Use of Mosunetuzumab in Lymphoma

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Disclosures

Research Support:

AstraZeneca, Mustang Therapeutics, Merck, Amgen, Genentech

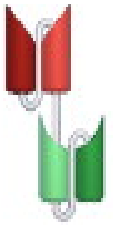
Consultancy:

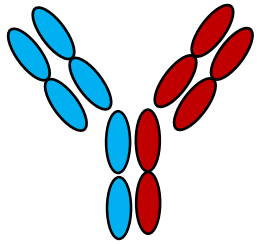
Kite Pharma/Gilead, Genentech/Roche, Beigene, ADC Therapeutics

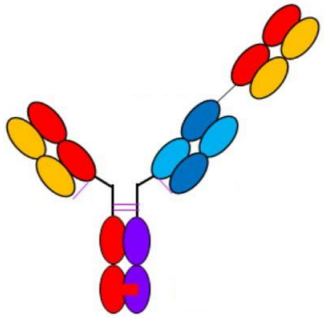
Bispecific Abs in B-NHL under Clinical Development

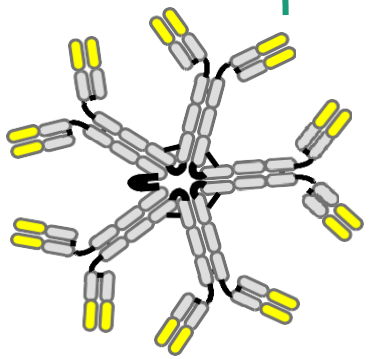
CD19

CD20









And many other variants

BITE® (1:1)

Blinatumomab

Full length IgG (1:1)

Mosunetuzumab

Odronextamab

Epcoritamab

Full length IgG (2:1)

Glofitamab

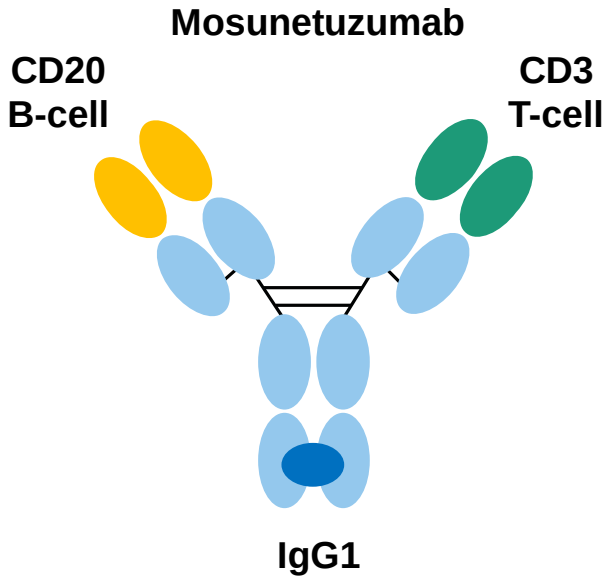
IgM(10:1)

IgM2323

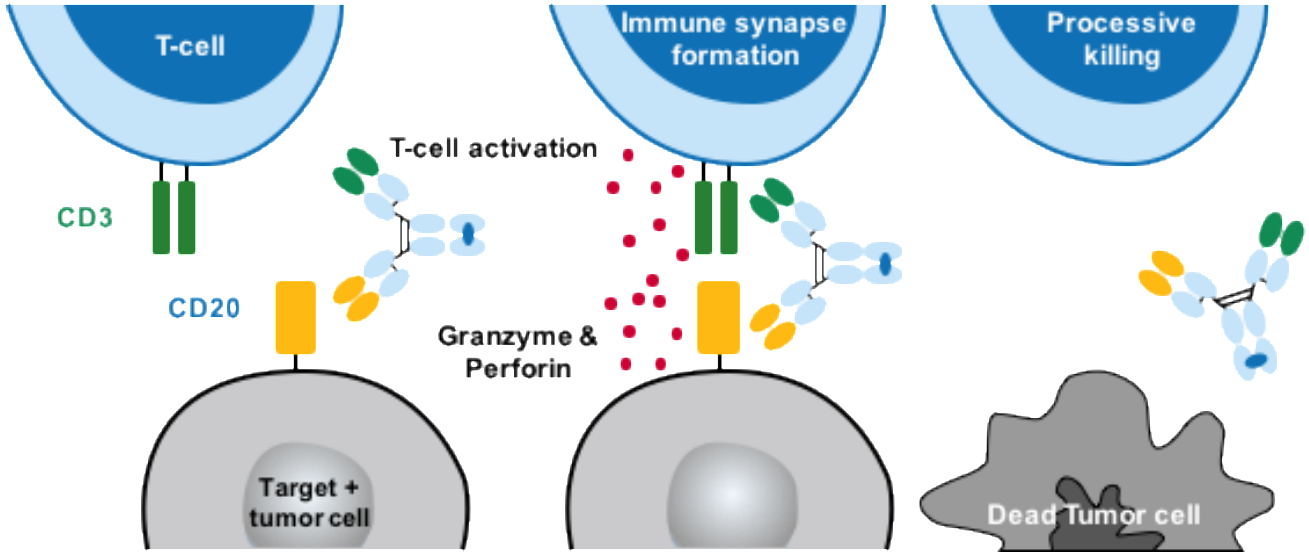
City of Hope®

Mosunetuzumab: a bispecific antibody targeting CD3 and CD20

- **Full-length humanized IgG1 antibody**
  - Longer half-life 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



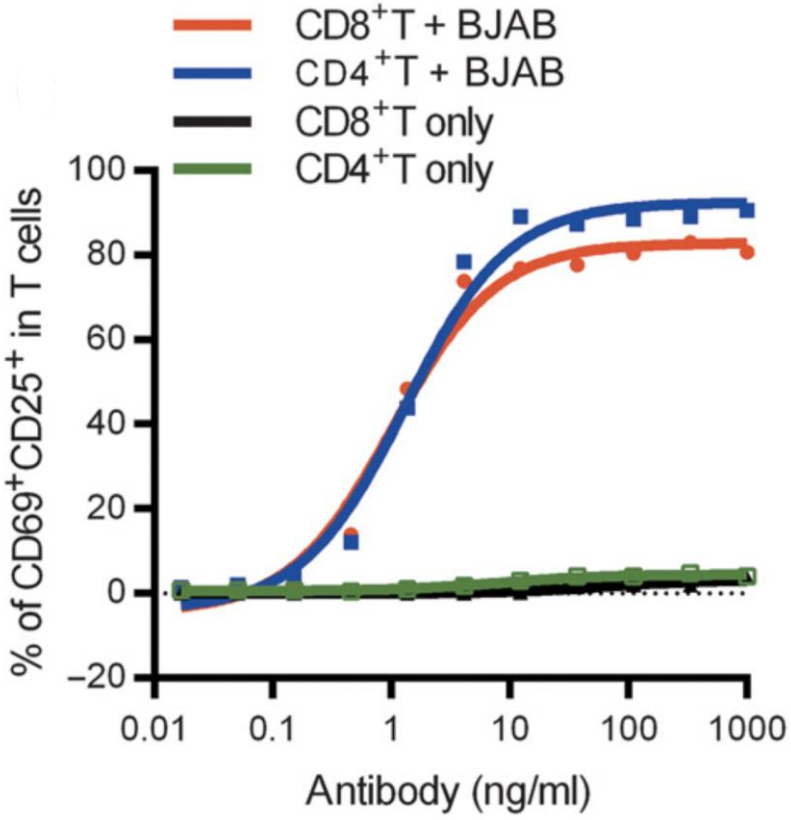
- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells
  - Conditional agonist: T-cell activation dependent on B-cell engagement
  - Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells

