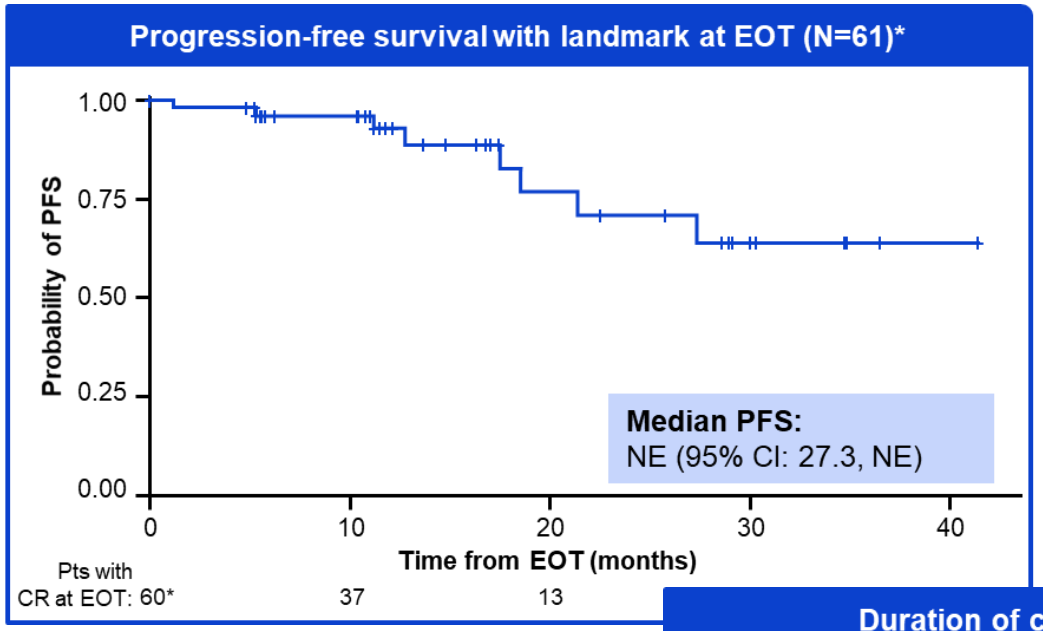
NP30179 phase 2 DLBCL expansion: Response rates at RP2D

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%]

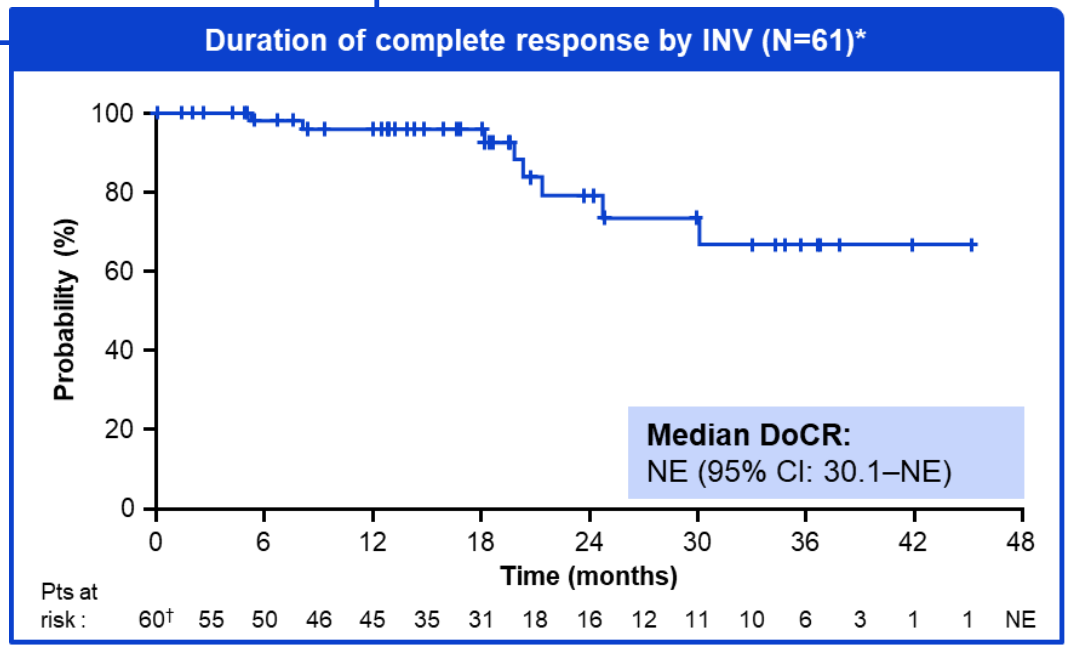
Prior CAR-T therapy			
Yes	52 (34%)	35% (22%, 49%)	
No	103 (66%)	42% (32%, 52%)	

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)

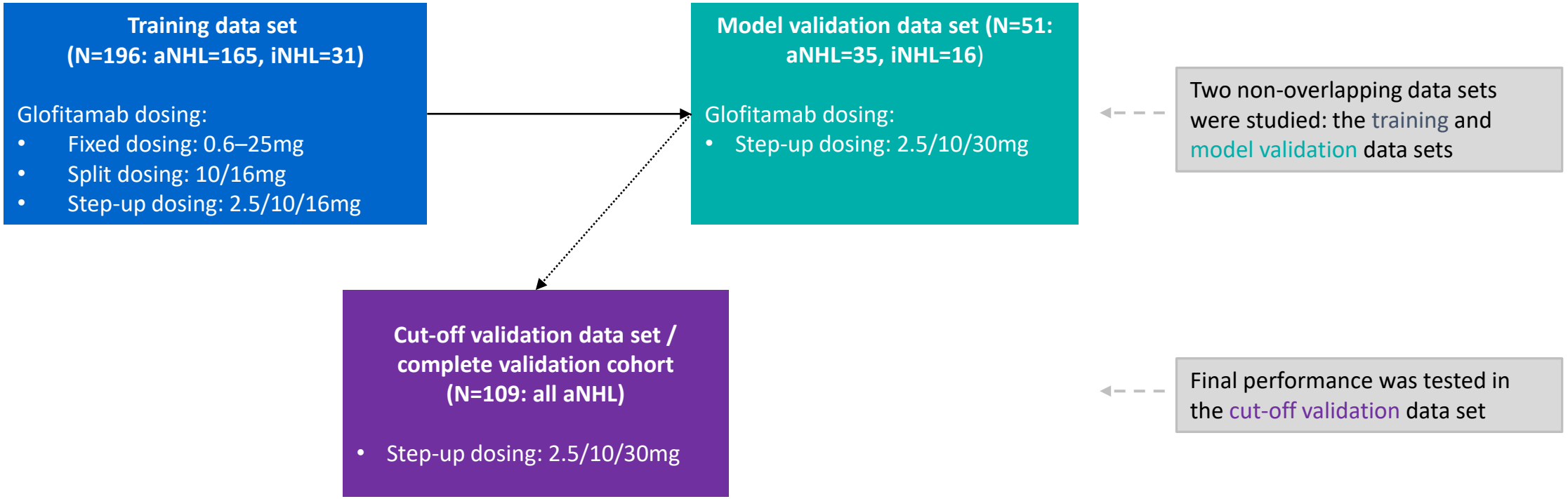


	N=61
Median DoCR follow-up from first CR, months (95% CI)	18.1 (14.8–20.7)
Median DoCR follow-up from EOT, months (95% CI)	11.5 (10.5–16.4)
Median DoCR, months (95% CI)	NE (30.1–NE)
24-months DoCR, % (95% CI)	79.1 (63.3–95.0)
CRs ongoing at CCOD, n (%)	52 (85.2)

