Glofitamab – CD20/CD3 Bispecific Antibody

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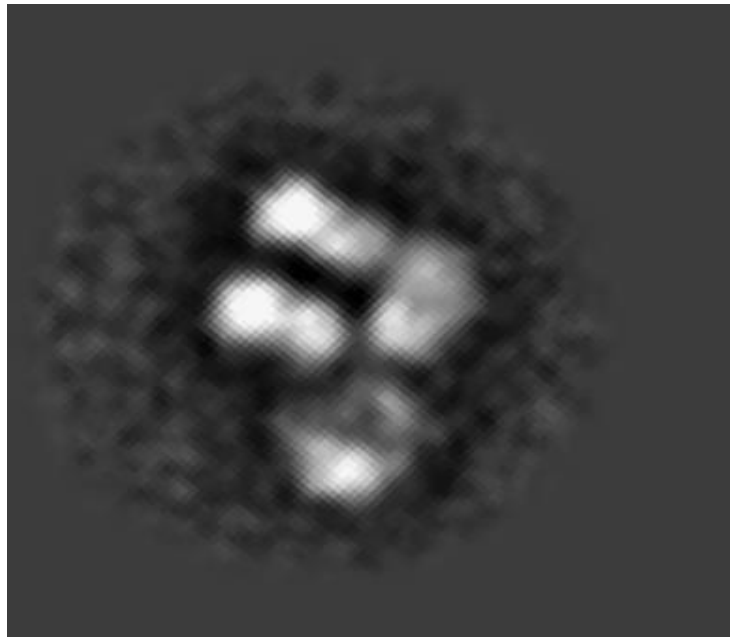
Disclosures

Company	Disclosure
Roche	Advisory boards, research support (direct and indirect), honoraria/speaking fees
Novartis	Advisory boards, research support (direct and indirect), honoraria/speaking fees
GenMab/Abbvie	Advisory boards
BMS	Advisory boards, research support (direct and indirect), honoraria/speaking fees
Kite/ Gilead	Advisory boards, research support (direct and indirect), honoraria/speaking fees
Takeda	Advisory boards, research support (direct and indirect), honoraria/speaking fees
Nkarta	Advisory boards,
AdiCet Bio	Advisory boards

Glofitamab is a full-length, fully humanised IgG1 bispecific antibody with two ‘Fab’ regions that bind to CD20 and one that binds to CD3 in a 2:1 (CD20:CD3) format

Two CD20 antigen-binding sites[1,2]
High-avidity, bivalent binding to CD20, which is expressed on the surface of B cells,[1,2,5] favours tumour targeting and retention, and facilitates combination therapy with standard-of-care anti-CD20 monoclonal antibodies[2]

Fab range of motion in TCB



Fab region[2]

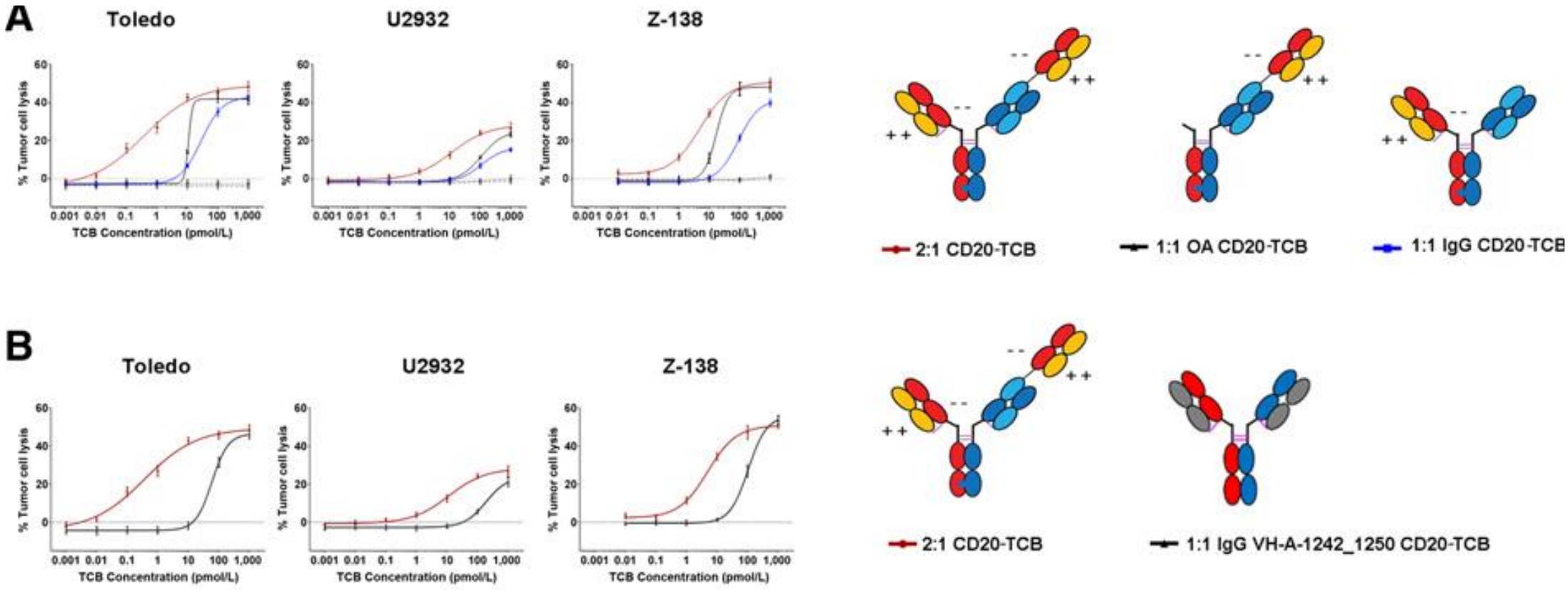
Head-to-tail fusion
Head-to-fail fusion of B- and T-cell binding sites via a flexible linker[1,2]

Fc region which extends the half-
ilent region abrogates
to prevent T-cell lysis[1,2]

et al. Clin Cancer Res 2018;24:4785–97
U. Drug Discov Today 2015;20:838–47

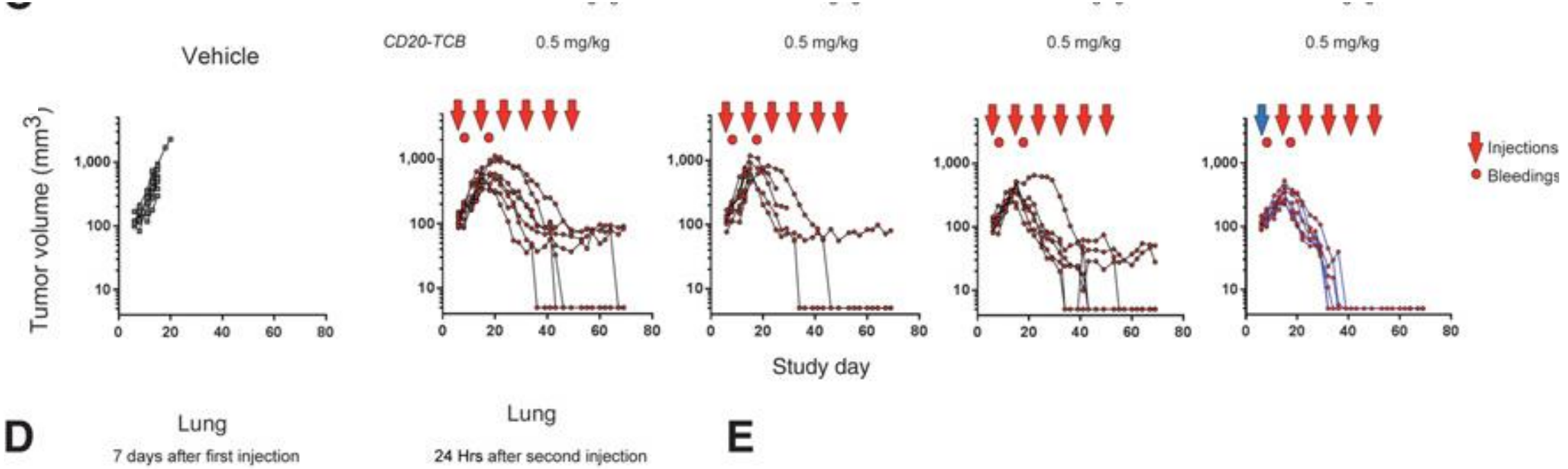
Slide courtesy of Roche, and Marina Bacac and Pablo Umana (modified)