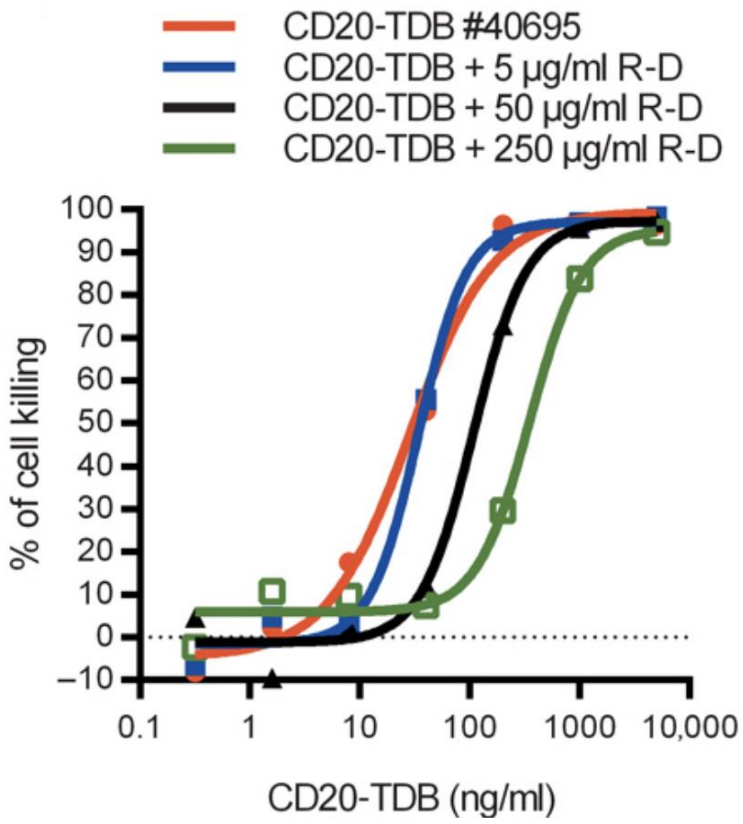


ADCC, antibody-dependent cell-mediated cytotoxicity

Sun et al. Sci Transl Med 2015

Mosunetuzumab's effector activity is target dependent





Sun et al. Sci Transl Med 2015

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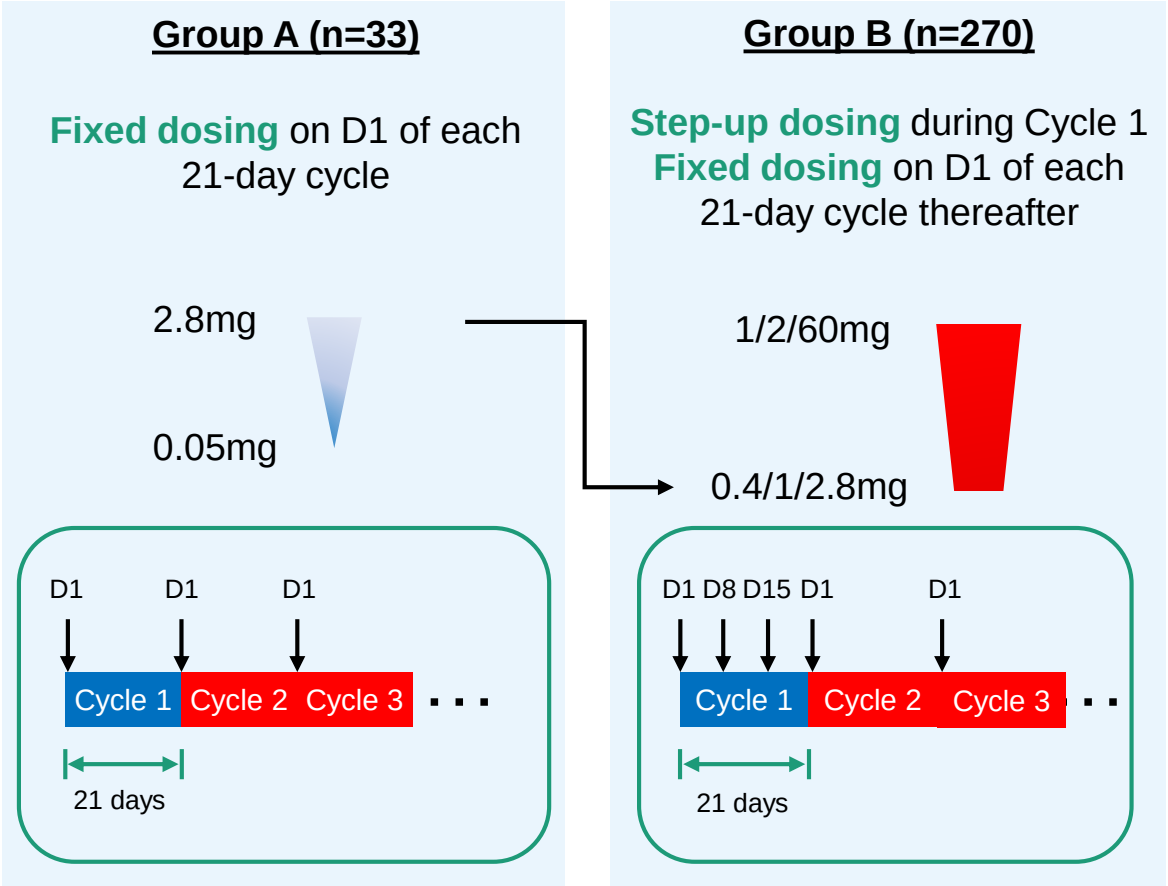
GO29781: study design

Open-label, multicenter Phase I/Ib study in R/R B-cell NHL patients (NCT02500407)



Primary objectives

- Safety, tolerability, MTD, best objective response (per Cheson 2007 criteria[1])
  - **Safety**: C1D1/D8/D15 dose levels: 0.4/1.0/**2.8** – 1.0/2.0/**60.0**mg
  - **Efficacy**: C1D1/D8/D15 dose levels: 0.4/1.0/**2.8** – 1.0/2.0/**40.5**mg‡

Key inclusion criteria

- R/R B-cell NHL after ≥1 prior regimen(s), ECOG PS 0–1
- No available therapy expected to improve survival (e.g. standard chemotherapy, autologous SCT)

Key exclusion criteria

- Prior CAR-T therapy within 30 days, prior allogeneic SCT

D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; R/R, relapsed/refractory; tr, transformed

Budde LE, et al. ASH 2018;
Sehn LE, et al. ICML 2019; Shuster S et al. ASH 2019.

Patient population

n (%)	*N=270**	
Median age, years (range)	**62**	**(19–96)**
Male	172	(63.7%)
ECOG PS 1 at baseline	164	(61.2%)[†]
Aggressive NHL	**180**	**(66.7%)**
DLBCL	117	(43.3%)
trFL	32	(11.9%)
MCL	23	(8.5%)
Other	8	(3.0%)
Indolent NHL	**85**	**(31.5%)**
FL	82	(30.4%)
Other	3	(1.1%)
Median prior systemic therapies, n (range)	**3**	**(1–14)[†]**
Prior CAR-T therapy	30	(11.1%)
Prior autologous SCT	77	(28.5%)
Refractory[‡] to last prior therapy	194	(71.9%)
Refractory[‡] to prior anti-CD20 therapy	233	(86.3%)

30 pts with prior CAR-T therapy

- 17 DLBCL, 8 trFL, 5 FL
- Median 5 lines of prior systemic therapies (range 3–14)
- 29 pts (96.7%) refractory to prior anti-CD20 therapy
- 25 pts (83.3%) refractory to last prior therapy
- 22 pts (73.3%) refractory to prior CAR-T therapy

CCOD (clinical cut-off date): Aug 9, 2019; *safety evaluable pts; [†]n=268, as two pts did not have data entered by CCOD; [‡]no response (PR or CR) or PD within ≤6 months of treatment; trFL, transformed FL;

Mosunetuzumab in B-NHL: Safety

- Most AEs are mild and transient, no cumulative or chronic AEs.
- Step up dosing allows higher dose escalation without increased AEs; CRS almost only in C1

CRS		
n (%) with ≥1 AE	*Safety evaluable pts (N=270)*	*Prior CAR-T pts (n=30)*
Any Grade	78 (28.9%)	8 (26.7%)
Gr 3	3 (1.1%)	1 (3.3%)
Use of tocilizumab for CRS	8 (3.0%)	1 (3.3%)