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

Prediction and mitigation of CRS

CRS after glofitamab: predictive model



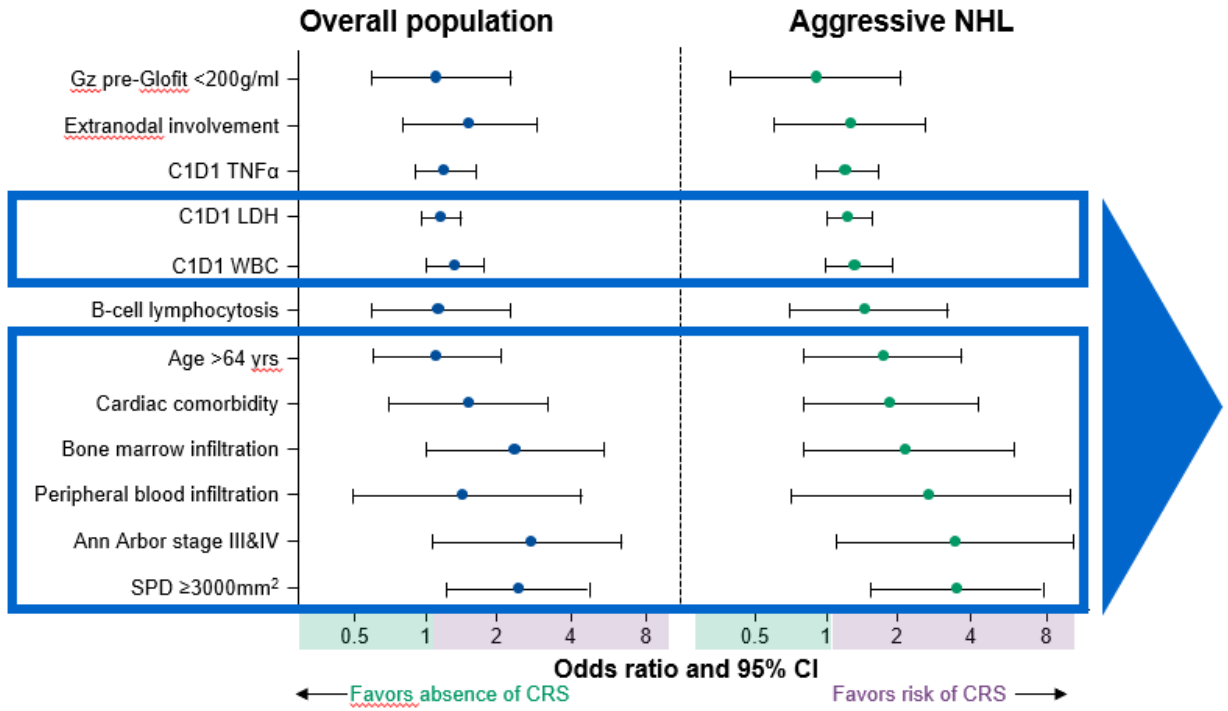
- Primary outcome was Grade ≥2 CRS in the week after first glofitamab dose, and included 65 CRS events (n=58/196 training, n=7/51 model validation)
- Training data set: associations validated between glofitamab dose, putative risk factors (i.e. demographics, clinical characteristics) and occurrence of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

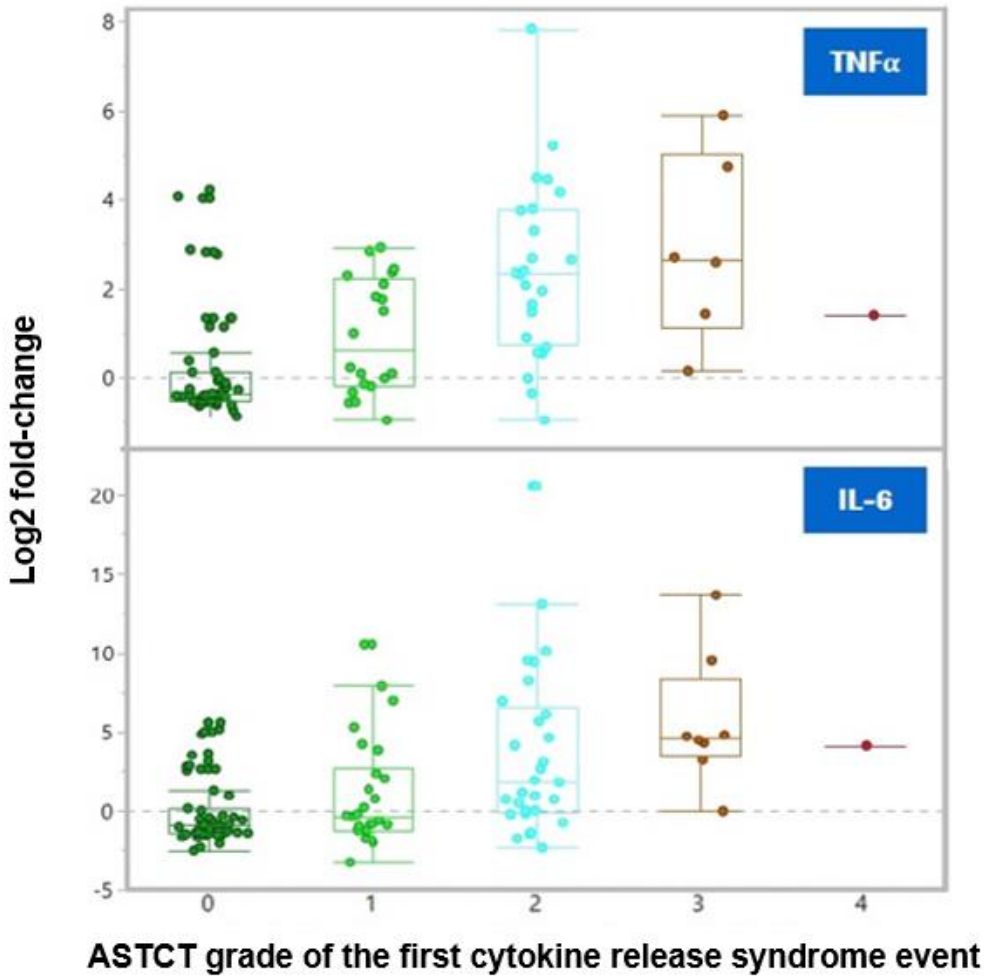
CRS risk score = weighted sum of (Weight * Parameter value at baseline), [0, 8.5].

Komanduri KV, et al. ASH annual meeting 2021.

IL-6 and TNFα induction is associated with CRS

- Induction of cytokines IL-6 and TNFα was observed after glofitamab
  - Peak magnitude of cytokine induction was associated with CRS incidence and severity
- Other cytokines were also associated with CRS incidence and severity:
  - IFNγ, IL-1β, IL-2, IL-8, IL-10, IL-15, IL-17, MIP-1β, MCP1