Glofitamab 2:1 structure: More potent *in vitro*



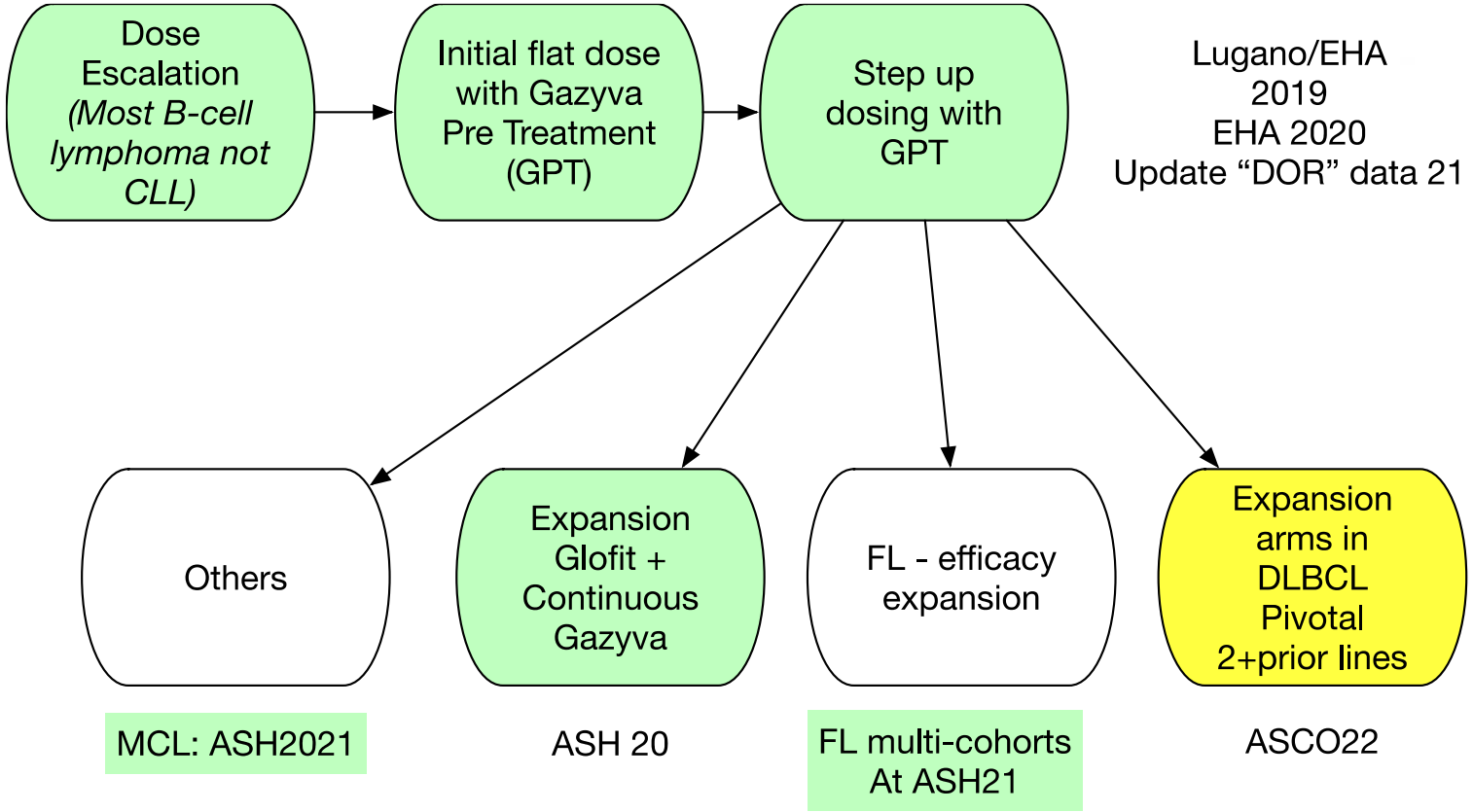
Bacac M, Colombetti S, Herter S, Sam J, Perro M, Chen S, Bianchi R, Richard M, Schoenle A, Nicolini V, Diggelmann S, Limani F, Schlenker R, Husser T, Richter W, Bray-French K, Hinton H, Giusti AM, Freimoser-Grundschober A, Lariviere L, Neumann C, Klein C, Umana P. CD20-TCB with Obinutuzumab Pretreatment as Next-Generation Treatment of Hematologic Malignancies. Clin Cancer Res. 2018;24(19):4785-97.

Glofitamab: active in the presence of saturating doses Obinutuzumab, which competes for binding (and mitigates CRS)



Bacac M, Colombetti S, Herter S, Sam J, Perro M, Chen S, Bianchi R, Richard M, Schoenle A, Nicolini V, Diggelmann S, Limani F, Schlenker R, Husser T, Richter W, Bray-French K, Hinton H, Giusti AM, Freimoser-Grundschober A, Lariviere L, Neumann C, Klein C, Umana P. CD20-TCB with Obinutuzumab Pretreatment as Next-Generation Treatment of Hematologic Malignancies. Clin Cancer Res. 2018;24(19):4785-97.

30179 trial: Phase 1 / 2 Pivotal – Dose determination and several expansion arms

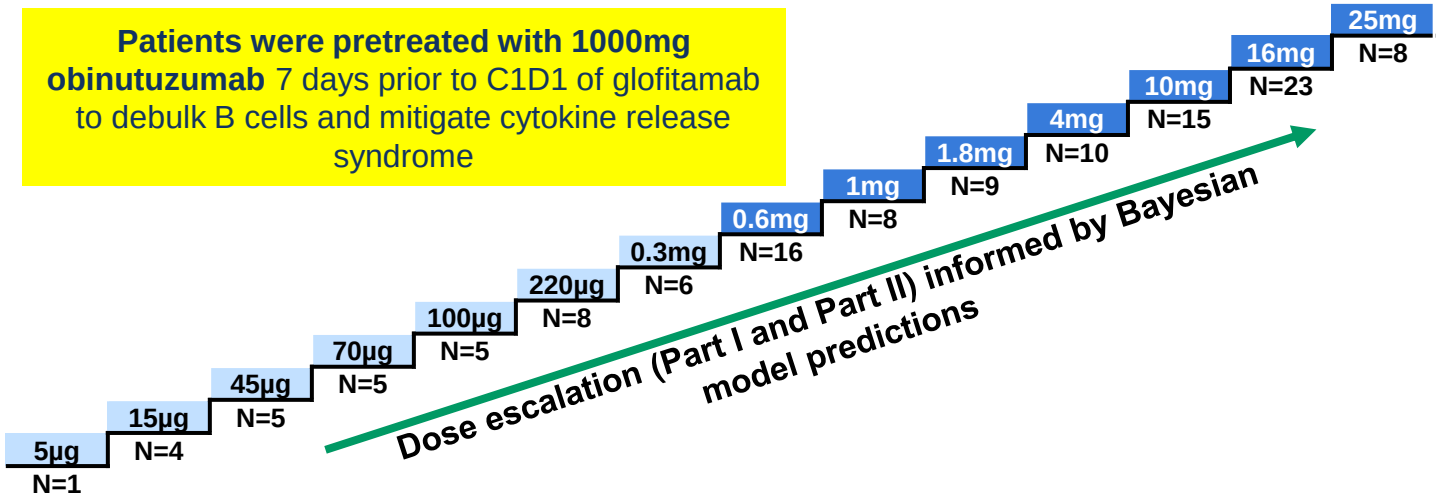


NP30179 (NCT03075696) is an ongoing Phase I dose-escalation study in patients with R/R NHL

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

Patients were pretreated with 1000mg obinutuzumab 7 days prior to C1D1 of glofitamab to debulk B cells and mitigate cytokine release syndrome



Part I – Dose escalation
Single patient cohorts (N=6)
5µg, 15µg or 45µg glofitamab IV
Switch to Part II triggered by Grade 2 treatment-related AE (neutropenia)

Part II – Dose escalation
Multiple patient cohorts (N=123)
Glofitamab IV Q2W for up to 12 14-day cycles
or
Q3W (from 10mg) for 8–12 21-day cycles

Part III – Dose expansion
R/R DLBCL or R/R FL (Grade 1–3a)
with ≥2L prior therapies (N=67)
Glofitamab IV Q3W for 8–12 21-day cycles
C1: 10mg, C2 onwards: 16mg (10/16mg)

Primary objective: Part I
Safety/tolerability

Primary objectives: Part II
Safety/tolerability, PK, MTD/OBD, RP2D

Primary objective: Part III
Efficacy and safety

Clinical cut-off date: 17 April 2020. 2L, two lines; AE, adverse event; C, Cycle; D, Day; DLBCL, diffuse large B-cell lymphoma; ECOG PS; Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IV, intravenous; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; OBD, optimum biological dose; PK, pharmacokinetics; Q2/3W, every 2/3 weeks; RP2D, recommended Phase II dose; R/R, relapsed/refractory

Patient demographics, baseline disease characteristics and NHL histology in all glofitamab cohorts

