7th POSTGRADUATE
Lymphoma
Conference

Update on Bispecifics in The Treatment of Indolent Lymphoma

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Donna Camilla Savelli Hotel

President:
P.L. Zinzani

Disclosures

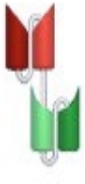
Disclosures of Elizabeth Budde

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen	x						
AstraZeneca	x					x	
ADC Therapeutics	x					x	
Genentech/Roche	x					x	
Gilead						x	
Merck	x						
Mustang Therapeutics	x						

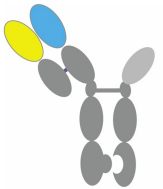
Bispecific T cell engagers in B-NHL/B-ALL

CD19

BITE®
(1:1)



Blinatumomab

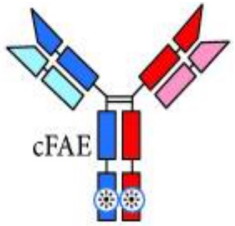


TNB486

CD20

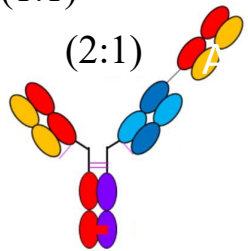
Full length IgG-like (1:1)

Mosunetuzumab

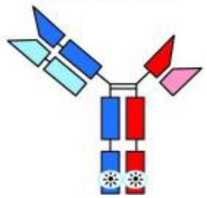


Epcoritamab

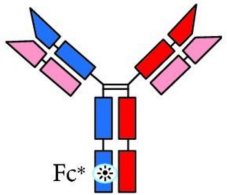
(2:1)



Glofitamab

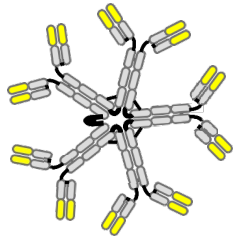


Plamotamab



Odronextamab

IgM (10:1)



Imvotamab

IgM2323

Bispecific T cell engagers in B-NHL/B-ALL

	structure	Target: CD3 ratio	t1/2	Adminis-tration	Fc binding	Complement binding	CD3 recognition
blinatumomab	scFv	1:1	20 min	i.v.	No	No	CD3δε
mosunetuzumab	IgG1	1:1	7-21d	i.v./subq	minimal	No	CD3δε
epcoritamab	IgG4	1:1	7-21d	subq	minimal	No	CD3ε
glofitamab	IgG1	2:1	7-21d	i.v.	minimal	No	CD3ε
TNB486	IgG4	1:1	7-21d	i.v.	minimal	No	CD3δε
Imvotamab	IgM	10:1	3-7d	i.v.	Yes	Yes	CD3δε

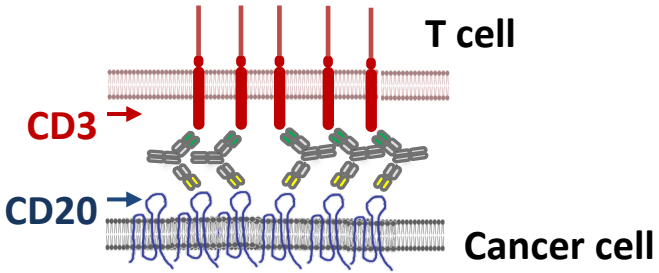
Antibody design related Factors: Efficacy and safety

- Affinity and avidity to target
- CD3 activation strength
- Half life
- Route of administration

BsAb TCE: MOA

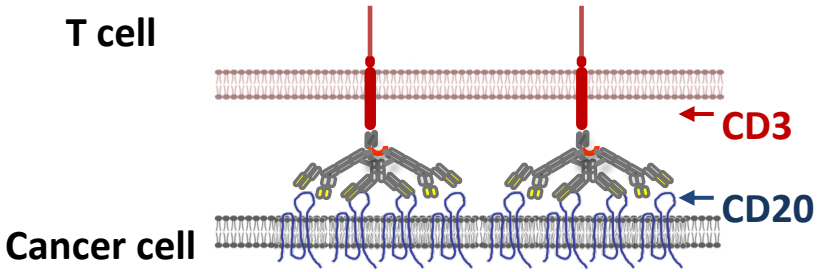
IgG or ScFV based TCE
CD20:CD3 1-2:1

Supraphysiologic T-cell stimulation?



IgM2323
CD20:CD3 10:1

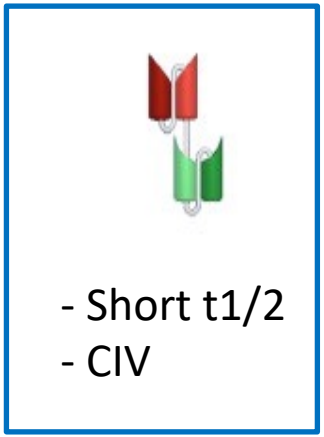
More physiologic T-cell stimulation?



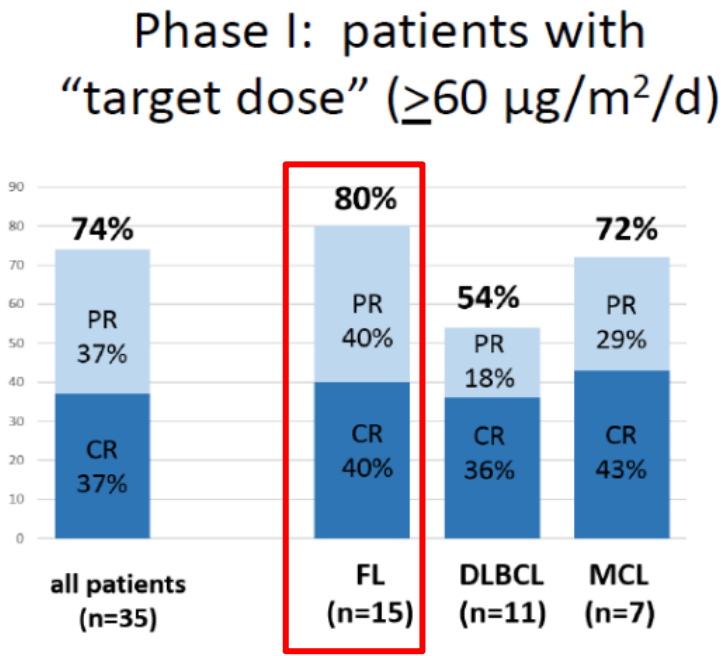
Does a more controlled T-cell activation lead to improved safety profile?