Neurotoxicity (NAE)				
n (%) with ≥1 AE	*Safety evaluable pts (N=270)*		*Prior CAR-T pts (n=30)*	
Any Grade	118	(43.7%)	13	(43.3%)
Gr 1	74	(27.4%)	7	(23.3%)
Related Gr 3	3	(1.1%)	1	(3.3%)

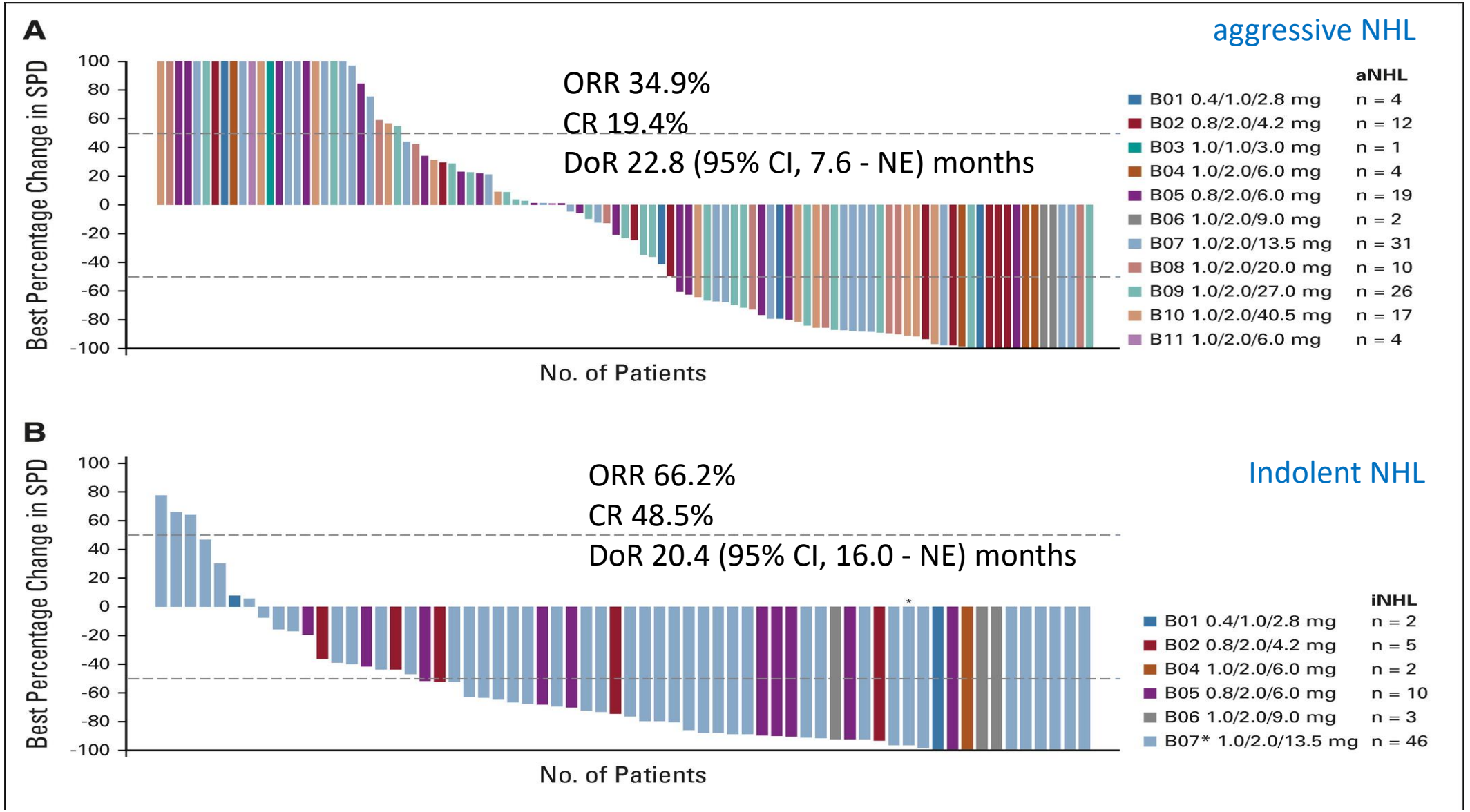
- **Only 2.6% (7/270) patients discontinued due to AEs**
- Outpatient treatment
- RP2D: 1mg/2mg/60mg C1; 30mg q3wks C2 and on

- Most common Neurologic AEs:

headache (15.6%), insomnia (9.3%), dizziness (9.3%)

Shuster et al ASH 2019; Budde et al. JCO 2022

Efficacy of Mosunetuzumab



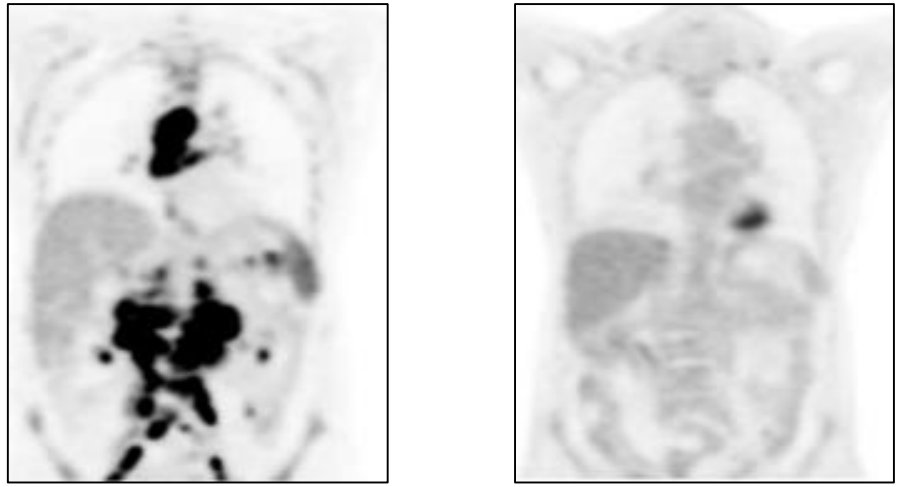
Budde et al. JCO 2022

Patients with prior CAR-T therapy -> Mosunetuzumab GO29781

Efficacy

	*N**	*ORR, n (%)*	*CR, n (%)*
All histologies	18	7 (38.9%)	4 (22.2%)
• DLBCL	9	2 (22.2%)	2 (22.2%)
• trFL	5	1 (20.0%)	0 (0.0%)
• FL	4	4 (100%)	2 (50.0%)

Day -12 (baseline) **After Cycle 3 of mosunetuzumab**



CAR-T PCR: ≤50 copies/µg DNA 380 copies/µg DNA

- *8 months in CR off treatment*

Case

- 58-year old patient with R/R FL
- 8 prior lines of systemic treatment
  - Refractory to prior anti-CD20 and alkylating agents
  - Relapsed after CD19-CAR-T therapy
  - Progressed on checkpoint inhibitor and no response to PI3K inhibitor

Exploratory biomarkers

- Expansion of lymphocytes (including residual CAR-T cells in 2/8 tested pts)
- CR to mosunetuzumab observed **with** or **without** CAR-T expansion

*efficacy-evaluable pts: pts who were enrolled for at least 3 months, or had response data available at any time, or discontinued treatment for any cause; CCOD: Aug 9, 2019

Shuster et al. 2019 ASH

Mosunetuzumab use in post CAR T Nonresponders

69 yo with double expressor DLBCL

Prior therapies: RCHOP x6 (2006), RCHOP x6 + XRT (2012), Cyclophosphamide (10/2018), Axi-Cel