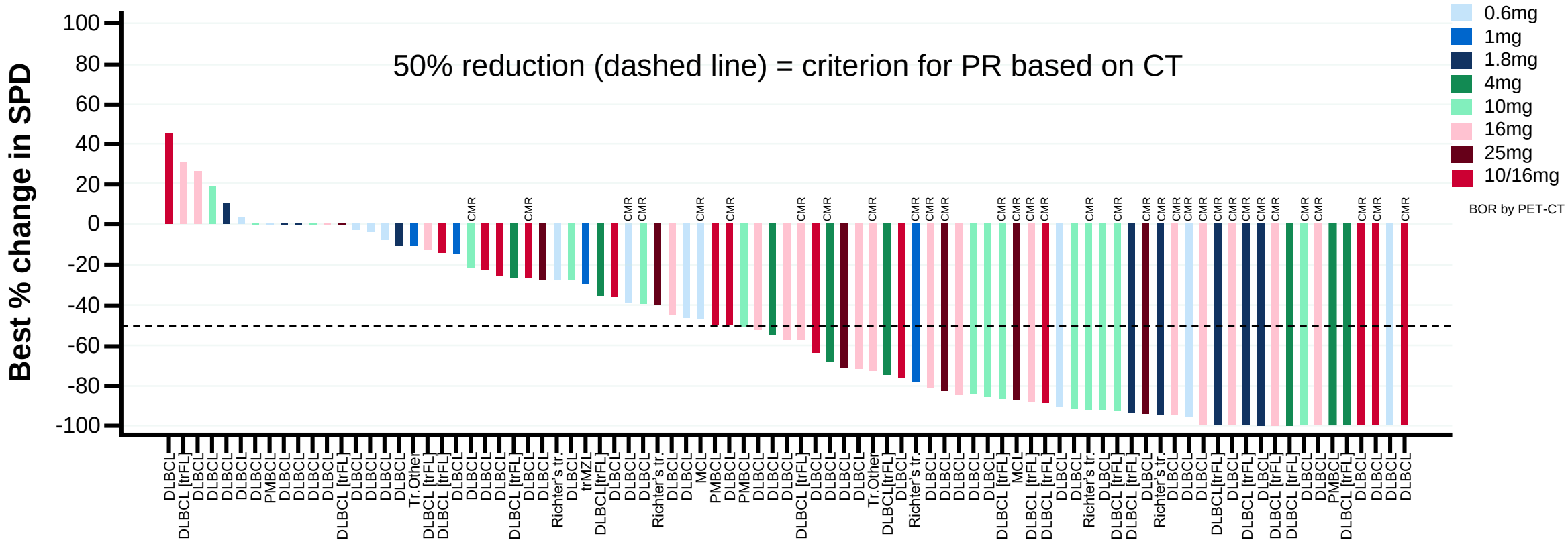
	All glofitamab cohorts ***(N=171)***
Median age, years (range)	64 (22–85)
Male gender, n (%)	100 (58.5)
Prior lines of therapy, median (range)	3 (1–13)
Prior ASCT, n (%)	41 (24.0)
Prior CAR-T therapy, n (%)	3 (1.8)
Refractory status, n (%)	
Refractory to any prior therapy	155 (90.6)
Refractory to any prior anti-CD20 therapy	144 (84.2)
Histology subtype, n (%)	
Diffuse large B-cell lymphoma	73 (42.7)
FL Grade 1–3a	44 (25.7)
trFL	29 (17.0)
Richter's transformation	10 (5.8)
Primary mediastinal large B-cell lymphoma	3 (1.8)
Others*	12 (7.0)

Pooled data from patients who received glofitamab at any fixed dose and at the RP2D (2.5/10/30 mg)

Clinical cut-off date: 3 August 2020. *For all patients, "other" histologies includes FL grade 3B (n=2), mantle cell lymphoma (n=6), high-grade B-cell lymphoma (n=1), DLBCL transformed from marginal zone lymphoma (n=1), DLBCL transformed from isolated cervical immunoblastic lymphoma (n=1), and DLBCL transformed from Waldenström, (immunocytoma; n=1). Please see notes for abbreviations.

Adapted from: Hutchings M, et al. J Clin Oncol 2021 (online ahead of print)

Antitumor activity* in aggressive non-Hodgkin lymphoma†



Clinical cut-off date: 17 April 2020. n.b. Patients enrolled in the 10/16mg cohort after September 2019 are not included as the data were captured in a separate database. *≥0.6mg cohorts; assessed by computed tomography (CT) and Lugano criteria.[1]
†Aggressive NHL includes DLBCL, transformed FL, PMBCL, MCL, transformed MZL and Richter's transformation
BOR, best overall response; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; PR, partial response; Richter's tr, Richter's transformation; SPD, sum of the longest diameters; tr, transformed

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68

Adverse events (AEs) of special interest

	≥0.6 mg cohorts (N=156)	*Comments*
Cytokine Release Syndrome (CRS)[1] All grade Grade ≥3	 88 (56.4%) 5 (3.2%)	• Gr ≥3 CRS events: 1.8 mg (G3, n=1); 4 mg (G3, n=1); 10/16 mg (G3, n=1); 25 mg (G3, n=1; G4, n=1) • 26 (16.7%) patients received tocilizumab
Neurological adverse events* All grade Grade ≥3	 47 (30.1%) 3 (1.9%)	• Headache (n=14, 9.0%), insomnia (n=7, 4.5%) and anxiety (n=5, 3.2%) were the most common NAEs • 'ICANS†-like' AEs included confusion in 7 patients (G1, n=3; G2, n=2, G3, n=2); aphasia in 1 patient (G3), depressed level of consciousness in 1 patient (G2), mental status change in 1 patient (G1), neurotoxicity in 1 patient (G2)
Neutropenia‡ All grade Grade ≥3 Febrile neutropenia	 48 (30.8%) 40 (25.6%) 2 (1.3%)	• Neutropenia generally responsive to GCSF • Did not lead to treatment discontinuation • No relationship with infection at this time

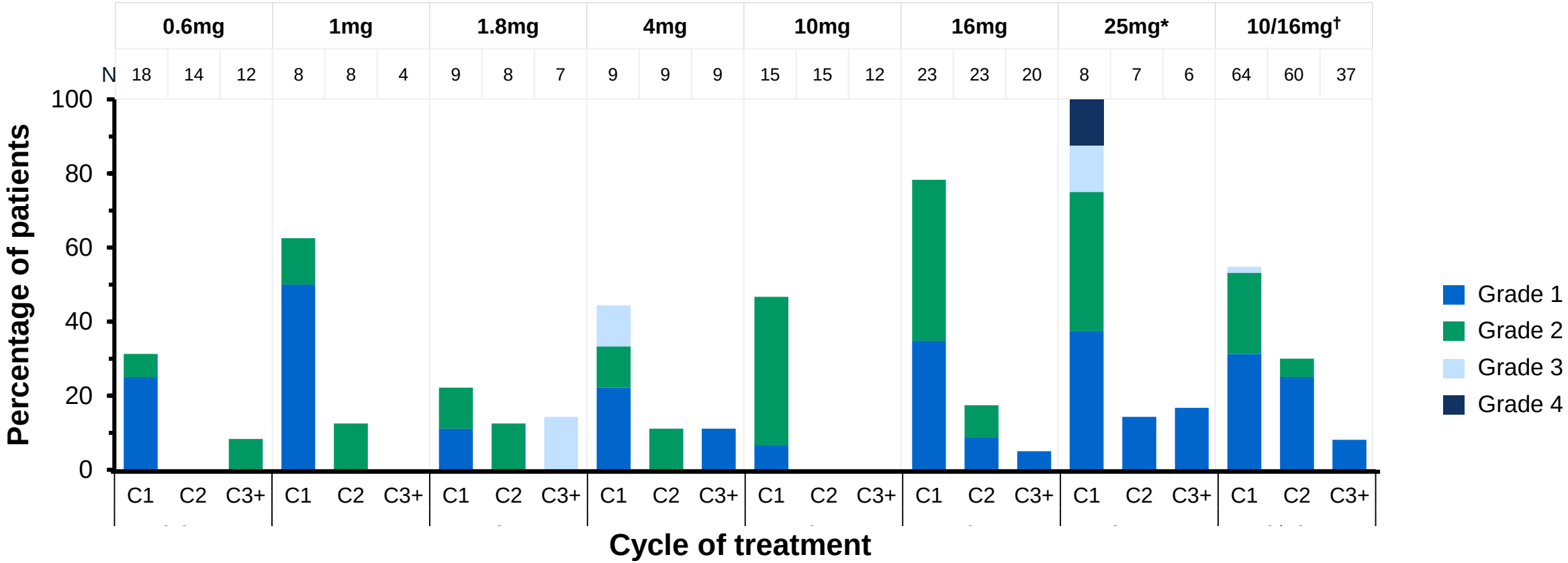
Clinical cut-off date: 17 April 2020. *Any preferred terms included in the Nervous System Disorder and Psychiatric Disorders System Organ Class; Grade ≥3 neurologic adverse events by preferred term: facial paralysis, radiculopathy and aphonia (n=1, each); †'ICANS-like AEs' including confusion, aphasia, depressed level of consciousness, encephalopathy and mental status change were based on manual adjudication by Roche team; ‡Includes the preferred terms neutropenia and neutrophil count decreased