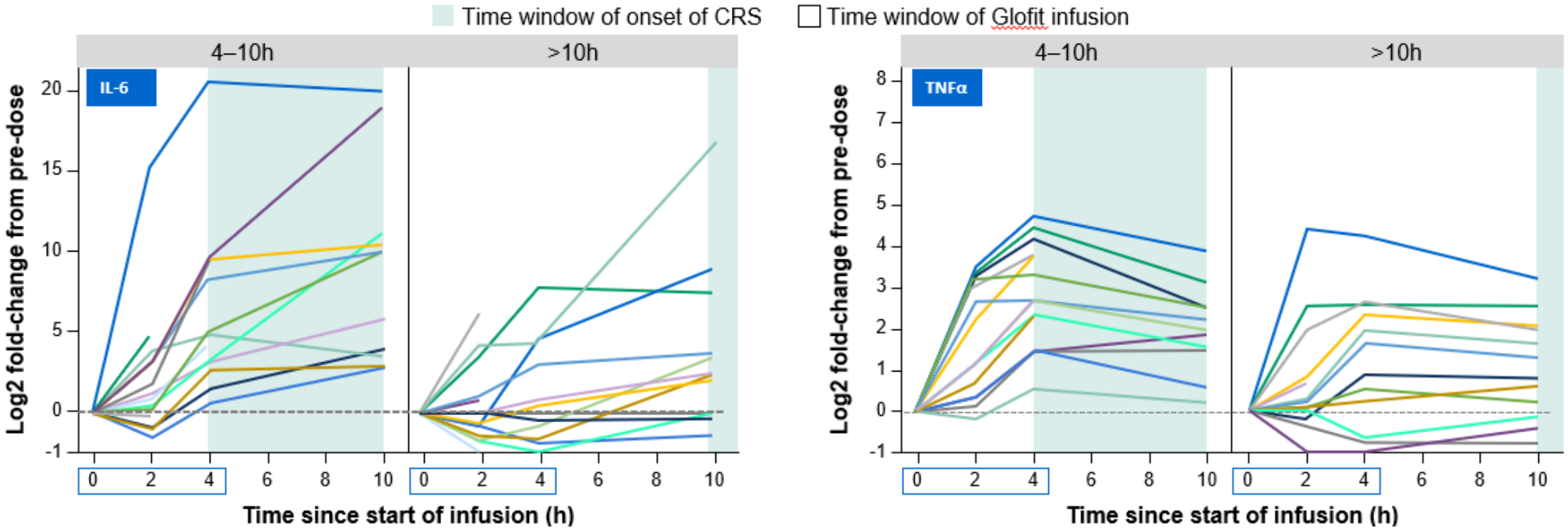
Maximum change from baseline in IL-6 and TNFα during first 4 hours of glofitamab infusion



Komanduri KV, et al. ASH annual meeting 2021.

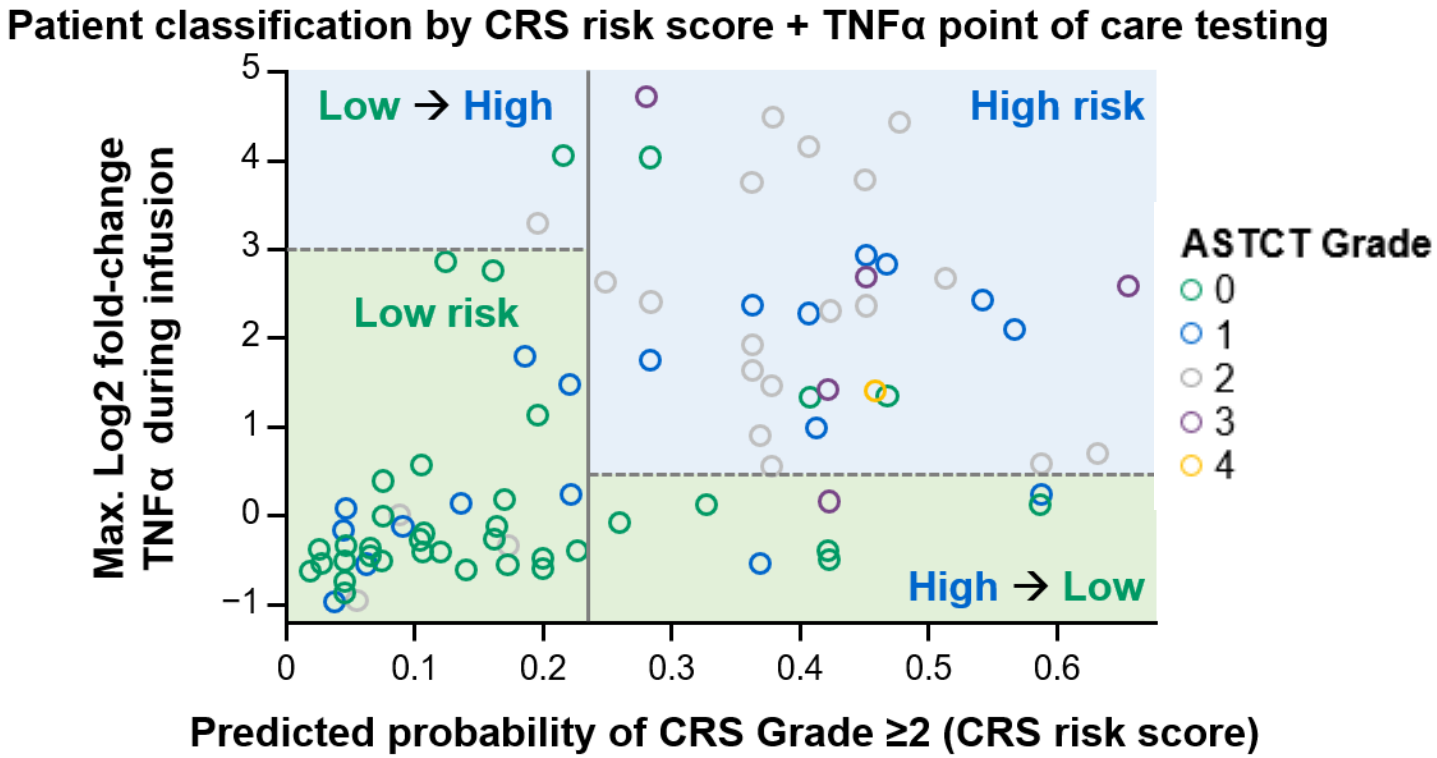
Cytokine changes were observed before CRS onset

- Cytokine induction is detectable in time window preceding CRS onset for most patients who will experience Grade ≥2 CRS
- TNFα peaks earlier than IL-6 and is a more sensitive indicator of impending CRS



Komanduri KV, et al. ASH annual meeting 2021.

Improved predictive performance of CRS risk score by addition of early on-treatment changes in TNFα levels



Addition of TNFα testing improved the model

Classified as **'Low risk'** (60%):

- N=4 false negative: experienced grade ≥2 CRS
- N=50 true negatives (NPV=93%)

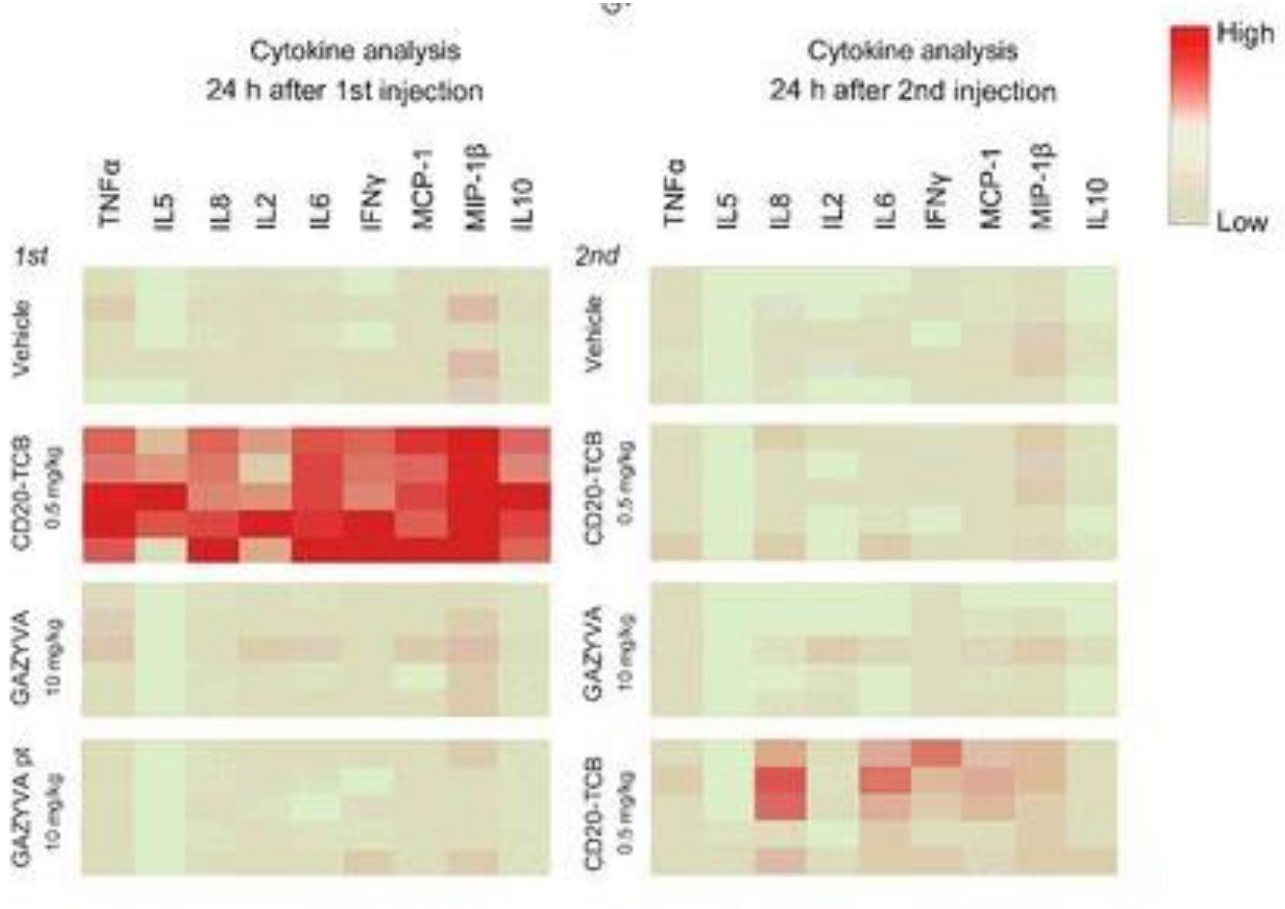
Classified as **'High risk'** (40%):