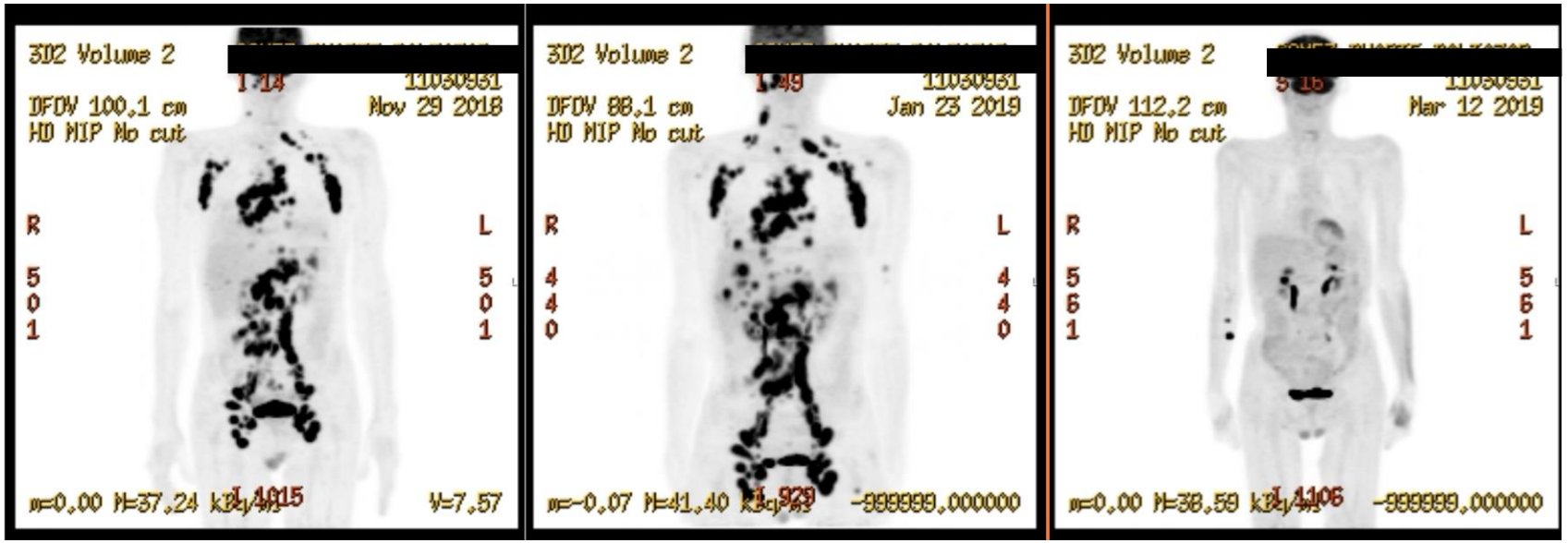
D0 Axi-cel

IRB#15391
D1C1 Mosun/TDB

Pre Axi-Cel, Day -7

Post Axi-Cel D+38

D37 Mosun/TDB



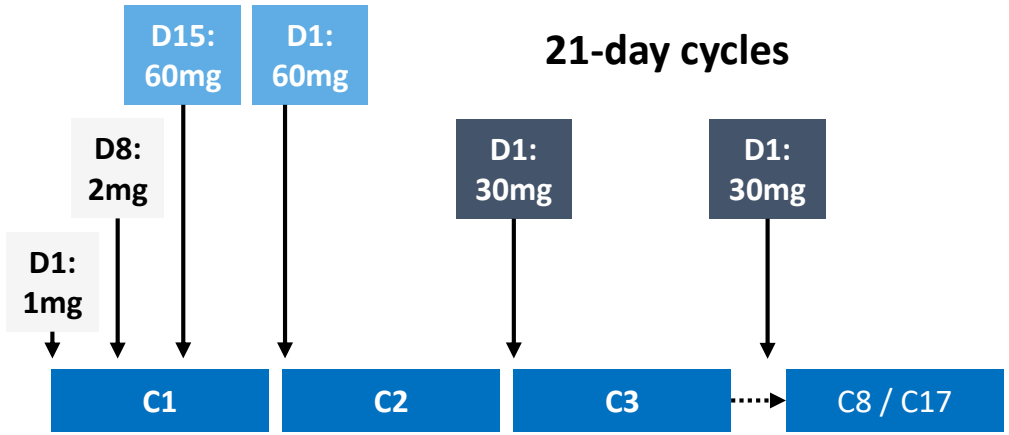
Single-arm, pivotal Phase II expansion in patients with R/R FL and ≥2 prior therapies

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



Endpoints

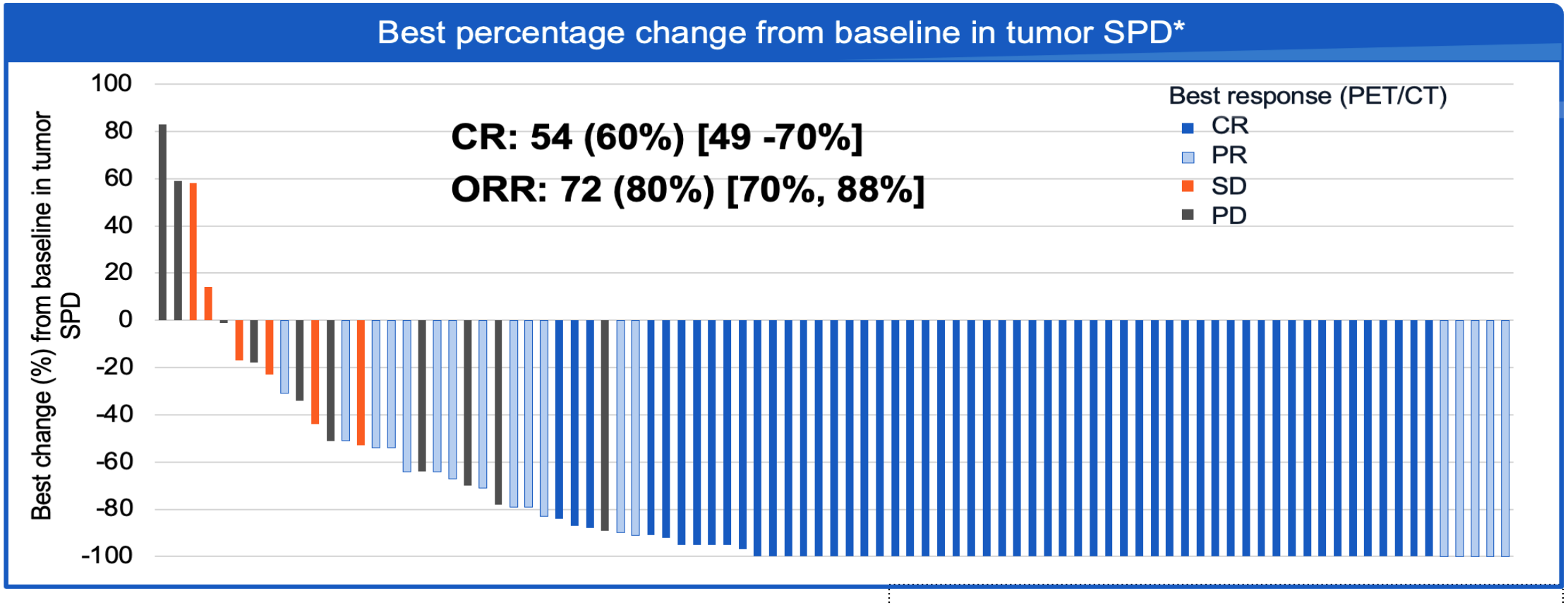
- Primary: CR (best response) rate by IRF* – assessed vs 14% historical control CR rate[1]
- Secondary: ORR, DoR, PFS, safety and tolerability

*assessed by CT and PET-CT using Cheson 2007 criteria[2]; Ab, antibody; CR, complete response; CT, computed tomography; D, Day; DoR, duration of response; IRF, independent review facility; ORR, objective response rate; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; Q3W, once every 3 weeks; SD, stable disease

1. Dreyling et al. J Clin Oncol 2017;35:3898–905
2. Cheson et al. J Clin Oncol 2007;25:579–86

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)

Median PFS:
17.9 months (95% CI: 10.1, NE)

Budde et al. ASH 2021

Adverse event overview

N (%)	N=90
AE	90 (100%)
Mosunetuzumab related*	83 (92.2%)
Grade 5 (fatal) AE	2 (2.2%)†
Mosunetuzumab related*	0
AE leading to discontinuation of treatment	4 (4.4%)‡
Mosunetuzumab related*	2 (2.2%)‡
ICANS*	4 (4.4%)
Grade 3†	0

N (%)	N=90
CRS (any Grade)*	40 (44.4%)
Grade 1	23 (25.6%)
Grade 2	15 (16.7%)
Grade 3	1 (1.1%)
Grade 4	1 (1.1%)†
Serious AE of CRS (any Grade)	21 (23.3%)‡
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–23.7)
C1D15–21	26.6 (0.1–390.9)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	10 (11.1%)
Tocilizumab for CRS management	7 (7.8%)