G, Grade; GCSF, granulocyte-colony stimulating factor; ICANS, immune effector cell-associated neurotoxicity syndrome

1. Lee DW, et al. Blood 2014;124(S2):188–95

Cytokine release syndrome (CRS) events were mostly Grade 1 or 2 and occurred predominantly in Cycle (C) 1

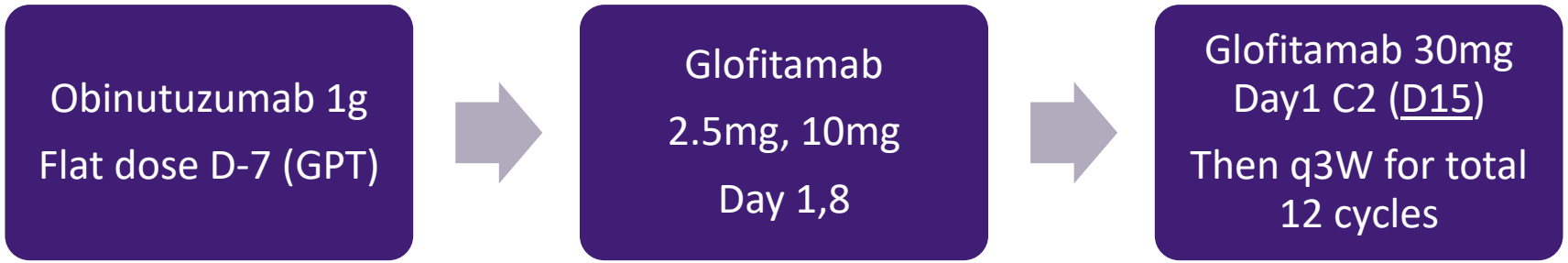
- Median time to the incidence of CRS[1] was **10.5 hours** from first glofitamab infusion (C1)
- The increased frequency and severity of CRS events tended to increase with escalating doses



Clinical cut-off date: 17 April 2020. *Based on observed events, 25mg as first C1 dose on fixed dosing schedule was determined to exceed maximum tolerated dose; †patients received 10mg glofitamab as first C1 dose and 16mg from C2 onwards

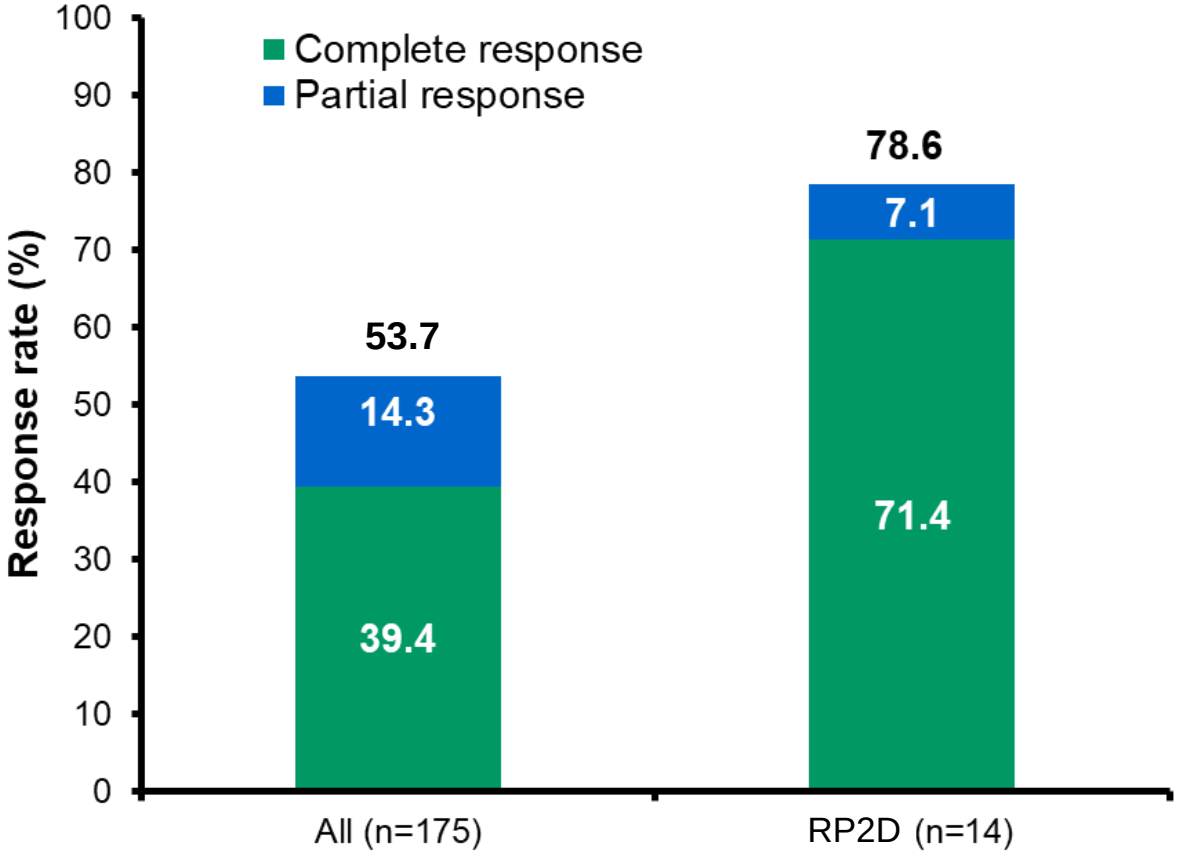
1. Lee DW, et al. Blood 2014;124(S2):188–95