1. Faroudi et al. Proc Natl Acad Sci U S A. 2003;100:14145–50
2. Purbhoo et al. Nat Immunol. 2004;5:524–30
3. Itoh et al. J Exp Med 1997;186:757–6

The bispecific T-cell engager (BiTE) antibody: Blinatumomab in relapsed/refractory NHL: Study 104



- Short t1/2
- CIV



- Neurotoxicity

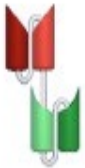
NT is dose limiting.
All grades 70%
≥ Grade 3: 20%
Tremor, speech disorder and encephalopathy
22% discontinuation from study

MTD: 60ug/m²/d

Study schema: cycle 1 (4-8 weeks), followed by 4-week consolidation
NT mitigation strategy: step up dosing (single, double), +/- concomitant steroids use.

M. Goebeler, et al. J Clin Oncol 2016; 34: 1104-11.

What's ongoing for Blinatumomab in the clinic ?



- Different administration strategy, subq
- Prolong half life
- Combinational therapy

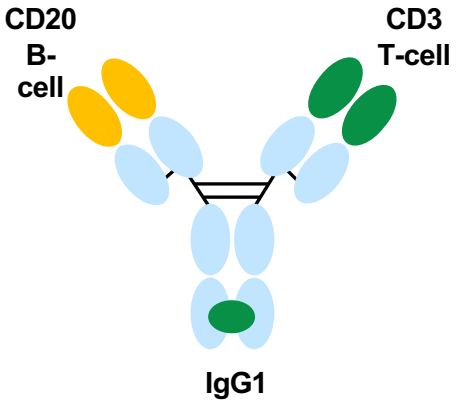
Blinatumomab + Lenalidomide in relapsed/refractory NHL (NCI#9924)
Phase 1: B-NHL including 4 FL

Induction →	Consolidation →	Maintenance
Blina d1-56 Len 3 dose levels	Blina-len x 6 cycles	Len max 26 cycles

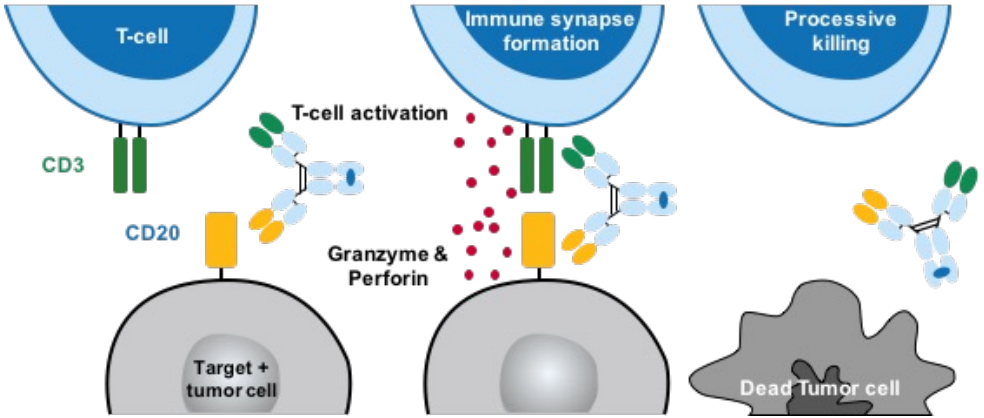
Othman et al. ASH 2022

Mosunetuzumab: a bispecific antibody targeting CD3 and CD20

- **Full-length humanized IgG1 antibody**
  - Longer t1/2 than fragment-based drug formats
  - PK properties enable once weekly to q3w dosing
  - Does not require *ex-vivo* T-cell manipulation
  - Off the shelf, readily available treatment



- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells
  - T-cell activation dependent on B-cell engagement
  - Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells



ADCC, antibody-dependent cell-mediated cytotoxicity

Sun et al. Sci Transl Med 2015

GO29781 Study: pivotal phase II expansion in FL Overview

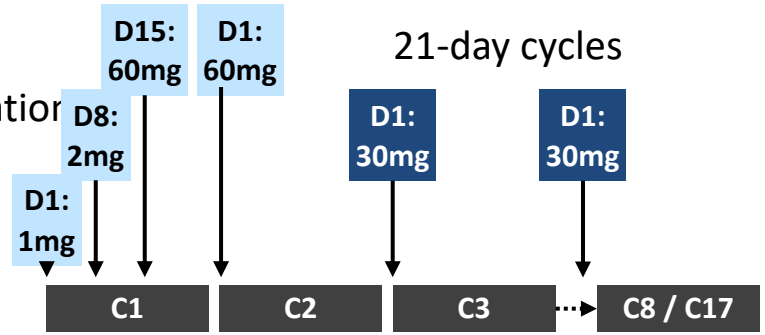
- Single-arm, pivotal Phase II expansion in patients with R/R FL and ≥2 prior therapies

Key inclusion criteria

- FL (Grade 1–3a)
- ECOG PS 0–1
- ≥2 prior regimens, including
  - ≥1 anti-CD20 Ab
  - ≥1 alkylating agent

Mosunetuzumab administration

- Q3W IV administration
- C1 step-up dosing (CRS mitigation)
- **Fixed-duration treatment**
  - 8 cycles if CR after C8
  - 17 cycles if PR/SD after C8
- **No hospitalization requirement**