- **Mosunetuzumab had a manageable safety profile. AEs leading to discontinuation were uncommon.**

*AE considered related to treatment by the investigator; †mosunetuzumab unrelated: malignant neoplasm progression and unexplained death (1 patient each); ‡mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each); AE, adverse event; Gr, Grade ;

Mosunetuzumab in comparison with CD19CAR T cells in FL

	target	Enrolled /treated	age	Median prior lines	Prior ASCT	POD24	ORR/CR	
Mosun	CD20	90/90	60 (29-90)	3 (2-10)	21%	52%	80%, 60%	PFS 17.9 months
Axi cel	CD19	124124	60 (53-67)	3 (2-4)	24%	55%	94%, 79%	12 months PFS 77.5%
Tisa cel	CD19	98/97	57 (29-73)	4 (2-13)	36.1%	62.9%	86%, 69%	12 months PFS 67%

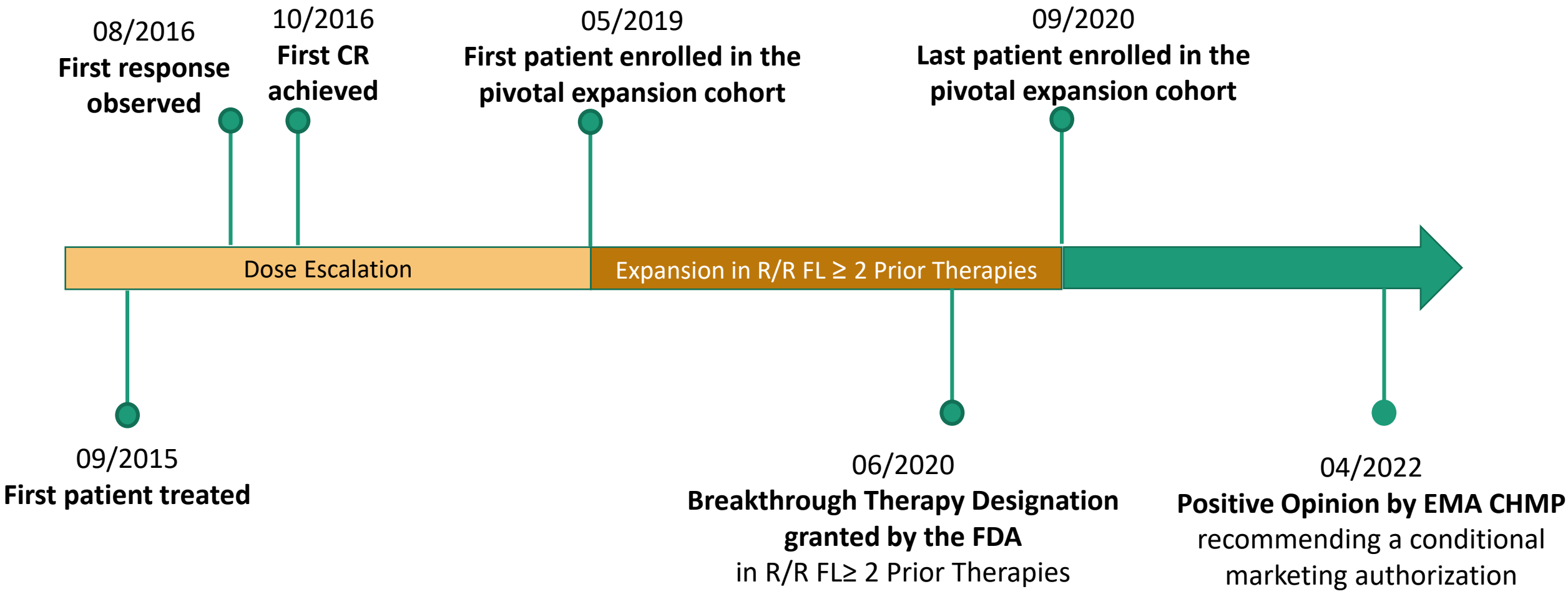
	CRS		NT		Infection
	Any grade	≥ Grade 3	Any grade	≥ Grade 3	Any grade
Mosun	44%	0	4%	0	20%
Axi cel ZUMA-5	78%	6%*	56%	15%	18%**
Tisa cel ELARA	49%	0	37.1%	3% 3 gr3, 1 gr4	19%

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

Budde et al. ASH 2021;
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



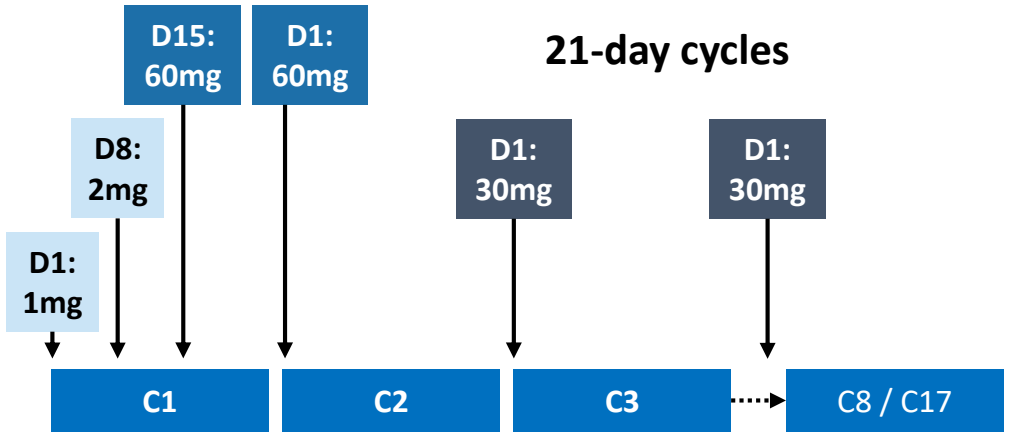
GO29781 (Mosunetuzumab): Single-arm, Phase II expansion in patients with R/R DLBCL and ≥2 prior therapies

Key inclusion criteria

- DLBCL (PMBCL, tFL, HGL)
- ECOG PS 0–1
- ≥2 prior regimens, including
  - ≥1 anti-CD20 Ab
  - ≥1 anthracycline

Mosunetuzumab administration

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



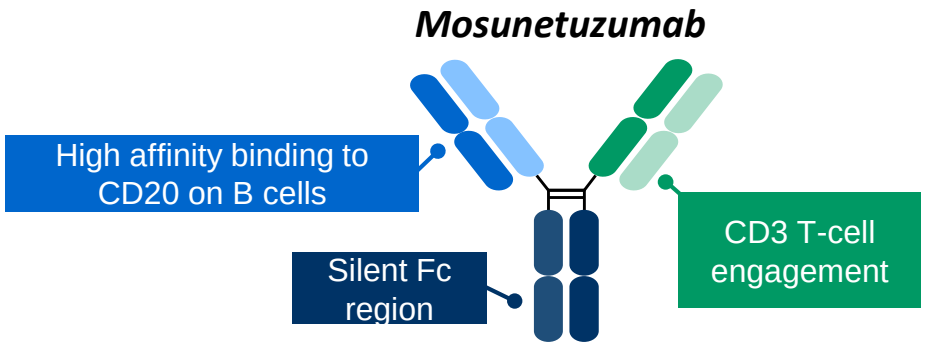
Endpoints

- Primary: CR (best response) rate by IRF
- Secondary: ORR, DoR, PFS, safety and tolerability