Glofitamab go-forward dosing

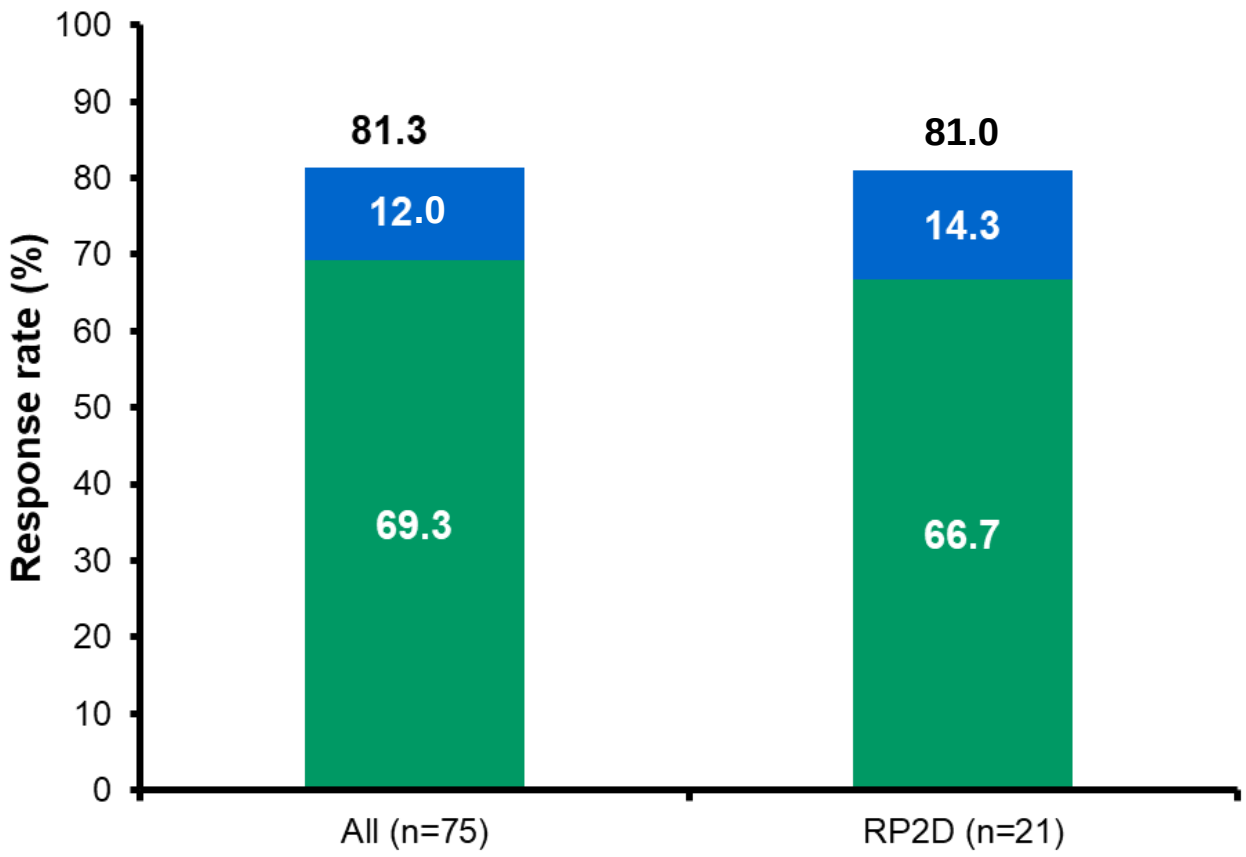


ASH 2021 update

aNHL*
ORR 53.7%, CR 39.4%



iNHL*
ORR 81.3%, CR 69.3%

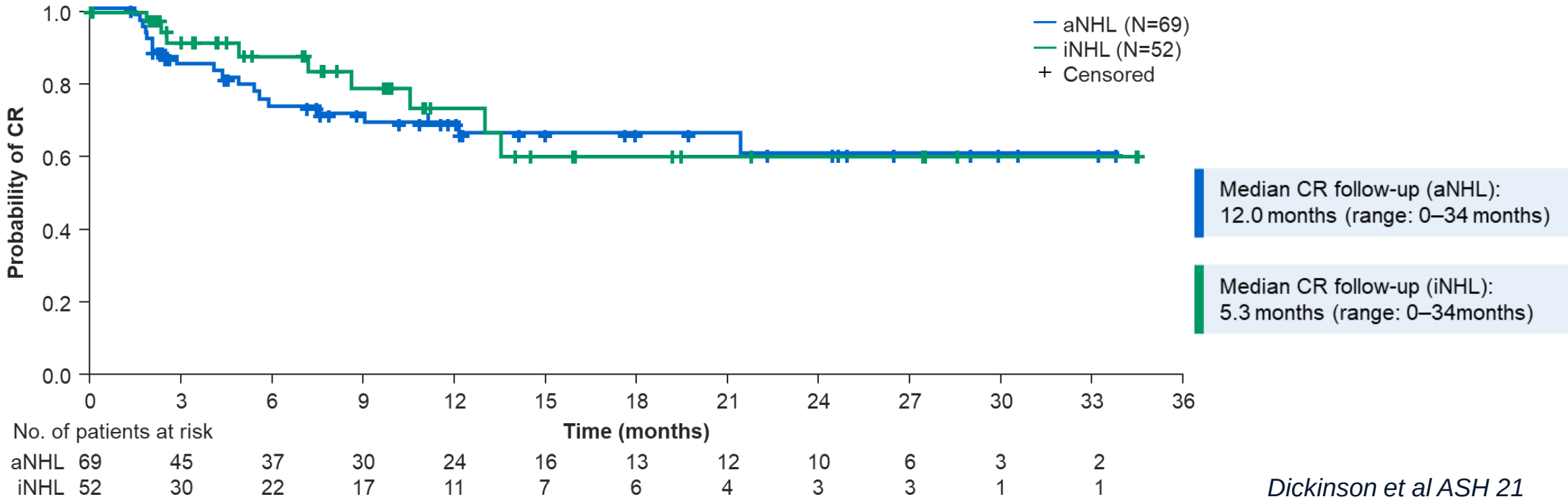


*Efficacy-evaluable population; best overall responses. CR, complete response; aNHL, aggressive non-Hodgkin lymphoma; iNHL, indolent non-Hodgkin lymphoma; ORR, overall response rate; RP2D, recommended phase 2 dose

Dickinson et al ASH 21

Durability of complete remission across ALL doses >0.6mg (fixed and step up dosing)

- Median follow-up of patients who achieved CR exceeded 12 months for patients with aNHL and median follow-up of CR was 5.3 months for iNHL
- Responses were durable beyond the end of treatment (approximately month 9):
  - **aNHL:** after a median CR follow-up of 12 months, 50/69 (72.5%) patients had an ongoing CR
  - **iNHL:** after a median CR follow-up of 5.3 months, 43/52 (82.7%) patients had an ongoing CR

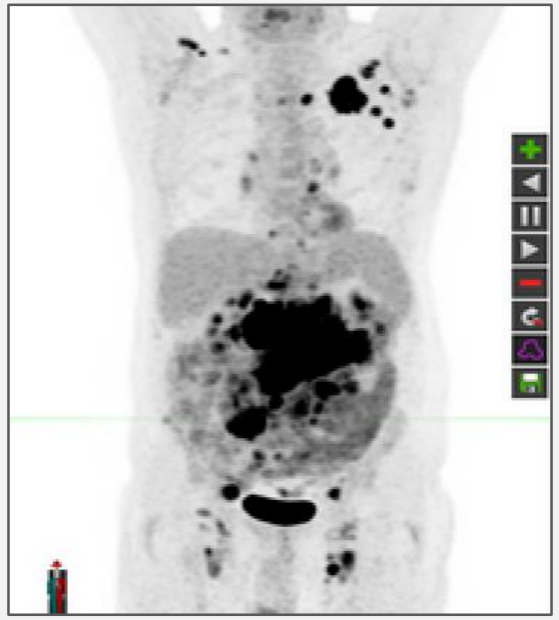


Dickinson et al ASH 21

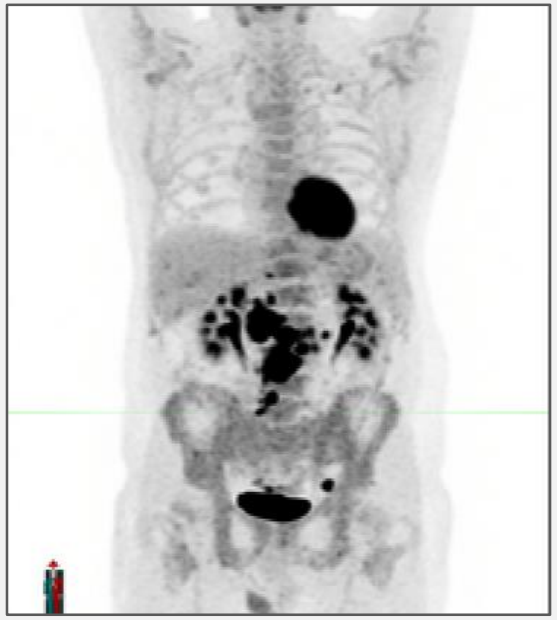
Patient case

64-year old male with transformed follicular NHL

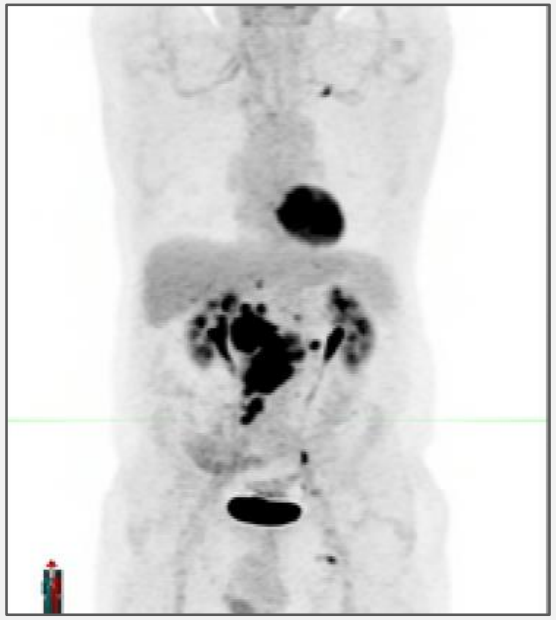
- PD (best response) on 3 prior lines of therapy



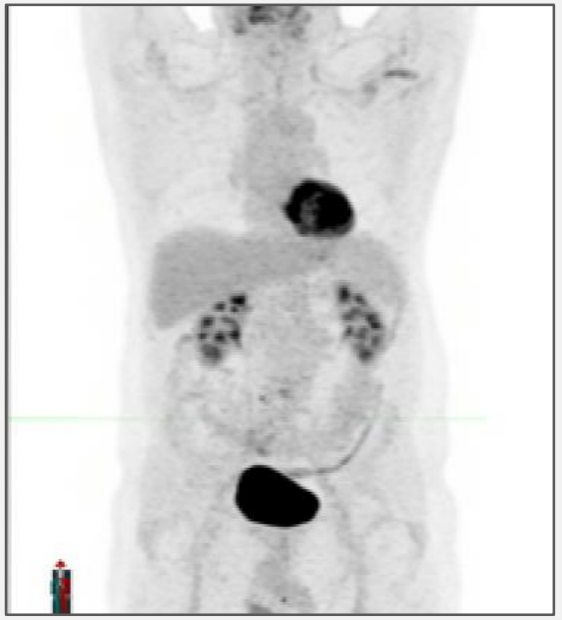
Diagnosis
(external hospital)