- N= 12 false positives: did not experience grade ≥2 CRS
- N=23 true positives (PPV=65%)

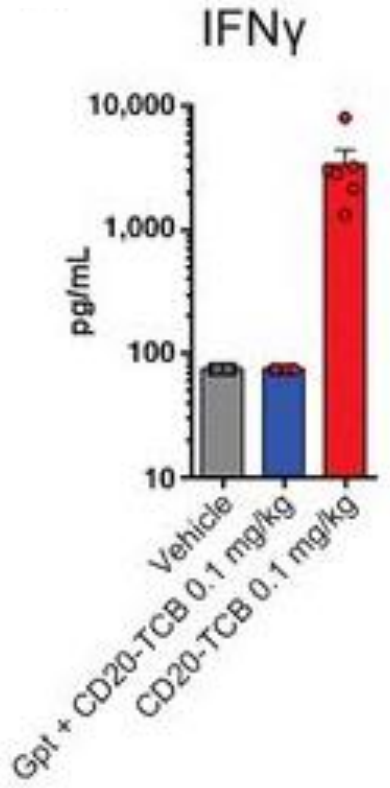
Landmark analysis in the training cohort, subset of patients with cytokine data available.

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



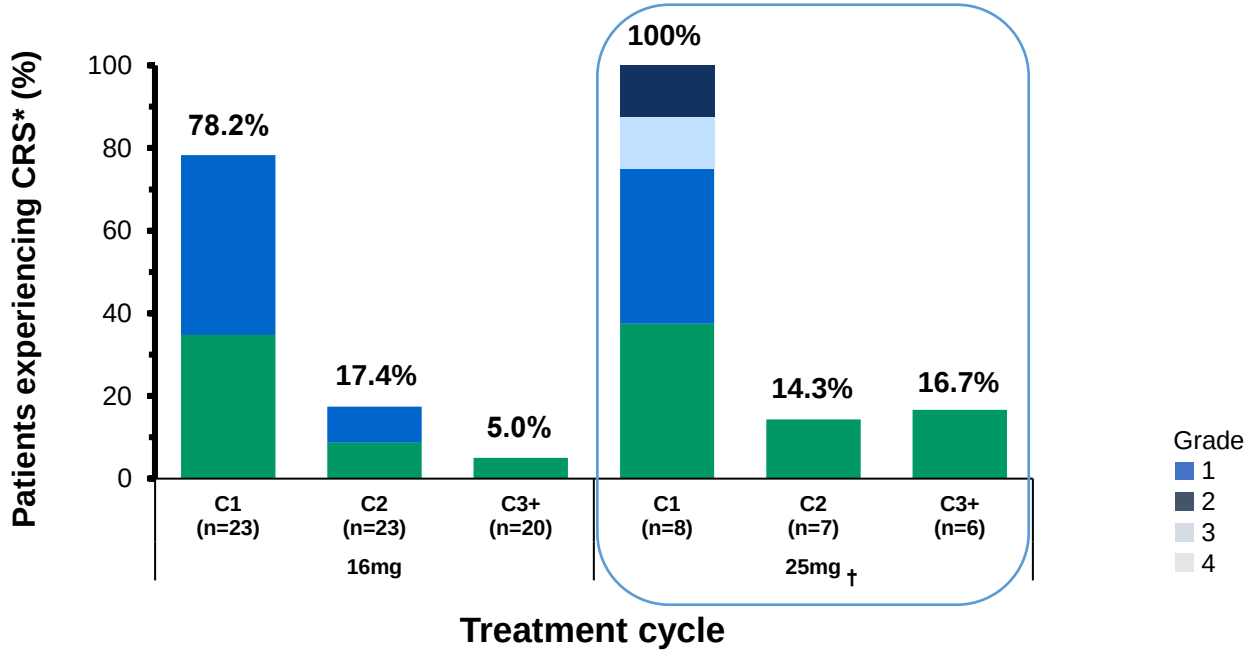
Toxicology study in cynomolgus monkey with administration of vehicle or obinutuzumab (50 mg/kg i.v.) at day 1 to reduce B-cell load

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

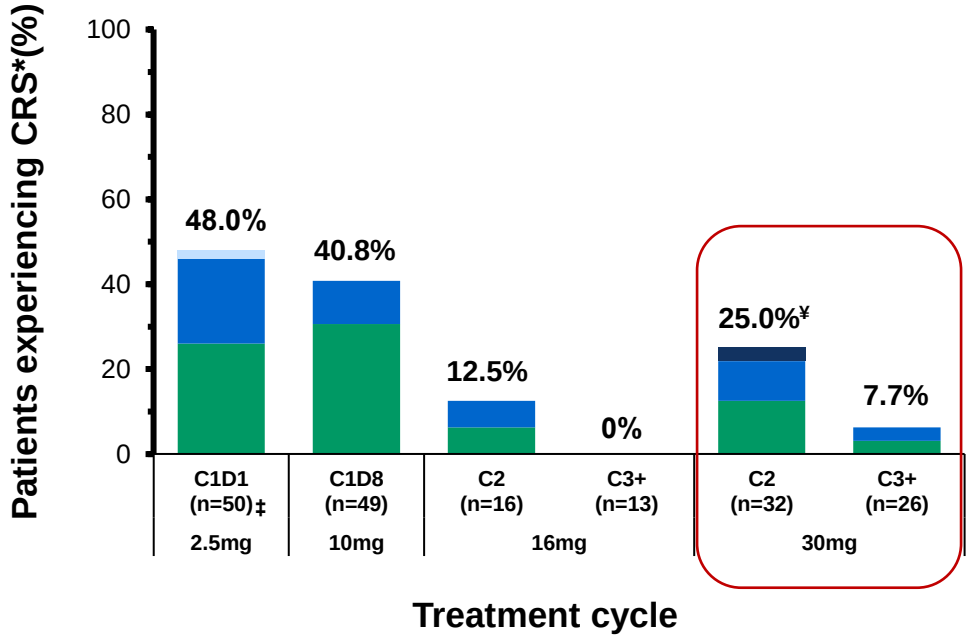
CRS frequency/severity: step-up dosing is necessary to reach the optimal dose of glofitamab