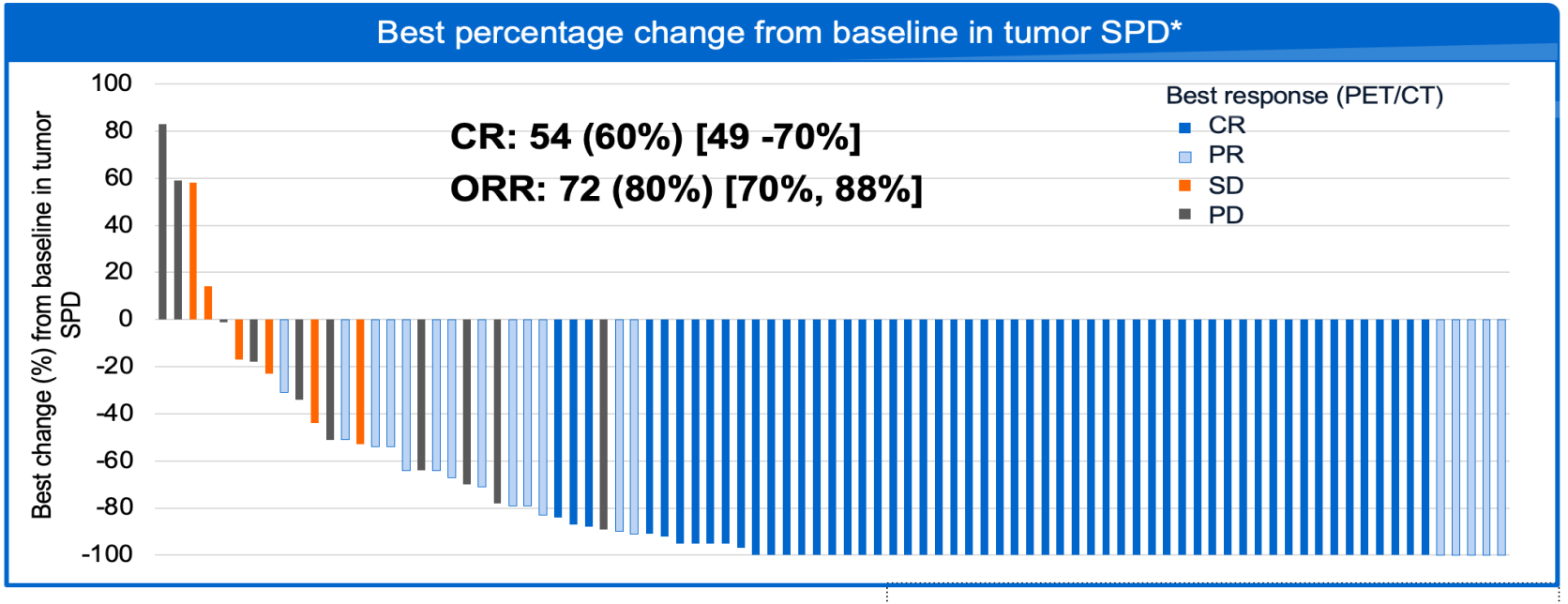


Endpoints

- Primary: CR (best response) rate by IRF* – assessed vs 14% historical control CR rate[1]
- Secondary: ORR, DoR, PFS, safety and tolerability

Budde et al. ASH 2021

Primary endpoint met: CR rate by IRF superior to historical control (14%, p<0.0001*)



Median time to CR:
3 mo (1.2, 18.9)

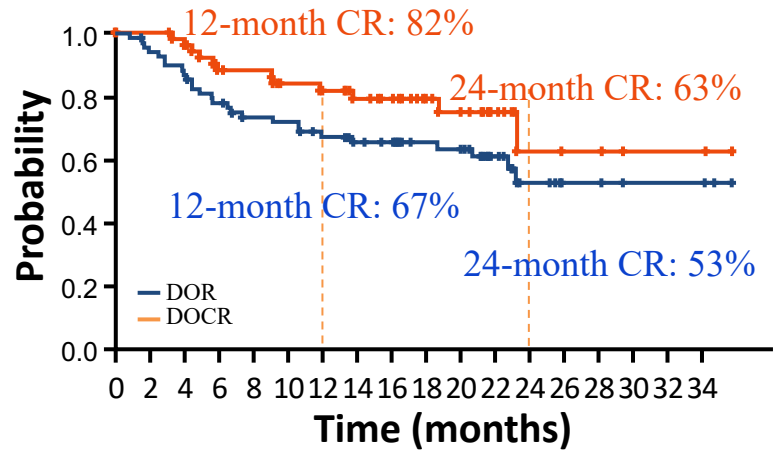
Median DoR:
22.8 months (range: 9.7, NE)

Budde et al. ASH 2021

Durability of responses

Efficacy endpoint by investigator assessment	N=90
Median DOR, months (range), n=70	NR (21–NR)
24-month DOR (95% CI)	53% (38–68)
Median DOCR, months (range), n=54	NR (23–NR)
24-month DOCR (95% CI)	63% (38–88)
Median PFS, months (range)	24 (12–NR)
24-month PFS (95% CI)	48% (36–60)
Median TTNT, months (range)	NR (18–NR)
24-month TTNT (95% CI)	56% (45–67)
Median OS, months (range)	NR (NR–NR)
24-month OS (95% CI)	87% (80–94)

DOR and DOCR



Durable responses: majority of patients in remission after 2 years

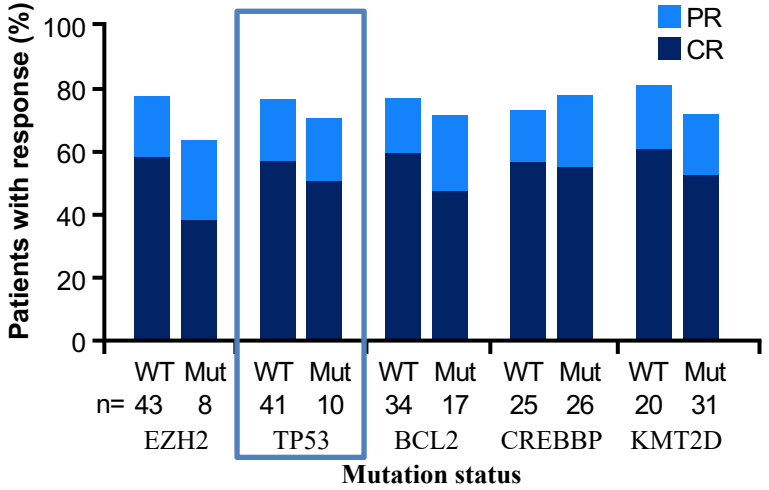
DOCR, duration of complete response; TTNT, time-to-next therapy.

Bartlett et al. ASH 2022

Best overall response by baseline tumor mutation status

- Whole exome sequencing performed in 51 available baseline biopsy samples to assess activity of mosunetuzumab in patients with known prognostic variants

Response by mutation status



Clinically meaningful response rates were observed in patients with common mutations, including those associated with poor prognosis

Bartlett et al. ASH 2022.