Post R-CHOP,
R-DHAP



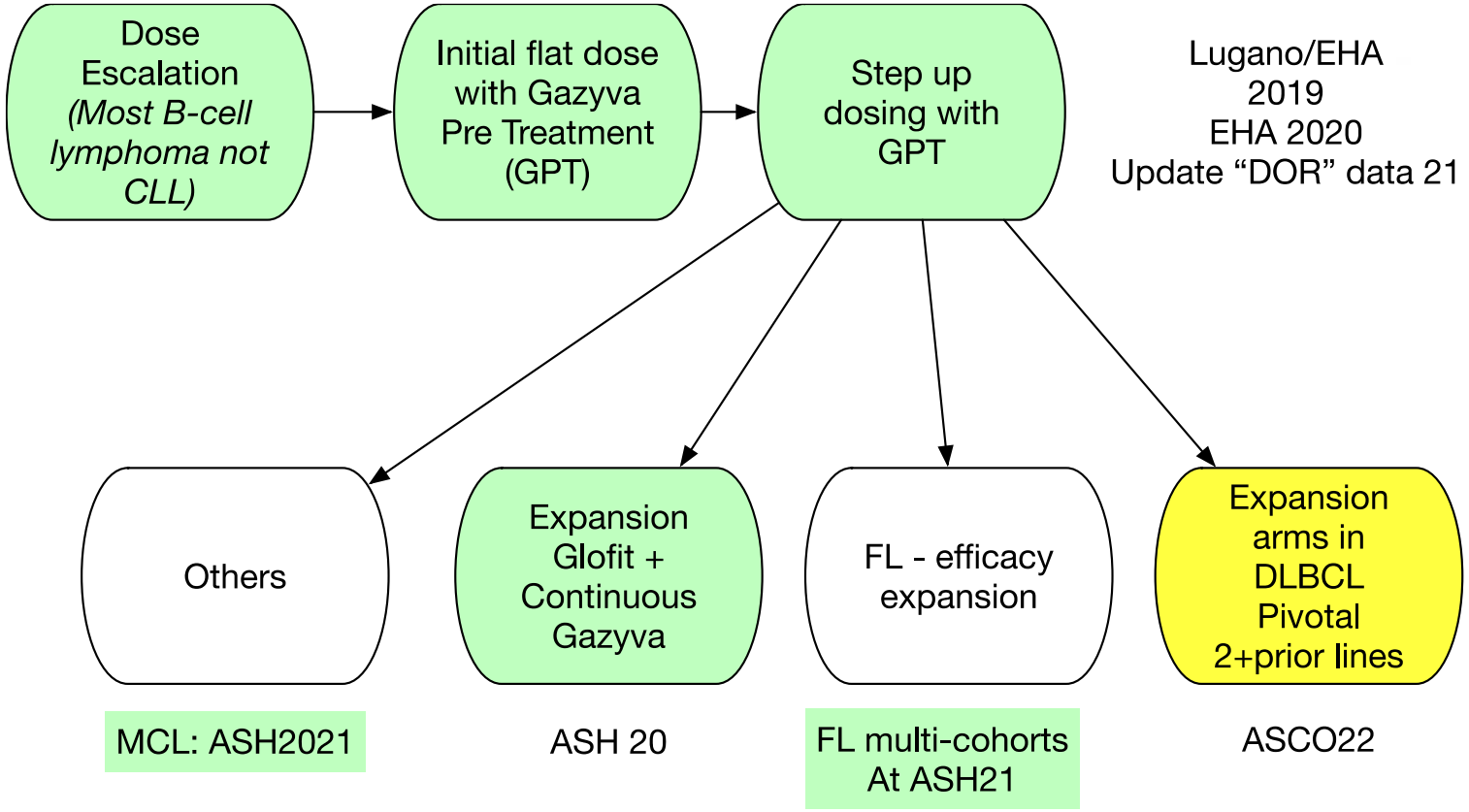
Baseline
(post-R-Gem-Vino)



Pre-C3 assessment

Courtesy of Michael Dickinson and Mary Ann Anderson; Peter MacCallum Cancer Centre

30179 trial: Phase 1 / 2 Pivotal – Dose determination and several expansion arms



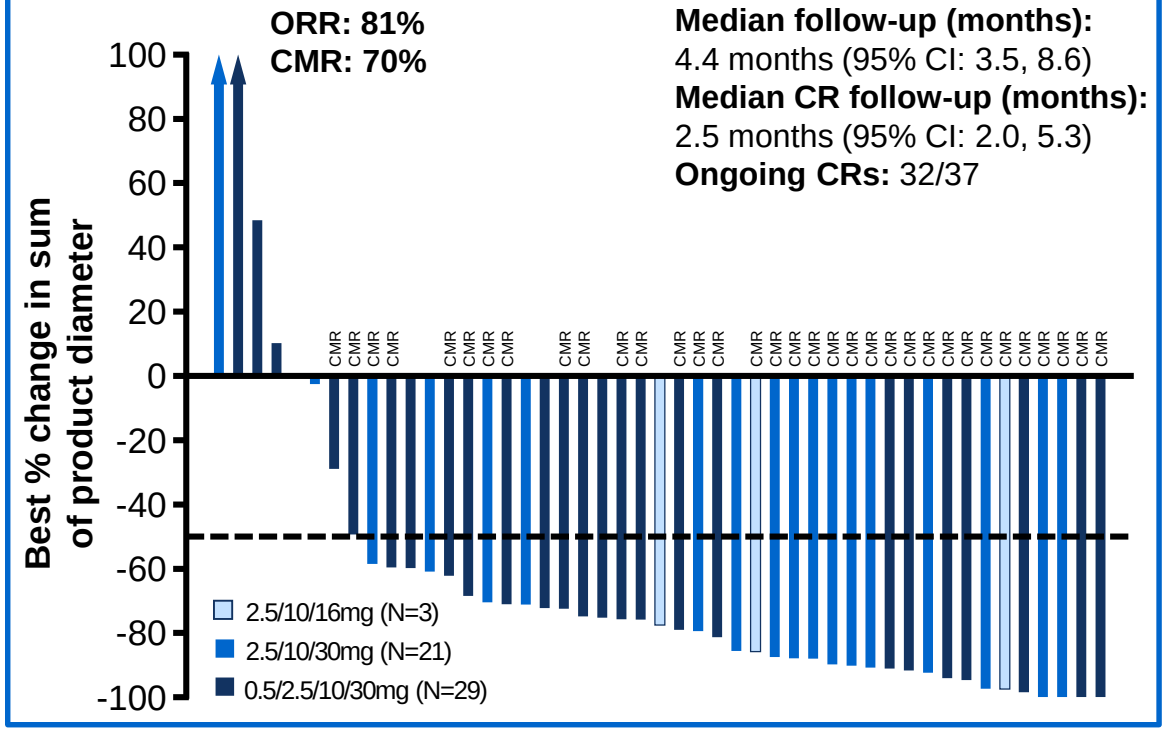
Early correlates of response (Hypothesis generating)

- Lower levels of baseline CRP, IL6 and IL8 associated with complete remission
- The percentage and intensity of CD20 staining (H score) and percentage of proliferating (Ki67+) tumor cells were not associated with CR
- Trend toward a higher of CD8+ T cells signature the tumor at baseline in those achieving CR
- No association (yet) with cell of origin
- Negative association for CR in those with PD1 high signature at baseline, MYC targets signature, *TP53*mut