- **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*

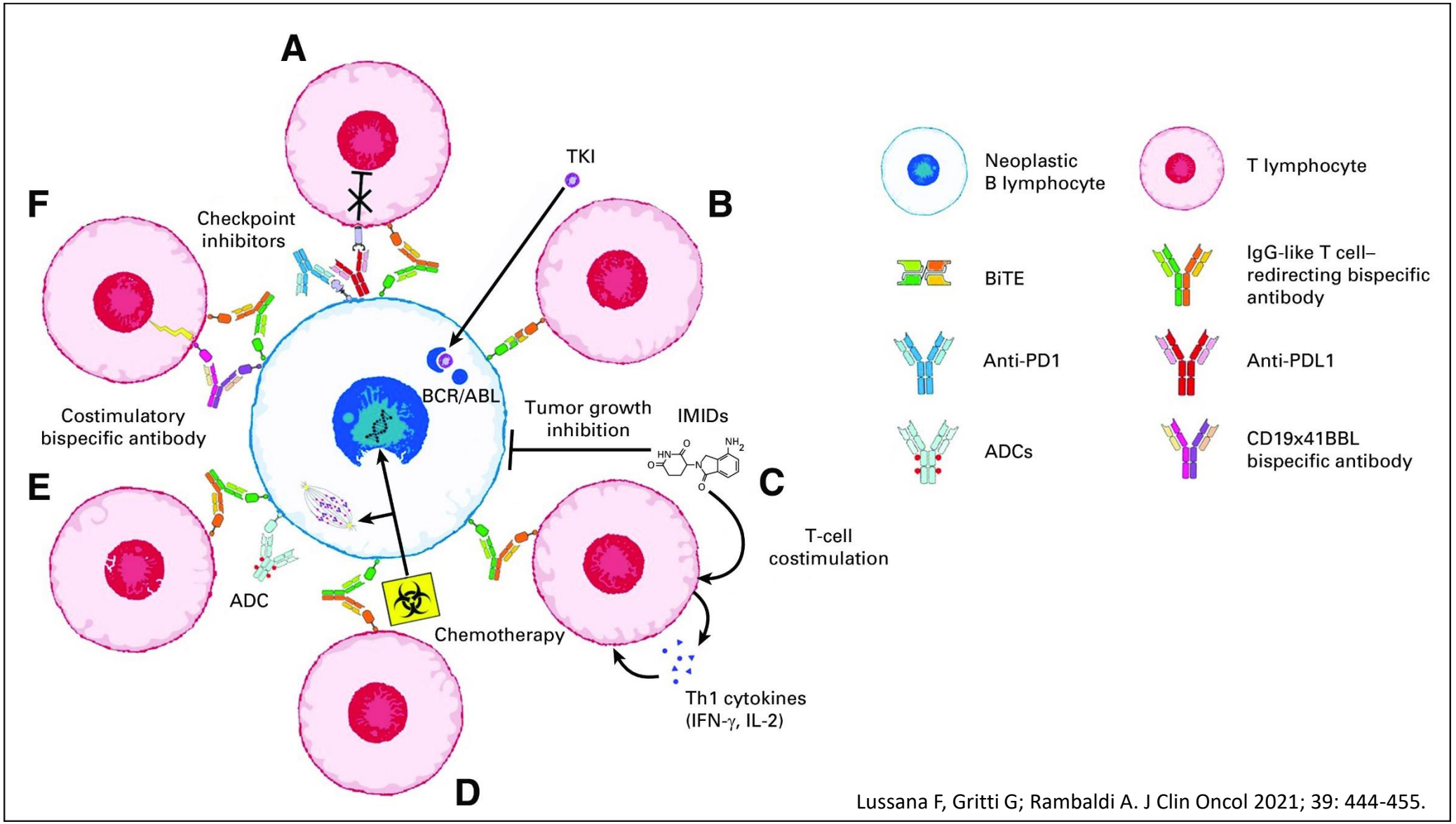
- **Neurological toxicity**
  - Difficult to interpret significance/relatedness in some datasets
  - CTCAE-defined neurologic AEs consistent with ICANS are uncommon and mostly mild e.g. Gd≥3 in 3% of patients with Glofitamab

- **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

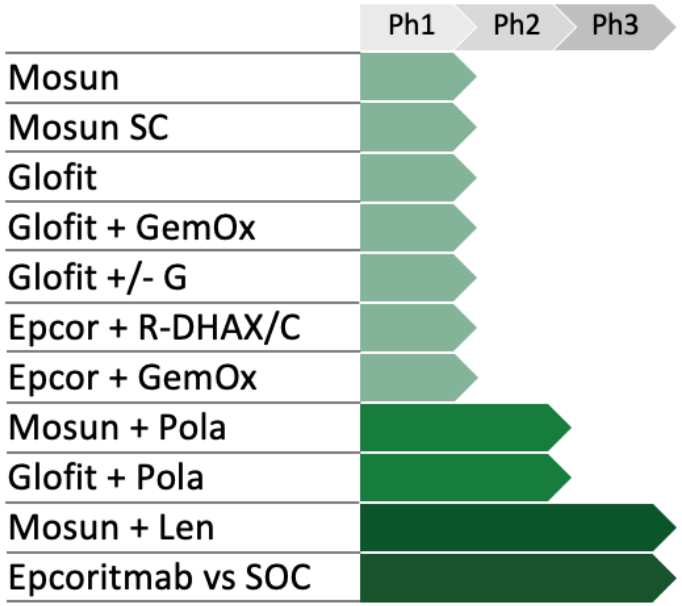
How to get deeper and more durable responses?



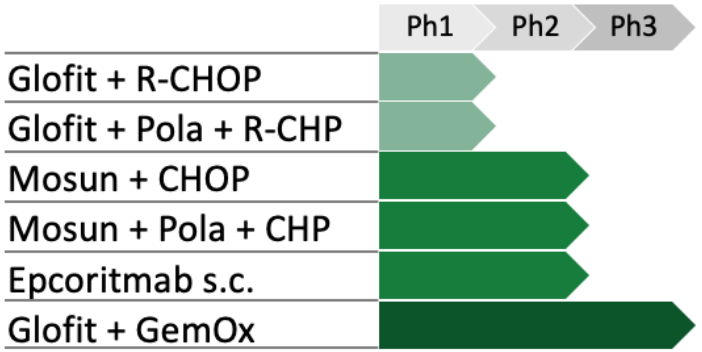
Lussana F, Gritti G; Rambaldi A. J Clin Oncol 2021; 39: 444-455.