Tumor response and CRS occurrence: No Association

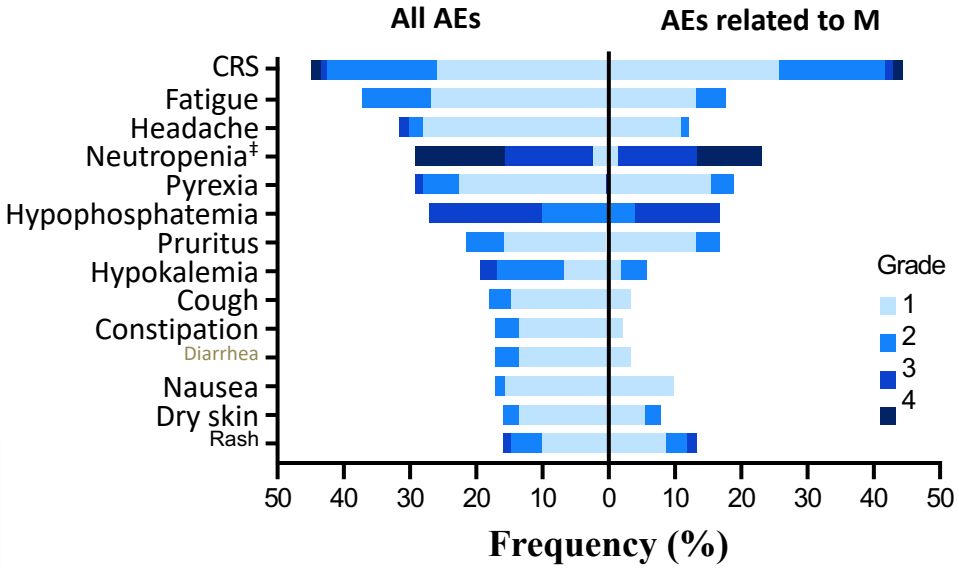
Efficacy endpoints by investigator assessment	CRS (n=40)	No CRS (n=50)
ORR	78%	78%
CR	65%	56%
Median DOR, months (95% CI)	23 (11–NR)	NR (19–NR)
18-month DOR, (95% CI)	65% (48–83)	66% (51–81)
Median DOCR, months (95% CI)	23 (12–NR)	NR (NR–NR)
18-month DOCR, (95% CI)	66% (47–86)	91% (80–100)

No correlation observed between the occurrence of CRS and tumor response

Safety Profile

Adverse events (AEs)	N=90
AE	100%
Mosunetuzumab related	92%
Grade 3/4 AE	70%
Mosunetuzumab related	51%
Serious AE	47%
Mosunetuzumab related	33%
Grade 5 (fatal) AE	2%*
Mosunetuzumab related	0
AE leading to treatment discontinuation	4%†
Mosunetuzumab related	2%

AEs (≥15%) by grade and relationship with mosunetuzumab



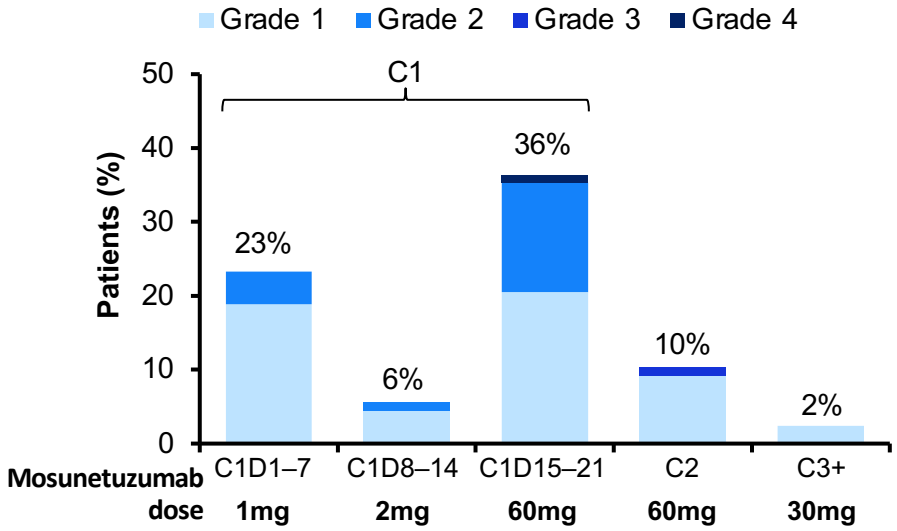
No new serious AEs, Grade ≥3 AEs, or treatment-related AEs were reported with 10 additional months of follow-up

*Malignant neoplasm progression (n=1) and unexplained death (n=1). †Mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each).
‡Grouped term including preferred term 'neutropenia' and 'neutrophil count decreased'.

CRS summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade)	44%
Grade 1	26%
Grade 2	17%
Grade 3	1%
Grade 4	1%
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–24)
C1D15	27 (0.1–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	11%
Tocilizumab for CRS management	8%
Events resolved	100%

CRS by cycle and grade



CRS was predominantly low grade and during Cycle 1
All CRS events resolved; no new events were reported with 10 months of additional follow-up

Bartlett ASH 2022

Mosunetuzumab in comparison with CD19CAR T cells

	target	Enrolled /treated	age	Median prior lines	Prior ASCT	POD24	ORR/CR	PFS
Mosun	CD20	90/90	60 (29-90)	3 (2-10)	21%	52%	80%, 60%	mPFS 24 mo
Axi cel	CD19	124/124	60 (53-67)	3 (2-4)	24%	55%	94%, 79%	12mo PFS 78%
Tisa cel	CD19	98/97	57 (29-73)	4 (2-13)	36%	63%	86%, 69%	12mo PFS 67%