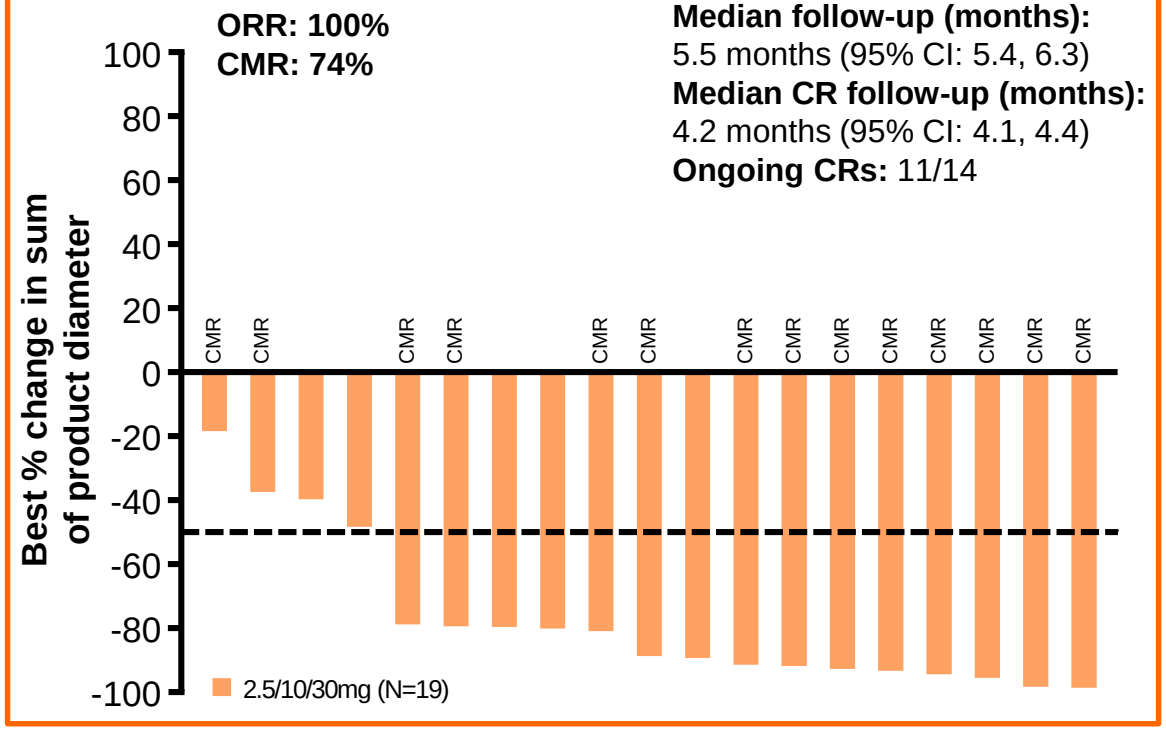
Broske AE, Korfi K, Belousov A, Wilson S, Ooi CH, Bolen CR, Canamero M, Alcaide EG, James I, Piccione EC, Carlile DJ, Dimier N, Umana P, Bacac M, Weisser M, Dickinson M. *Pharmacodynamics and molecular correlates of response to glofitamab in relapsed/refractory non-Hodgkin lymphoma*. **Blood Adv**. 2022;6(3):1025-37.

Antitumor activity in R/R FL

Glofitamab monotherapy*



Glofitamab in combination with obinutuzumab



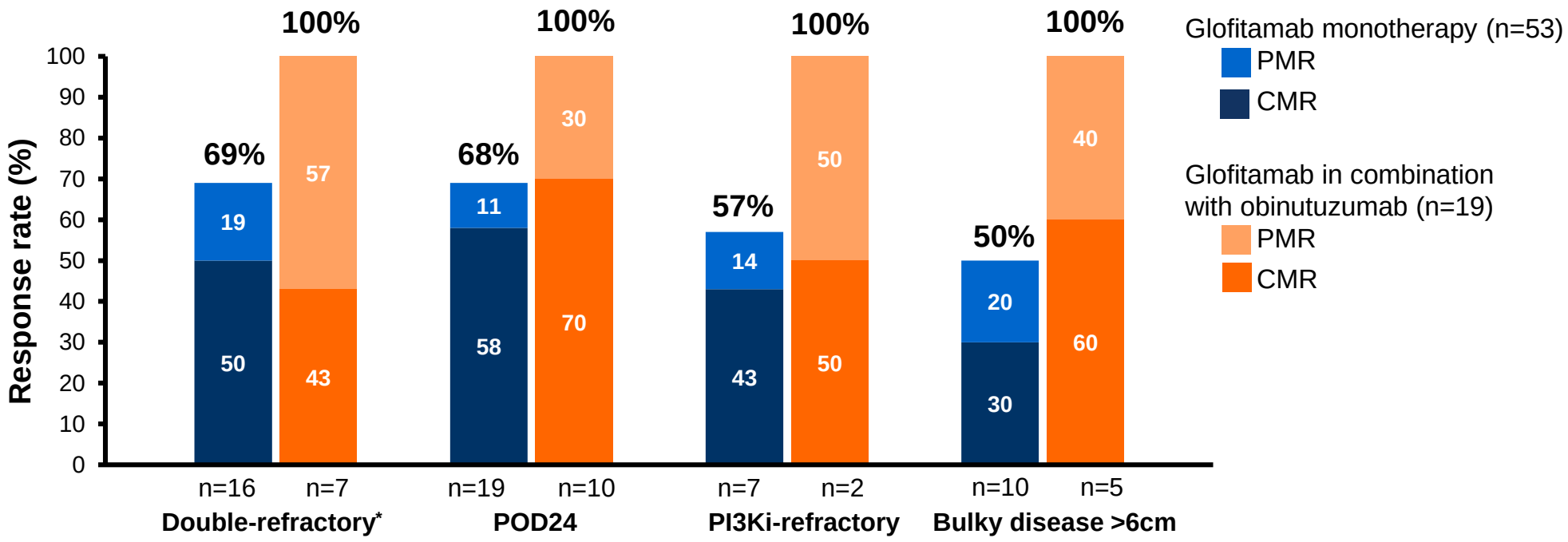
- **Deep responses observed across glofitamab dosing regimens; most complete responses were ongoing**

*Change in SPD not reported for six patients due to missing data at time of data snapshot. Reference line at -50% indicates the reduction required for PR based on CT. ORR, overall response rate, CMR, complete metabolic response

Morschhauser,Carlostella, Dickinson….Bachy ASH2021

Response rates in high-risk subgroups

Glofitamab as monotherapy or in combination with obinutuzumab



- **High and consistent response rates in high-risk patient population**

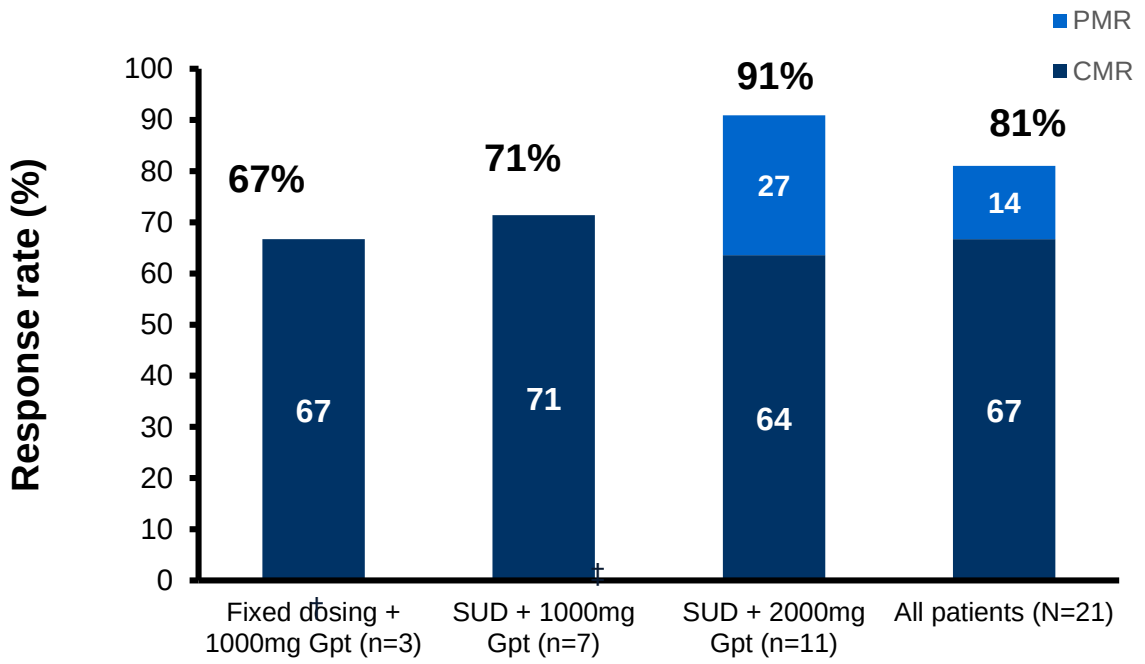
*Patients refractory to anti-CD20 antibodies and alkylating agents.