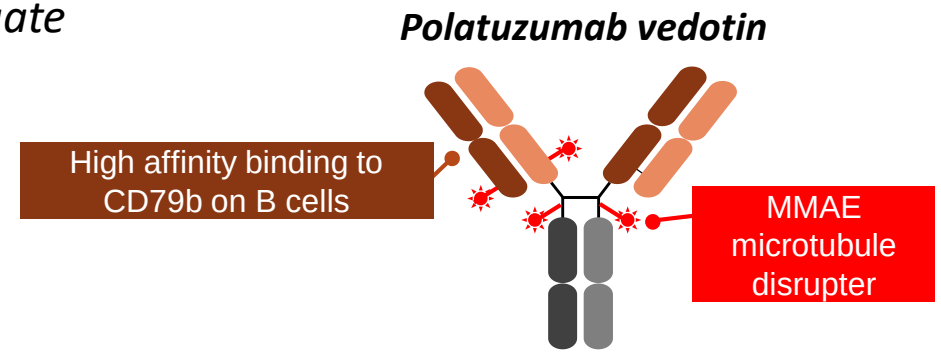
Status: Completed

Mosunetuzumab + Polatuzumab for aggressive B-NHL

- **Mosunetuzumab (M):** *CD20xCD3 (1:1) bispecific antibody*
  - engages and redirects T cells to eliminate malignant B cells[1]
  - off-the-shelf availability[1]
  - durable efficacy and acceptable toxicity as monotherapy in patients with R/R B-NHL[2]



- **Polatuzumab vedotin (Pola):** *anti-CD79-vc-MMAE antibody drug conjugate*
  - evaluated in combination with chemotherapy (BR, R-CHOP)[3,4]



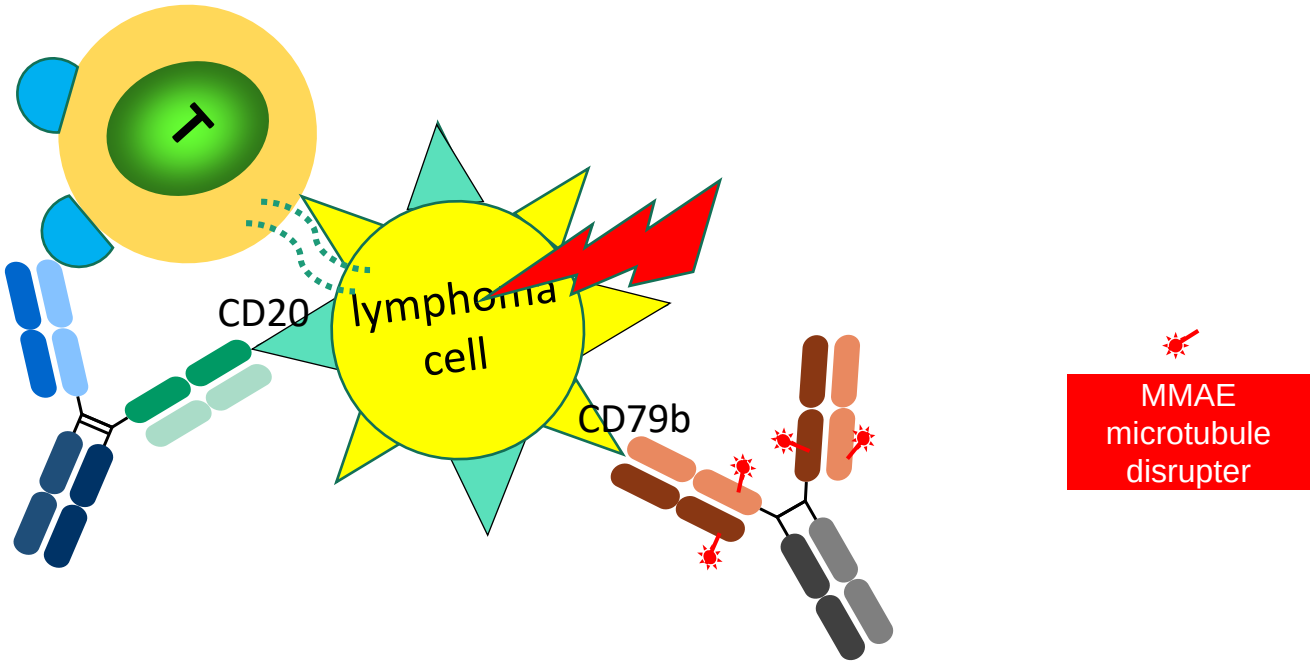
- **Ongoing Phase Ib/II study (NCT03671018)[5]**
  - evaluating M-Pola combination in R/R B-NHL

Aim: Share updated dose-escalation and dose-expansion results, with a focus on patients with R/R DLBCL

B-NHL, B-cell non-Hodgkin lymphoma; BR, bendamustine-rituximab; DLBCL, diffuse large B-cell lymphoma; MMAE, monomethyl auristatin E; R/R, relapsed/refractory

1. Sun et al. Sci Transl Med 2015;7:287ra70; 2. Budde et al. J Clin Oncol 2021 [in press]
3. Sehn et al. J Clin Oncol 2020;38:155–65; 4. Tilly et al. ASCO 2019
5. NCT03671018. Available at: https://clinicaltrials.gov/; 6. Budde et al. ASCO 2021

Mosunetuzumab+ polatuzumab



Study overview

- Phase Ib/II dose-escalation and dose-expansion study in patients with R/R B-NHL

Key inclusion criteria

- DLBCL (*de novo* DLBCL, transformed FL, or Grade 3b FL): Phase Ib AND Phase II
- FL Grade 1–3a: Phase Ib only

Primary objectives

- Efficacy of M-Pola in patients with R/R B-NHL
- Safety and tolerability of M-Pola in patients with R/R B-NHL

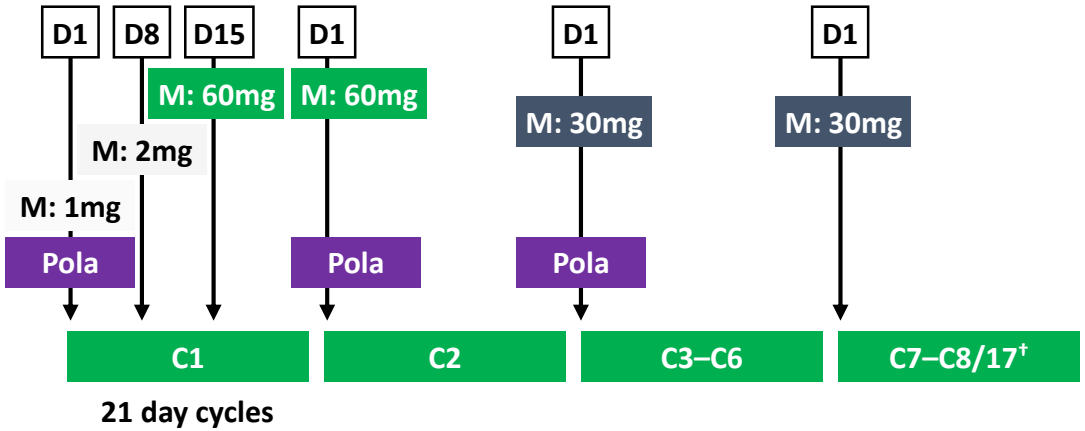
M-Pola administration in Phase II expansion*

Mosunetuzumab

- Q3W intravenous infusions at RP2D (C1–8/17)†
- C1 step-up dosing for CRS mitigation
- No mandatory hospitalization

Polatuzumab vedotin

- Q3W intravenous infusions (1.8mg/kg) (D1 C1–6)



*Mosunetuzumab administration in Phase Ib dose-escalation: C1D1 (1mg), C1D8 (2mg), C1D15 (9, 20, 40, or 60mg) and D1 of each subsequent cycle (9, 20, 30, 40, or 60mg)†; 6 patients received mosunetuzumab at RP2D and C1 hospitalization was mandatory; †patients who achieved CR discontinued mosunetuzumab after C8, while patients who achieved PR or SD continued mosunetuzumab for up to 17 cycles, unless PD or unacceptable toxicity occurred; C, Cycle; CR, complete response; CRS, cytokine release syndrome; D, Day; FL, follicular lymphoma; PD, progressive disease; PR, partial response; Q3W, once every 3 weeks; RP2D, recommended Phase II dose; SD, stable disease