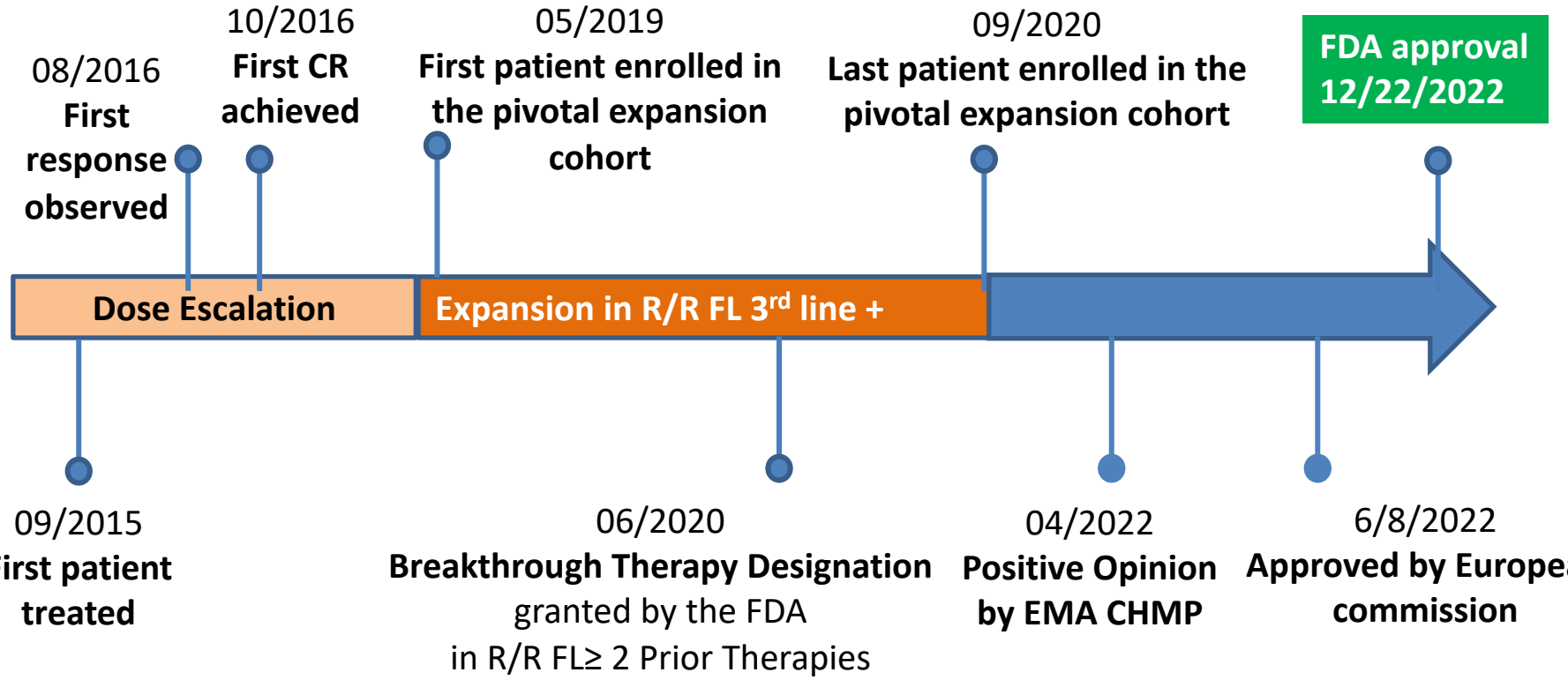
	CRS		NT		Infection
	Any grade	≥ Grade 3	Any grade	≥ Grade 3	Any grade
Mosun	44%	2.2%	4%	0	20%
Axi cel	78%	6%*	56%	15%	18%**
Tisa cel	49%	0	37%	3% 3 gr3, 1 gr4	19%

- 1 grade 5 event
- ** from all pts treated on ZUMA-5 including FL+ MZL

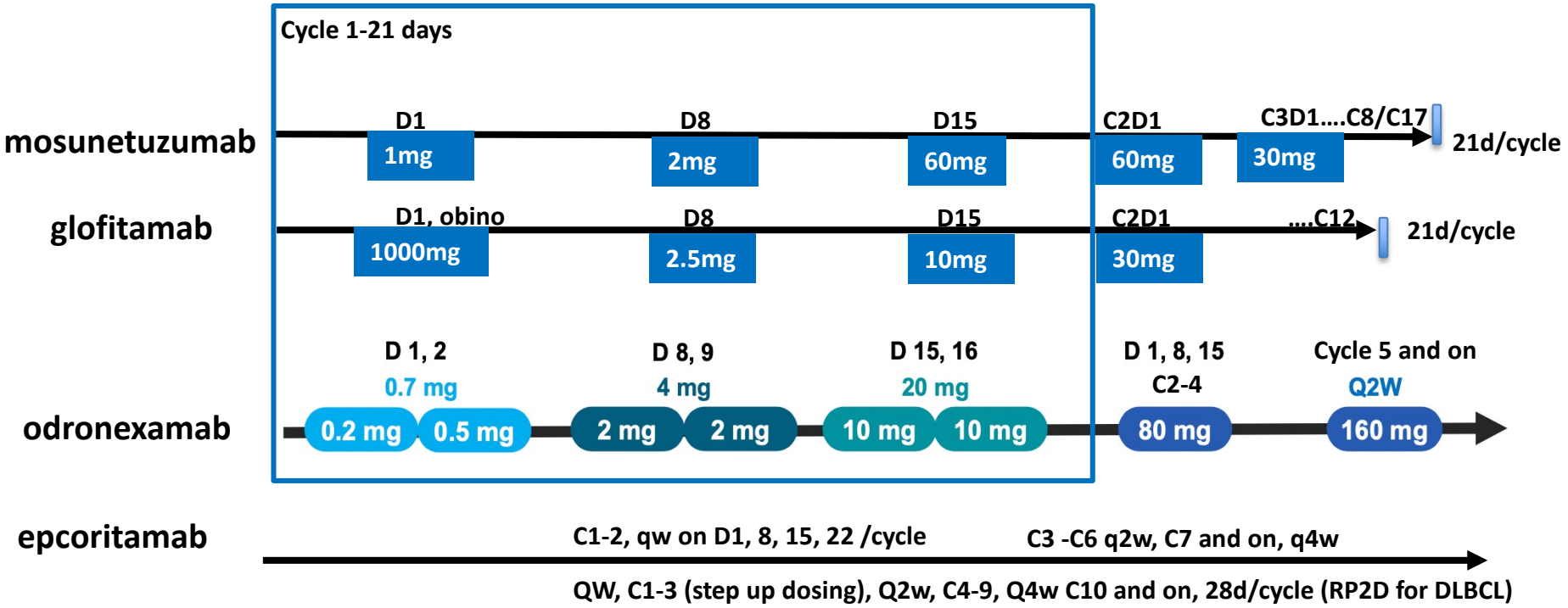
Budde et al. ASH 2021;
Bartlett ASH 2022;
Jacobson et al. Lancet Onc 2022;
Flower et al. Nat Med 2022