Morschhauser,Carlostella, Dickinson….Bachy ASH2021

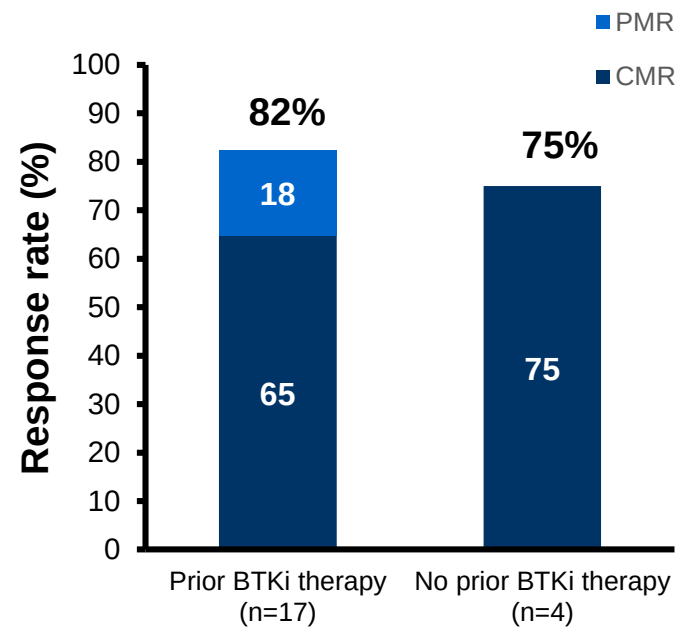
Response rates in MCL

Tycel, Dickinson et al. ASH 2021

Response rates[1] by glofitamab regimen*



Response rates[1] by prior BTKi therapy*



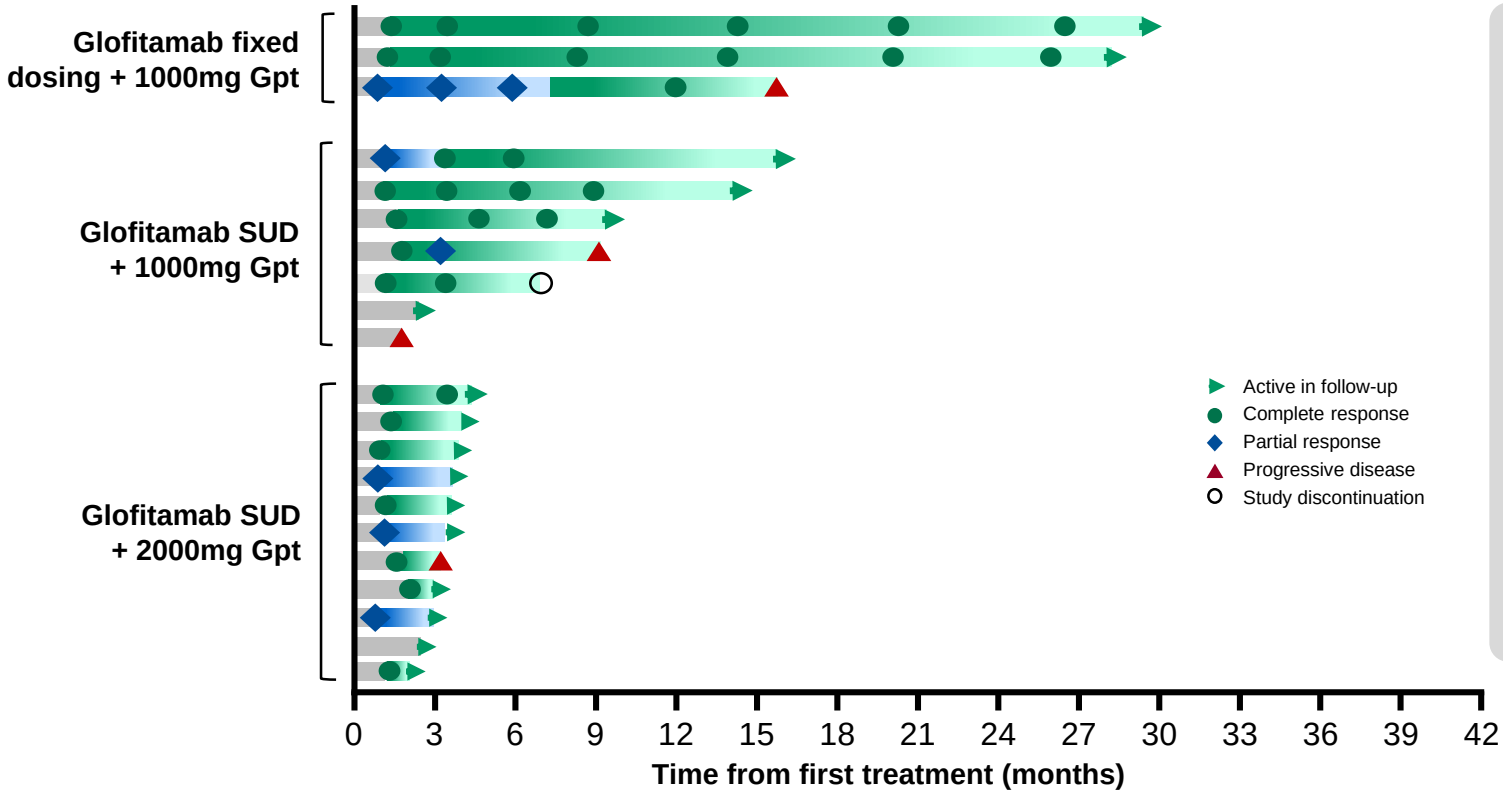
- **Glofitamab resulted in high response rates in patients with R/R MCL**

*21/29 patients were efficacy-evaluable: the secondary efficacy-evaluable population includes all patients who had a response assessment performed (investigator-assessed), or who were still on treatment at the time of their first scheduled response assessment (Lugano 2014 criteria)[1]. †Due to a data issue, the response (CR) from one patient is reported as missing. Two patients treated with a combination of glofitamab and obinutuzumab (G-combo); ‡One patient treated with G-combo. Gpt, obinutuzumab pretreatment; SUD, step-up dosing

1. Cheson, et al. J Clin Oncol 2014

Time on treatment and response

Duration of response in efficacy-evaluable patients*



- Median follow-up (months):
  - *Glofitamab fixed dosing + 1000mg Gpt:* ***25.9 months***
  - *Glofitamab SUD + 1000mg Gpt:* ***7.3 months***
  - *Glofitamab SUD + 2000mg Gpt:* ***1.3 months***
  - *All patients:* ***1.4 months***
- Median duration of CR follow-up: 2.4 months (range, 0.0–25.0)
- Median DOR was not reached
- At the data cut-off, 85.7% (12/14) patients with a CR remained in remission
- Median duration of response and median duration of CR were not reached

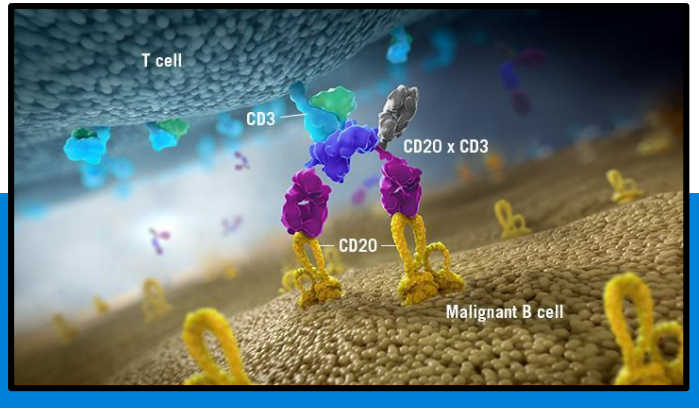
- **Most patients had ongoing responses at the time of the data cut-off**

*Secondary efficacy-evaluable population. Gpt, obinutuzumab pretreatment; SUD, step-up dosing

Tycel, Dickinson et al. ASH 2021

Clinical Development Plan

Courtesy of *Roche*



Pivotal DLBCL data at ASCO 2022

*Glofitamab Program**

CT.gov ID	Combination	Indication	Ph 1	Ph 2	Ph 3
NCT03075696	*Glofit*	R/R DLBCL			
NCT04657302	*Glofit*	R/R DLBCL (China)			
NCT04313608	*Glofit-GemOx*	R/R DLBCL			
NCT04408638	*Glofit-GemOx*	R/R DLBCL			
NCT05364424	*Glofit+R-ICE*	R/R DLBCL			
NCT05335018	*Glofit+Len+Poseltinib*	R/R DLBCL (Seoul)			
NCT03533283	*Glofit+Pola*	R/R NHL			
NCT04077723	*Glofit+4-1BB L*	R/R NHL			

CT.gov ID	Combination	Indication	Ph 1	Ph 2	Ph 3
NCT05219513	*Glofit+RO7443904*	R/R NHL			
NCT03467373	*Glofit+R-CHOP/ R-CHP-Pola*	1L DLBCL			
NCT04980222	*Glofit+R-CHOP*	1L DLBCL (ctDNA)			
NCT04914741	*Glofit+R-CHOP/ R-CHP-Pola*	1L DLBCL (High risk)			
NCT05169515	*Glofit+CELMoDs*	NHL			
NCT04889716	*Glofit+Obinutuzumab*	Post CAR T			
NCT04246086	*Glofit+Lenalidomide*	R/R FL			
NCT04703686	*Glofit*	R/R DLBCL, PMBL, MCL, t-iNHL CAR T			

[*Correct as of 13 May 2022]

Roche Sponsored | Investigator Initiated Study

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Simon Harrison
Maryanne Anderson
David Ritchie
Nicole O'Leary (CNC)
Adrian Minson (Fellow)
Mark Dowling (Fellow)

Trial Team B: Gillian Turner,
Sam Van Der Linde, Molly Robertson

Global investigators in the Roche 31079 trial

Scientists at Roche:
Linda Lundberg, David Peres-Callejo, Martin Weisser
Marina Bacac,Ann—Marie Broeske, Kathryn Humphrey and Pablo Umana


GHOST