Baseline patient and disease characteristics

N (%) unless stated	All patients N=63	DLBCL patients N=60
Median age, years (range)	68 (20–83)	68 (20–83)
Male	39 (61.9)	37 (61.7)
ECOG PS at entry		
0–1	59 (93.7)	56 (93.3)
2	4 (6.3)	4 (6.7)
Histology		
DLBCL	60 (95.2)	60 (100)
de novo DLBCL	44 (69.8)*	44 (73.3)
transformed FL	12 (19.0)†	12 (20.0)
Grade 3b FL	4 (6.3)	4 (6.7)
FL Grade 1–3a	3 (4.8)	0
Bulky disease (≥10 cm)	6 (9.5)	6 (10.0)

N (%) unless stated	All patients N=63	DLBCL patients N=60
Ann Arbor stage at entry		
I–II	13 (20.6)	12 (20.0)
III–IV	50 (79.4)	48 (80.0)
Number of prior lines of therapy		
1–2	24 (38.1)	24 (40.0)
3+	39 (61.9)	36 (60.0)
Median prior lines of therapy, range	3 (1–10)	**3 (1–8)**
Prior CAR-T therapy	25 (39.7)	24 (40.0)
Refractory to last prior therapy	48 (76.2)	46 (76.7)

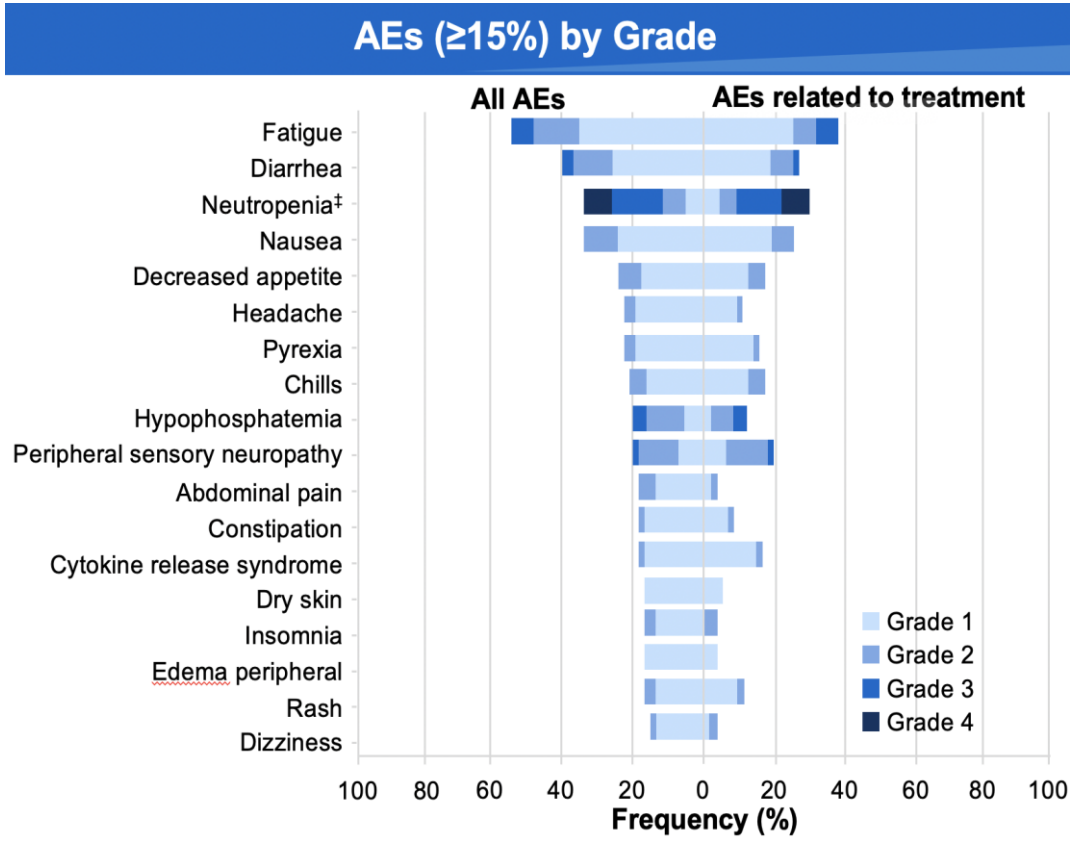
Cut-off date: March 15, 2021

*double-hit lymphoma: n=4; †double-hit lymphoma: n=4; CAR-T, chimeric antigen receptor-T cell; ECOG PS, European Cooperative Oncology Group performance status

Adverse event overview: manageable safety profile

- Median time on study: 5.7 months (range: 0.7–27.5)

N (%)	N=63
Grade 5 (fatal) AE*	3 (4.8)†
M-Pola related	1 (1.6)
AE leading to M discontinuation	5 (7.9)
M related	3 (4.8)
AE leading to Pola discontinuation	8 (12.7)
Pola related	6 (9.5)
CRS (any Grade)*	11 (17.5)
Grade 1	10 (15.9)
Grade 2	1 (1.6)
Grade 3	0
ICANS any grade	5 (7.9)
Grade 3-4	2 (3.2)

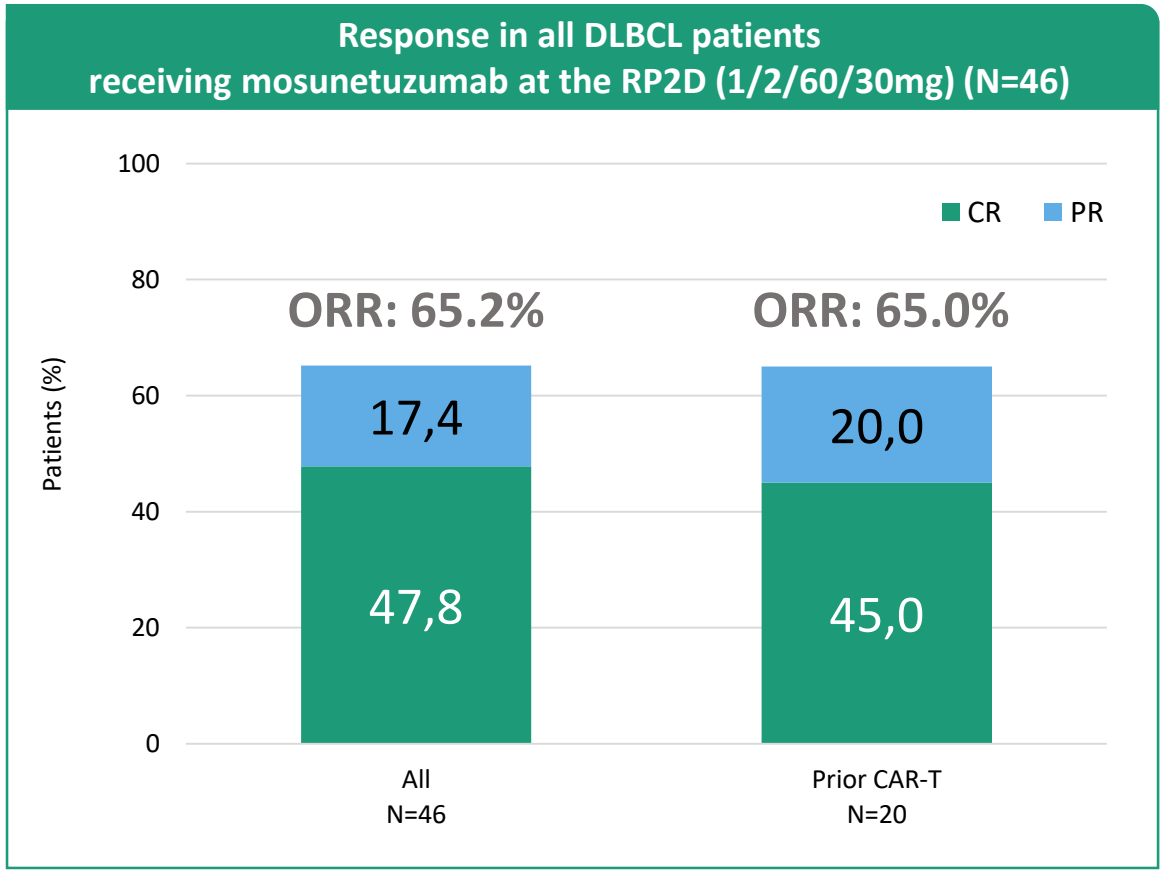


- **The majority of AEs were low Grade;**
- **all CRS & NT resolved.**

*excluding 9 Grade 5 AEs of PD; †treatment-related: pneumonia (1 patient); treatment-unrelated: respiratory failure and sudden cardiac death (1 patient each); ‡grouped term including Preferred Term 'neutropenia' and 'neutrophil count decreased'; AE, adverse event;