Mosunetuzumab in relapsed/refractory B-NHL

GO29781: a Ph1/2 open-label, multicenter study in relapsed/refractory NHL



BsAb/TCE in iNHL Development: Step-up dosing for CRS mitigation



Premed: Dex 20mg for each dose in C1 and the first full dose (epcoritamab prednisone 100mg prior the first 4 doses)

BsAb/TCE in iNHL Development

	Pt#	Dose (mg)	ORR/CR	CRS(%)All/≥ gr3	Note
Odronexamab FL, >2L	68 63	i.v. 1/20/80 0.7/4/20*	72%/61.8% 75.5%/71.7%	55.9%/5.9% 57.1%/1.6%	12 mo: 65% Infection: 65.6% gr3: 32.1%
Glofitamab FL, > 1L	43	i.v. phase 1 Step up	81%/70%	71%/8%	12 cycles total Obino x 1 pretreatment
Epcoritamab FL, > 2L	10	s.c. phase 1 step up	9 ORR/ 5 CR	59%/0%	Subq
TNB486 FL, > 2L	12	i.v. Phase 1 Step up	5 ORR/5 CR	n/a	Yet to determine RP2D
IGM2323 FL, > 2L	6	i.v. phase 1 step up	100-300mg 3 ORR/3 CR	n/a	Yet to determine RP2D (100mg?)

BsAb/TCE in iNHL Development: CRS/Infusional reaction mitigation

	Premed Steroids
mosunetuzumab	20mg dex C1D1, 8, 15, & C2D1
glofitamab	20mg dex C1D1, 8, 15, C2D1, & C3D1
odronexamab	20mg dex C1D1&2, 8&9, 15&16, C2D1 10mg Dex 12-24h before C1D1, 8, 15
epcoritamab	Prednisone 100mg daily on days 1-4, days 8-11, day 15-18, days 22-25

Does Subq injection lower the CRS risk?

Phase I/II study (NCT02500407) evaluating SC mosunetuzumab with C1 step-up dosing

- R/R B-NHL
- ECOG PS 0–1
- R/R to ≥1 (dose-escalation) or ≥2 (dose-expansion) prior lines of systemic therapy

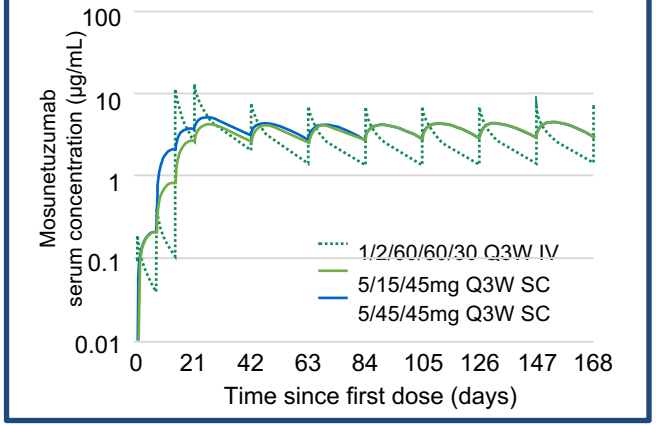
Step up dosing in C1	Dose (mg)
Group 1	5/15/45
Group 2	5/45/45
Group 3	5/90/45

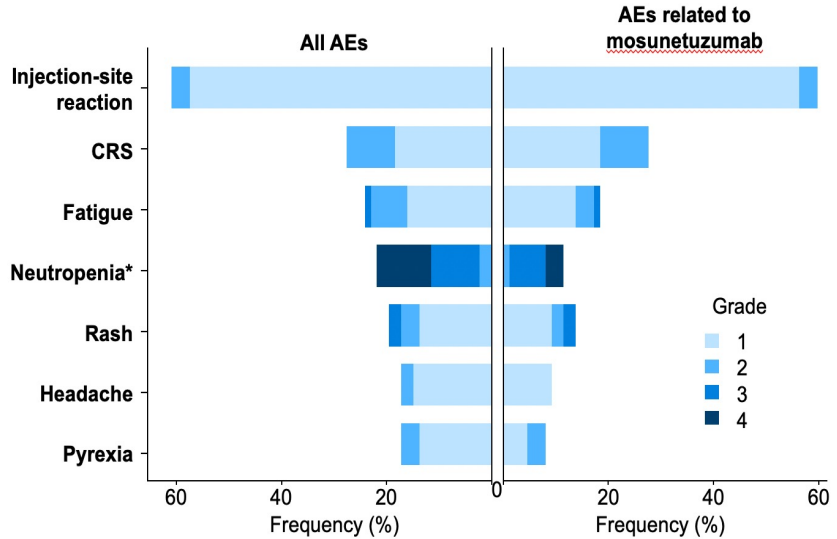
Budde et al. ASH 2022

Does Subq injection lower the CRS risk?

- SC mosunetuzumab showed high bioavailability (>80%) and offered a favorable PK profile relative to IV with comparable exposure, reduced C_{max} and higher C_{trough}

Population PK: SC mosunetuzumab versus IV





CRS:

- all low grade (grade 1 +2); 38.5% group 1; 17.8% group 2 (RP2D)
- Median time to onset 1 day group 1; 2 days group 2

LLOQ, lower limit of quantification

Budde et al. ASH 2022

Work in Progress

- Moving to early lines and combining with other agents to further improve efficacy

	BsAb based regimen	iNHL
MorningSun	Mosunetuzumab	FL, MZL, 1st line
--	Mosun+ Len	FL, 1st line and > 1L
	Mosun + Pola	FL, 1st line, and > 1L
EPCOR-NHL-2	Epcoritamab+R2	FL; 1st line (Arm6) FL; > 2L (Arm 2b)
--	Glofit + Obino	FL, > 1L

Work in Progress: EPCORE NHL-2: arm 6 and arm 2b

- Multicenter, open-label phase Ib/II trial ()

Arm 6 N=41
- untreated CD20+ FL
- grade 1-3A;
- ECOG PS 0-2

Arm 2b N =76
- R/R CD20+ FL > 1 line;
- grade 1-3A;
- ECOG PS 0-2

→ **Epcoritamab** 48 mg SC*
QW for C1-2, Q4W for C3+ up to 2 yr
+
R² for C1-12†

→
- Primary endpoints: antitumor activity (ORR), safety
- Key secondary endpoint: DoR

→
- Primary endpoints: safety, antitumor activity

Falchi. ASH 2022. Abstr 611. Fachi. ASH 2022. Abstr 609.