Ongoing combination studies with bispecific CD3:CD20 antibodies in DLBCL

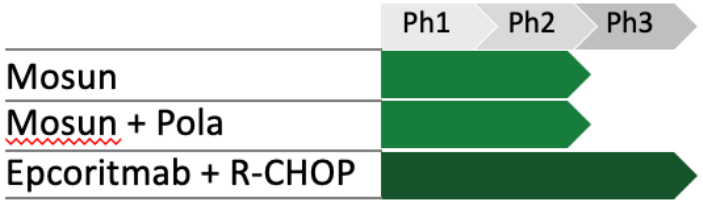
R/R DLBCL



1st Line DLBCL

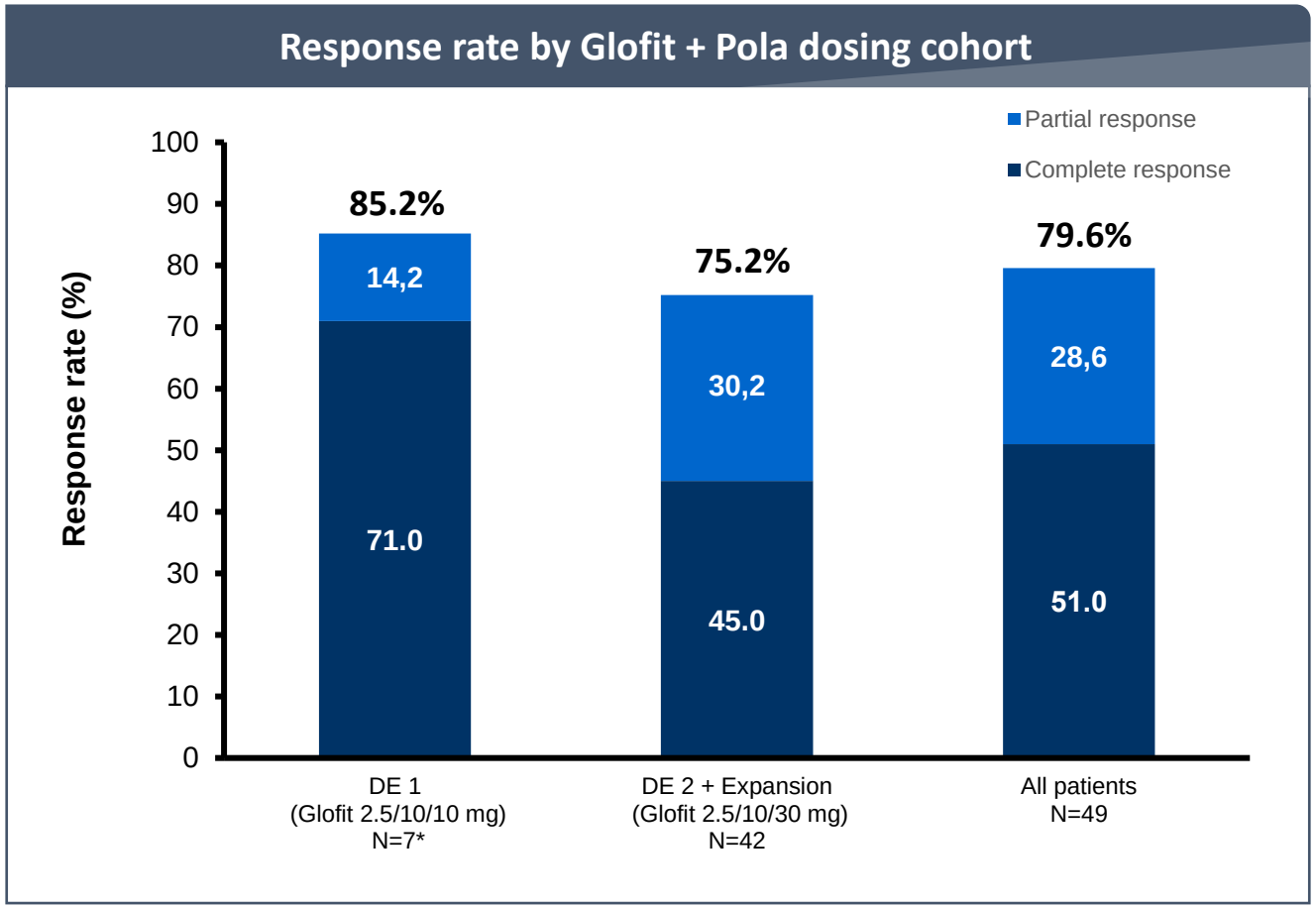


Elderly/Unfit DLBCL



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

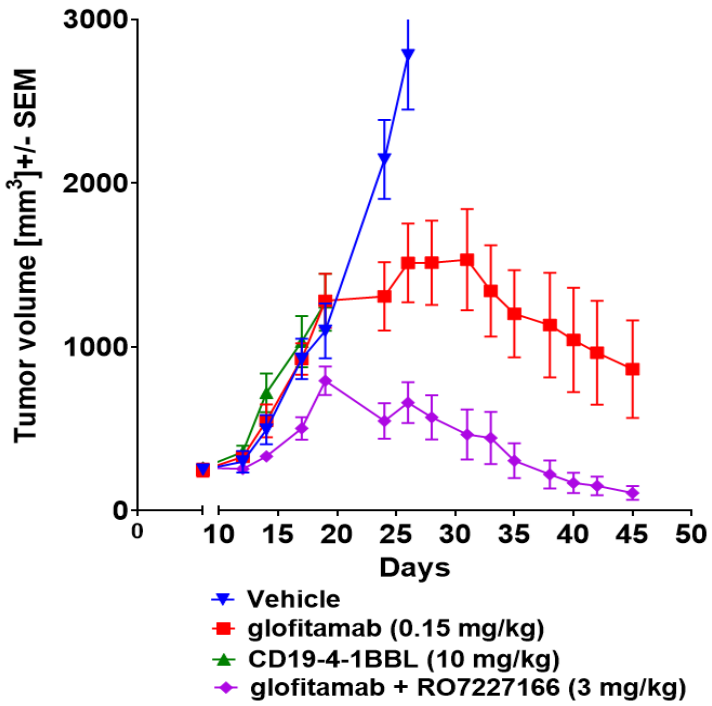
- **Glofit + Pola combination resulted in high response rates**

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

BP41072: Glofitamab + CD19-targeted 4-1BBL agonist

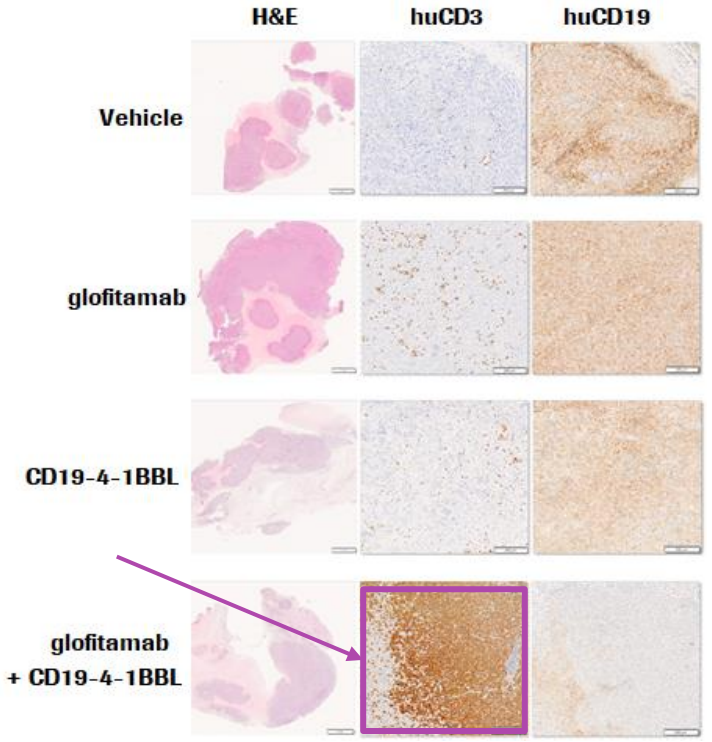
CD19 4-1BBL plus glofitamab is superior to glofitamab single-agent in vivo

Improved tumor growth inhibition

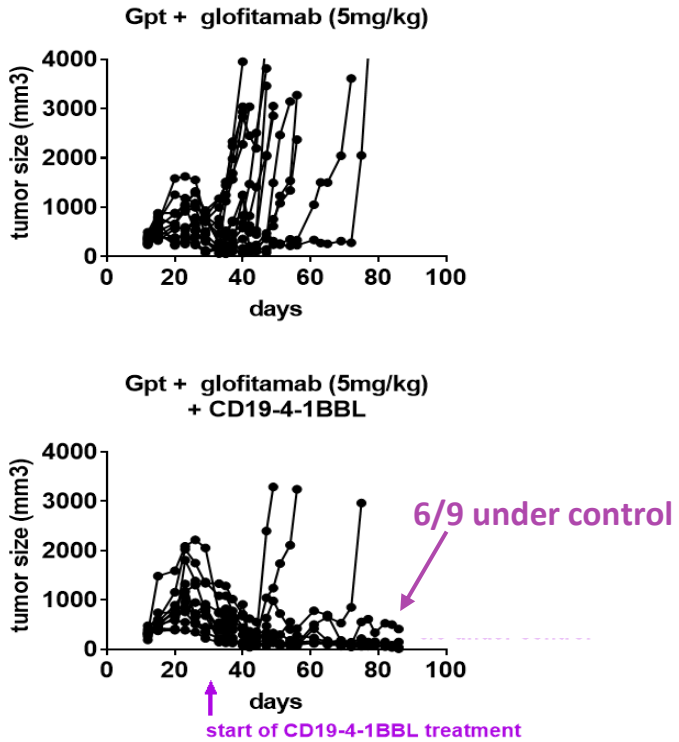


WSU DLCL2 s.c. in humanized mice

Significantly enhanced T cell infiltration



Prevention of tumor outgrowth during glofitamab monotherapy



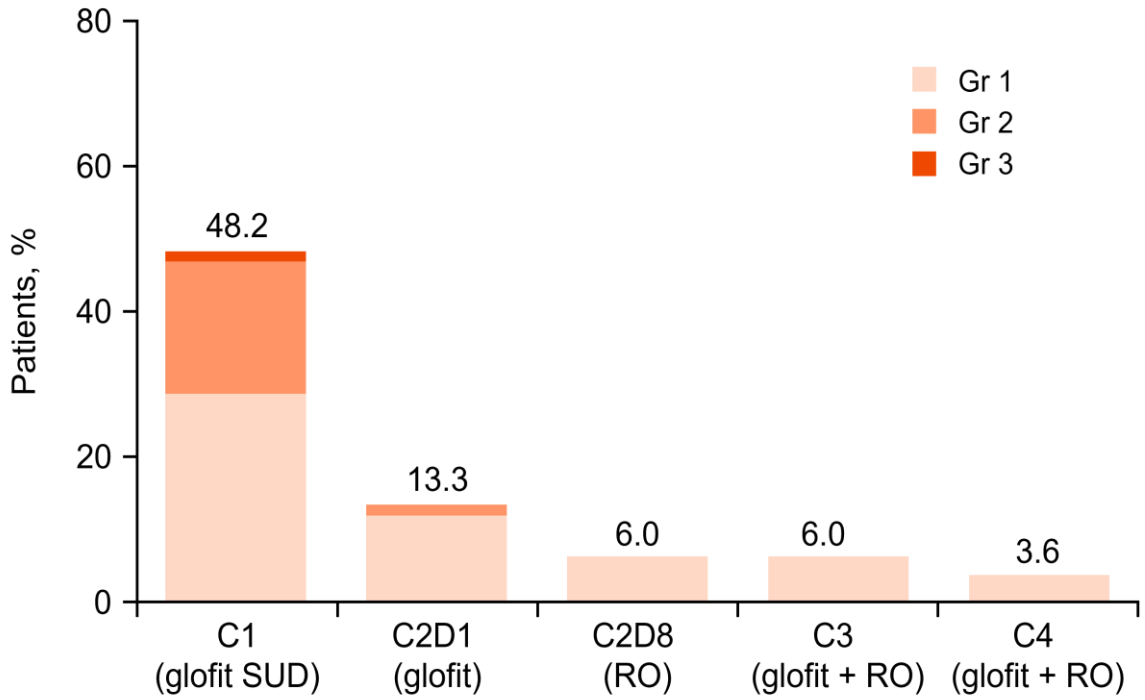
OCILY18 s.c. in humanized mice

Hutchings M, et al. ASH 2020. Abstract 3269.

BP41072: CRS profile consistent with glofitamab monotherapy

N (%) of patient with ≥1 CRS AE unless stated	N=83
Any Gr CRS	47 (56.6)
Gr 1	36 (43.3)
Gr 2	14 (16.9)
Gr 3	1 (1.2)
Any related CRS	47 (56.6)
CRS related to glofitamab only	44 (53.0)
CRS related to RO7227166 only	6 (7.2)
CRS related to glofitamab and RO7227166	6 (7.2)
SAEs	23 (27.7)
CRS leading to withdrawal	1 (1.2)
Median time to onset since last dose, days (range)	1 (0–8)
Median duration, days (range)	1 (0–7)

CRS by Cycle and Grade

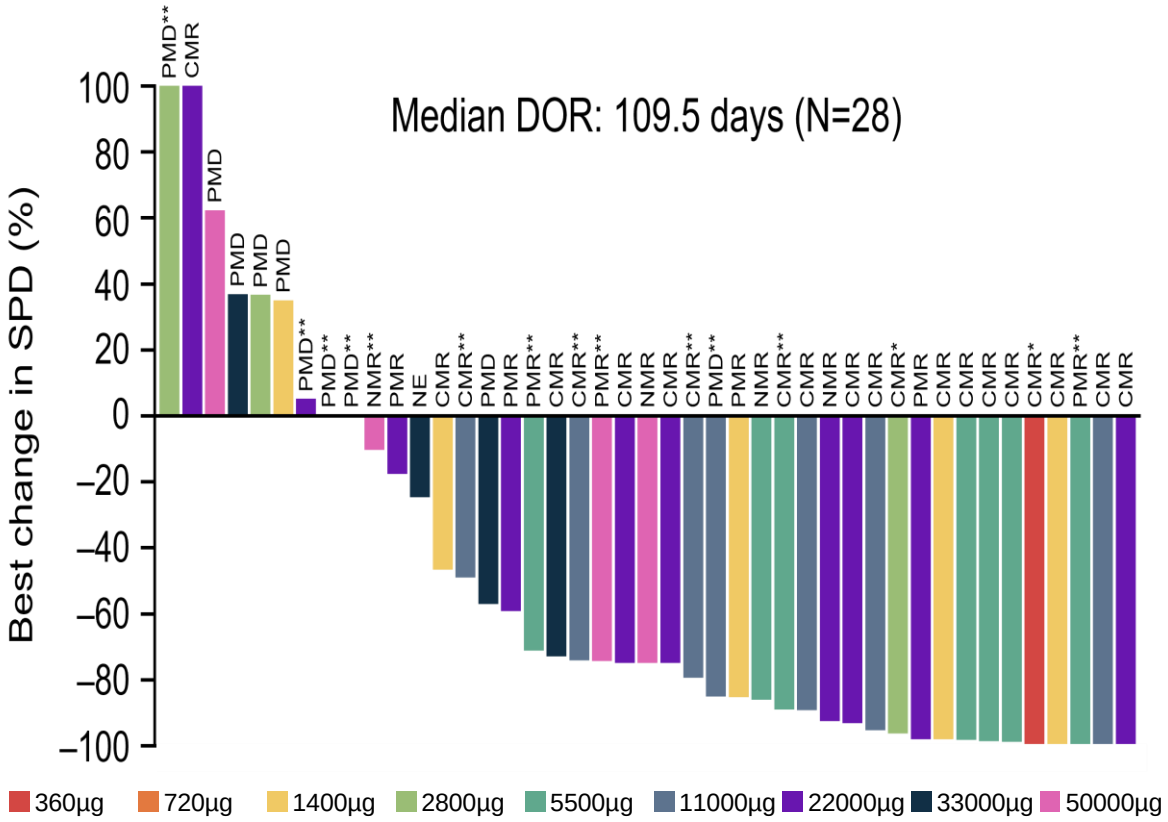


Most CRS events (94%) occurred during glofitamab step-up dosing and were Gr 1–2

Hutchings M, et al. ASH 2022. Abstract P4259.