Regimen: EPCORE+Rituximab+lenalidomide

TEAE, n (%)	1L FL (N = 41)	R/R FL (N = 76)
Median no. of epcoritamab cycles initiated (range)	--	6 (1-11)
Grade ≥3 TEAE ▪ Related to epcoritamab	30 (73) 14 (34)	53 (70) 29 (38)
Fatal TEAE*	2 (5)	3 (4)
Epcoritamab dose delay due to TEAE ▪ Related to epcoritamab	22 (54) 7 (17)	40 (53) 19 (25)
Epcoritamab discontinuation due to TEAE ▪ Related to epcoritamab	4 (10) 3 (7)	5 (7) 0

*1 patient each with COVID-19 pneumonia and septic shock in 1L FL arm and 3 patients with COVID-19 in R/R FL arm.

Falchi. ASH 2022. Abstr 611. Fachi. ASH 2022. Abstr 609.

CRS Outcome, n (%)	1L FL (N = 41)	R/R FL (N = 76)
CRS ▪ Grade 1 ▪ Grade 2	22 (54) 16 (39) 6 (15)	33 (43) 25 (33) 8 (11)
Median time to onset after first full dose, days (range)	3 (1-6)	2 (1-9)
CRS resolution	22 (100)	33 (100)
Median time to resolution, days (range)	4 (1-10)	2 (1-23)
CRS leading to tx d/c	0	0
Tocilizumab use	4 (10)	8 (11)

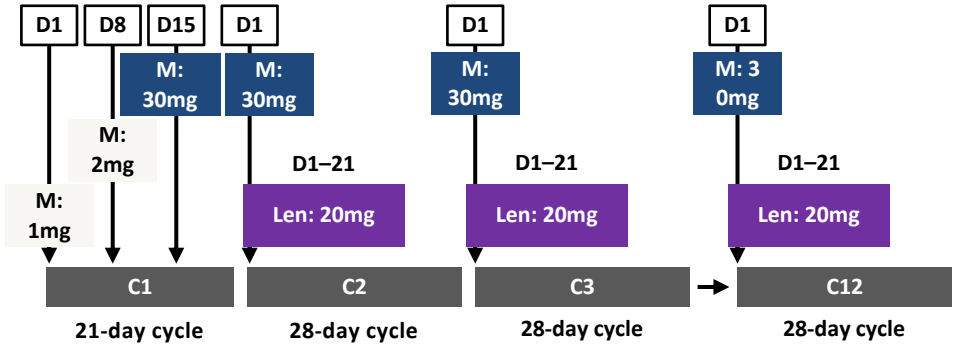
Best Overall Response, %	1L FL (n = 36)	R/R FL (n = 66)
ORR	94	95
▪ CMR	86	80
▪ PMR	8	15
SD	NR	3
PD	3	2

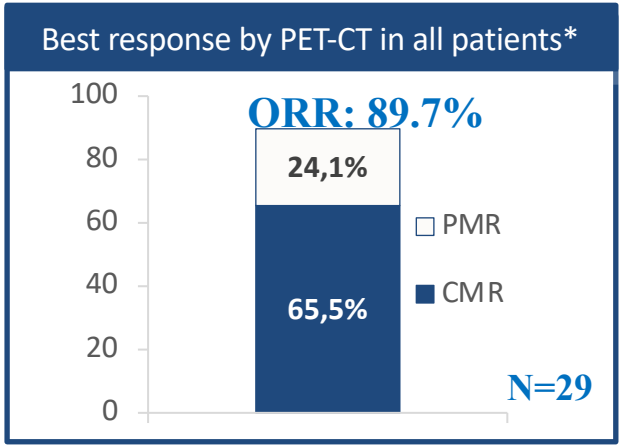
- No grade ≥3 CRS events were observed
- CRS timing was predictable; most cases occurred following first full dose

Falchi. ASH 2022. Abstr 611. Fachi. ASH 2022. Abstr 609.

GO40912: Phase 1b/2 Mosunetuzumab+ Lenalidomide (2L+)

- CD20+ FL Grade 1–3a
- R/R to ≥1 prior chemo-immunotherapy regimen including an aCD20 antibody; prior lenalidomide allowed
- ECOG PS 0–2





- CRS: 27.6% (No ≥ gr3)
- No AE led to mosun+len discontinuation

- **High ORR and CMR rate in overall population and in patients with high-risk disease**