BP41072: Efficacy

Best percent change in SPD among efficacy evaluable patients with R/R DLBCL



Response rates in efficacy evaluable patients with R/R aNHL and iNHL

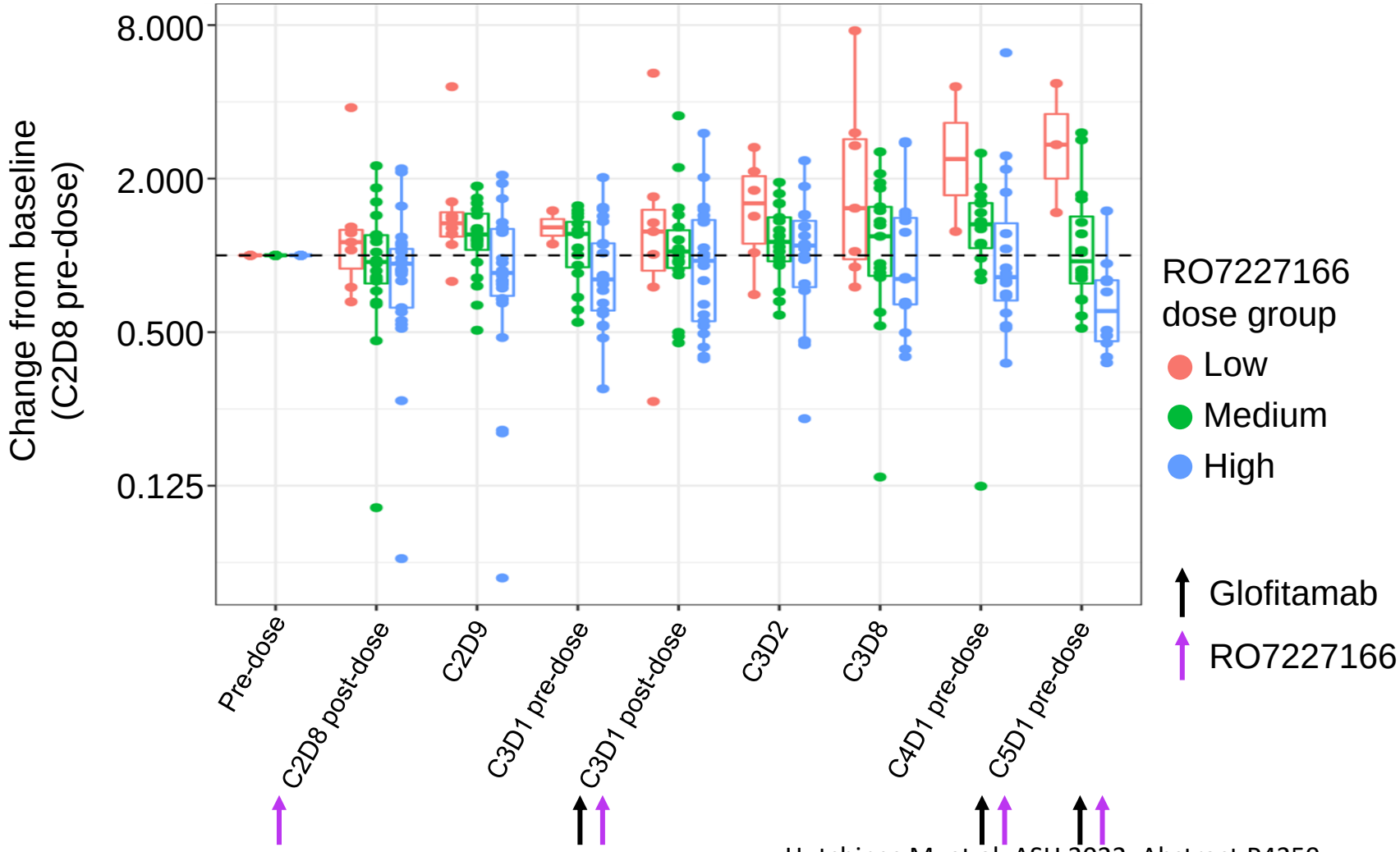
	N efficacy evaluable	CR rate	BOR rate
aNHL	45 (all DLBCL)	49%	65%
iNHL	24 (23 FL and 1 MZL)	74%	91%

The single patient with MZL achieved a PMR

Hutchings M, et al. ASH 2022. Abstract P4259.

BP41072: Preliminary PD biomarker data support the MOA of RO7227166

- RO7227166 reverses expansion of terminally differentiated PD1+ CD8 Temra cells in blood
- Dose relationship emerging at C3D8, C4D1 and C5D1
- Preventing T-cell exhaustion will lead to a more durable immune response to glofitamab and prevent relapse

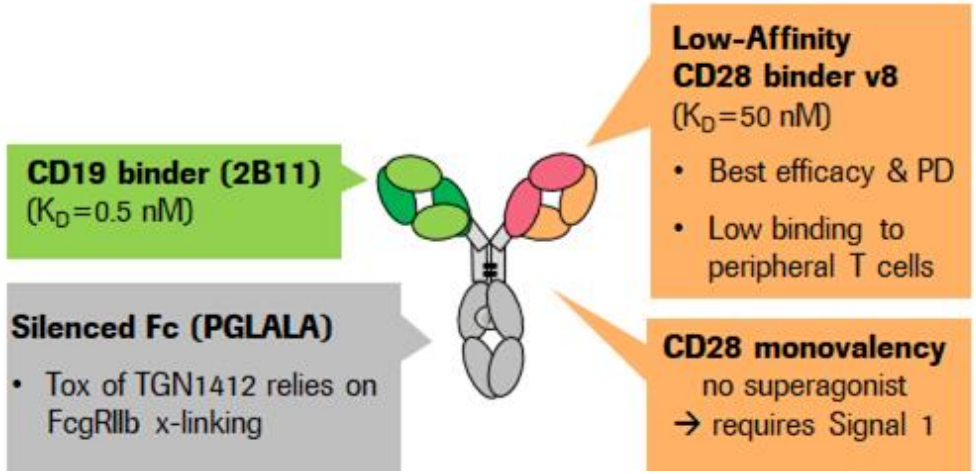


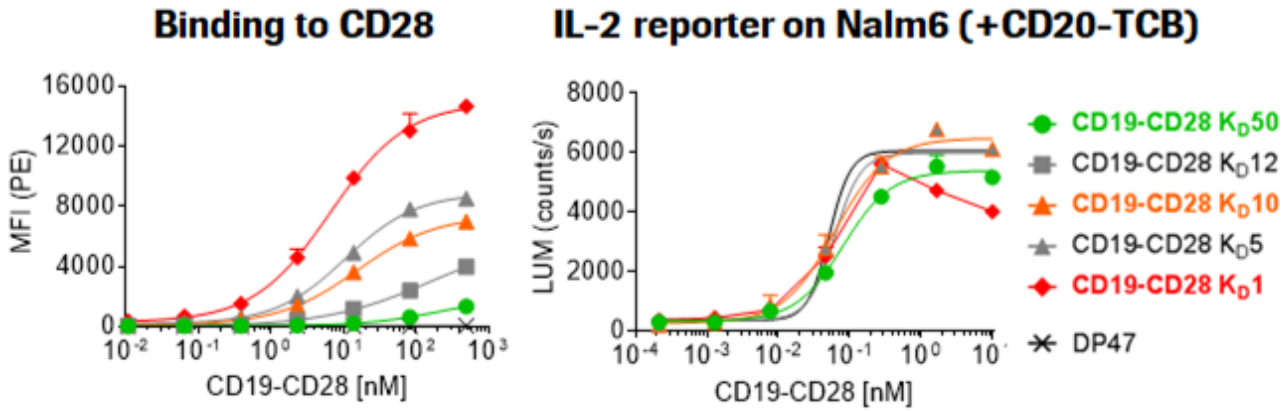
Hutchings M, et al. ASH 2022. Abstract P4259.

BP43131: Glofitamab + CD19-targeted CD28 agonist

Providing safe agonistic CD28 targeting w/o autonomous T cell activation

Reduce peripheral binding to CD28 w/o losing potency





Study design and preclinical data presented at ASH 2022: Dickinson M, et al. P1659

Conclusions

- Recent data from DLBCL phase 2 expansion cohort (33% with prior CAR-T):
  - Glofitamab: ORR 52%, CRR 39%
- 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

Acknowledgements

- Patients and their families
- Research nurses and study coordinators
- NP30179, NP39488, BP41072, BP43131 study teams and co-investigators