Phase 3 Celesmo

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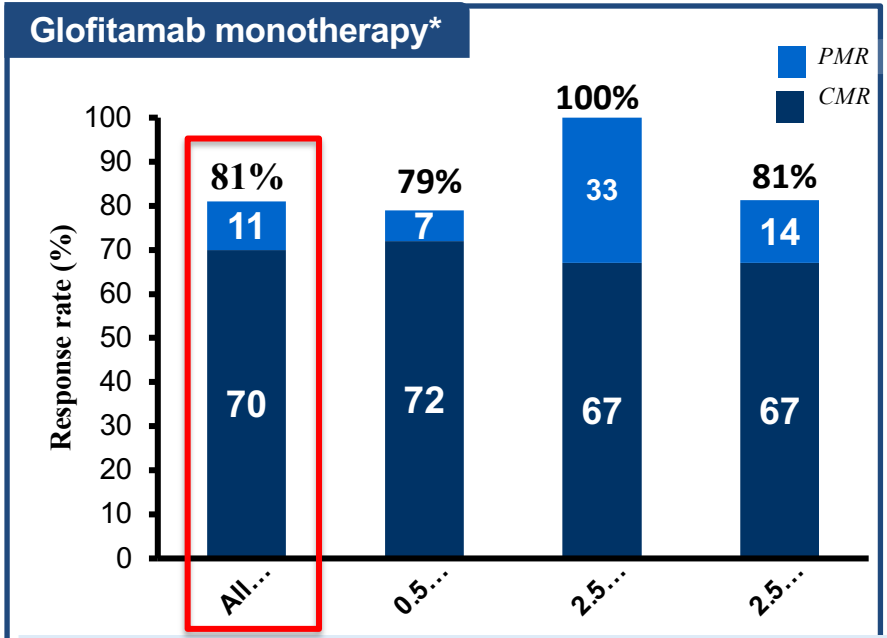
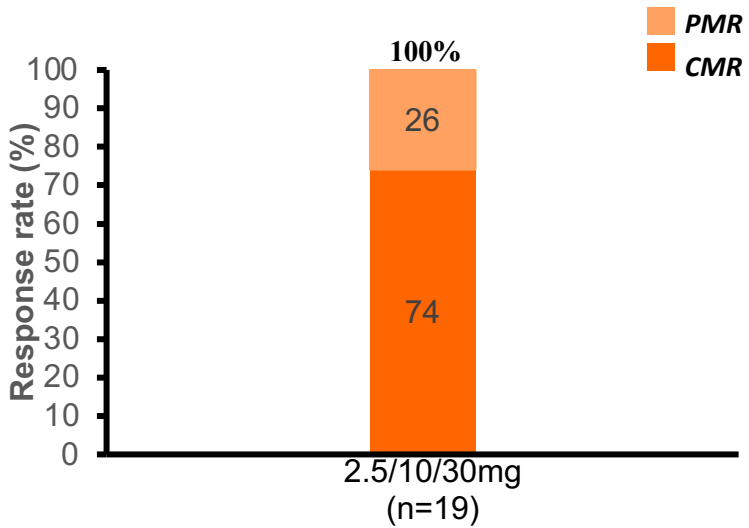
Response rates in R/R FL (Glofib +/- Obinotuzumab)

Population characteristics: *R/R FL Gr 1–3A; ≥1 prior systemic therapy; age ≥18 years; ECOG PS ≤1*

Glofitamab monotherapy*



Glofitamab in combination with obinutuzumab*



- **Glofitamab as monotherapy and in combination with obinutuzumab resulted in high response rates**

*Data cut-off: May 18, 2021. Best overall response. Secondary efficacy 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]. CMR, complete metabolic response; PMR, partial metabolic response

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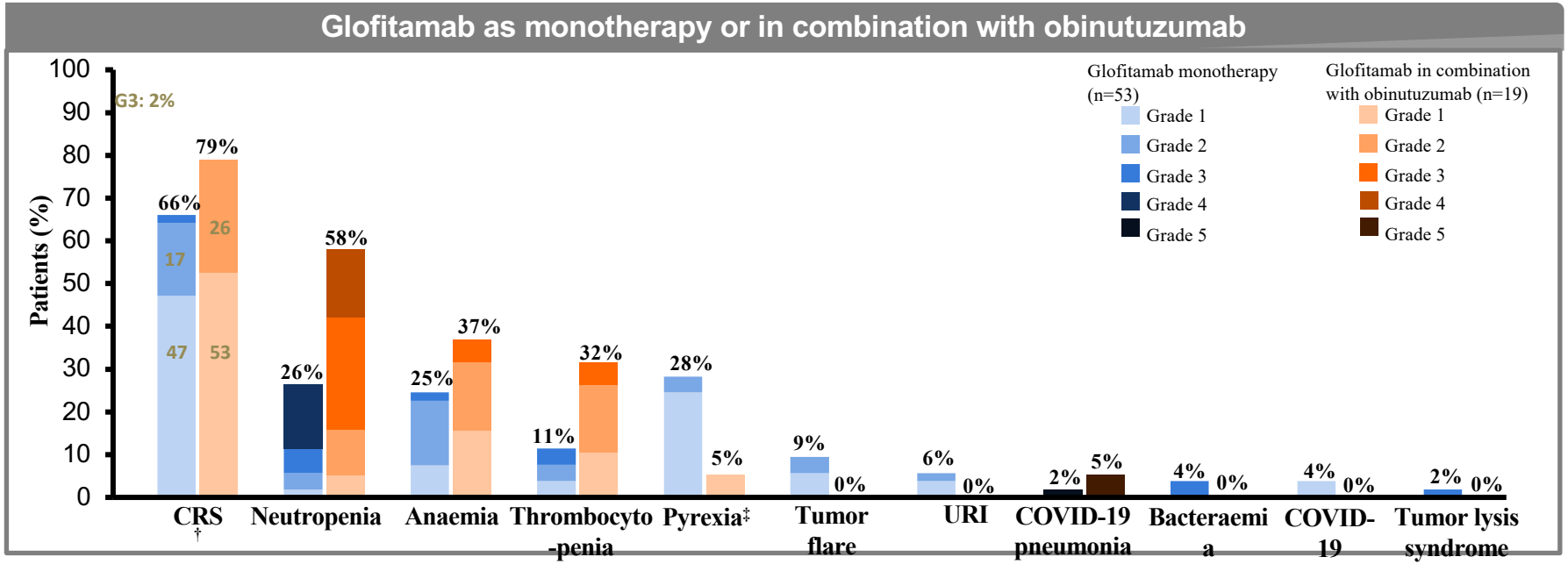
Common adverse events of clinical interest*



- **Myelosuppression was more common in patients who received glofitamab in combination with Obinutuzumab**
- **No ICANS or febrile neutropenia AEs were observed. Tumor flare occurred infrequently**

*No febrile neutropenia AEs were observed. †By ASTCT criteria. ‡Pyrexia events separate from CRS.

Work in Progress

	BsAb	iNHL
Phase 3 **Celesmo**	Mosun (iv)+ Len vs R2	FL, > 1line
Phase 3 **EPCORE -FL-1**	Epcor + R2 vs R2	FL, > 1line

Benchmarks for a “good” Bispecific Antibody/TCE

Efficacy	High
Target	Good sensor (low TAA expression, minimal off target effect)
Dosing requirement	Community & patient friendly i.e. Easy dosing; outpatient use; no maintenance
Safety	Low toxicity Mild or negligible (CRS, neurologic toxicity, infection) → NO REMS program

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