Response in DLBCL patients*

- Median duration of response in all DLBCL patients: NR (95% CI: 6.3, NE)



- Median PFS: 8.9 months (95% CI: 3.5, NE)
- PFS data are immature

- Of 29 patients who achieved CR, 28 (96.6%) remained in CR and 1 (3.4%) had PD
  - the patient with PD subsequently received retreatment and achieved a CR

- a randomized Phase III study is planned

Response assessed by investigators using Lugano 2014 criteria[1]; CI, confidence interval; NR, not reached

Budde et al. ASH 2021

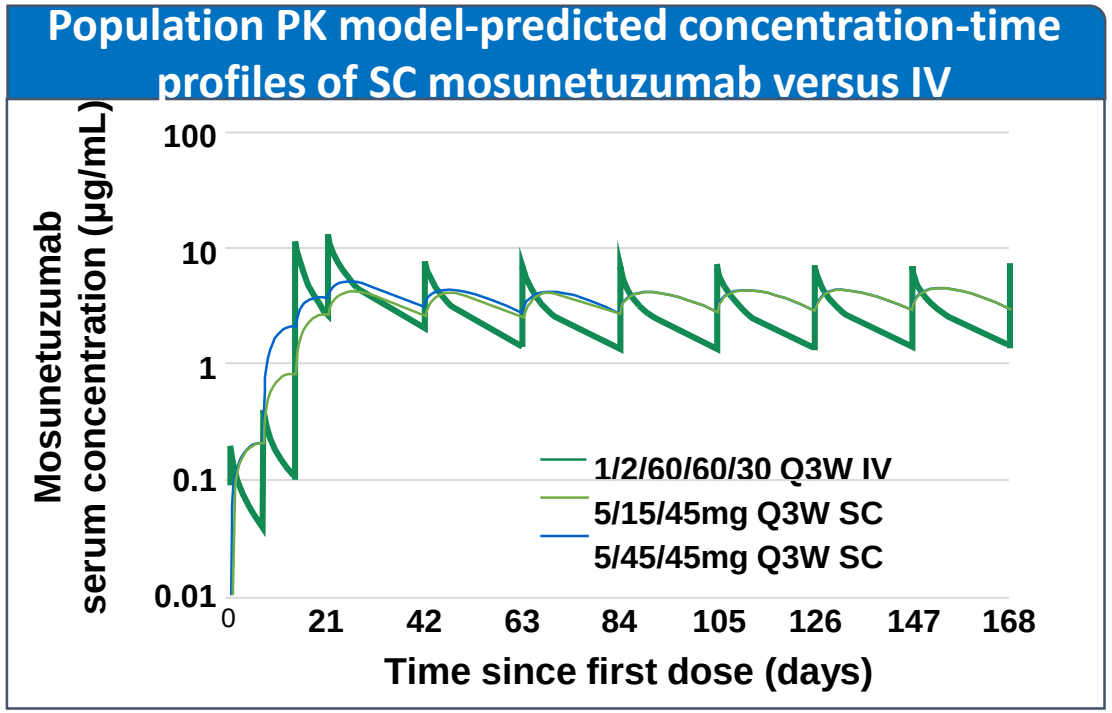
Mosunetuzumab: work in progress (FL)

- Mosun subq dosing

  high bioavailability

  .favorable safety profile

  .similar efficacy as iv dosing



- Mosun + lenalidomide (2L+ FL)

  Phase 1b ORR: 92%, CR: 77% (ASH 2021)

  Phase 3 Mosun+lenalidomide vs rituximab + lenalidomide (ongoing)

Bartlett et al. ASH 2021;

- Mosun in the 1st line FL setting coming

Mosunetuzumab: work in progress (aB-NHL)

GO40554 (NCT03677154): an ongoing Phase 1

elderly/unfit frontline use of single agent Mosunetuzumab in elderly/unfit pts with newly diagnosed DLBCL

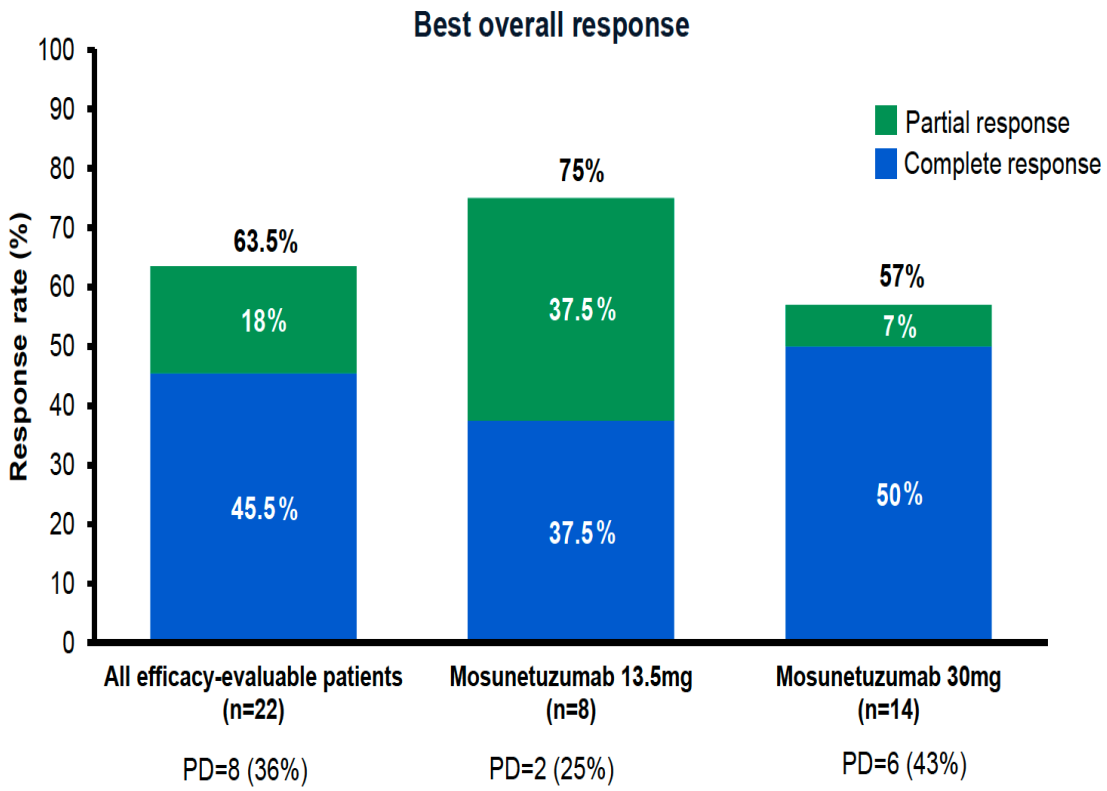
Key inclusion criteria

- Treatment naïve DLBCL or HGBL
- Age ≥80 years or 60–79 years with impairment in:
  - ≥1 ADL or
  - instrumental ADL or
  - inability to tolerate full dose CIT

Treatment Dosing
Cohort1:1/2/13.5mg
Cohort2:1/2/30 mg
Expansion:1/2/30mg

Summary of AEs, n (%)	1L DLBCL (N=29)
Any AE Treatment related	25 (86) 17 (59)
Serious AE Treatment related*	8 (28) 4 (14)
Grade 3–4 AE Treatment related†	9 (31) 4 (14)
Grade 5 (fatal) AE	0
AE leading to treatment discontinuation	0

Low rates of neutropenia (n=2; 7%) and Grade 3–4 infections (n=2; 7%) were observed



Olszewski et al. ASH 2020

Conclusions

- Mosunetuzumab, an antiCD20/CD3 T cell engager can induce frequent and durable complete remissions in heavily pre-treatment patients with r/r B-NHL

- Mosunetuzumab has a favorable safety profile and can be given in the outpatient setting.

- Ongoing effects (clinical trials, preclinical studies) aim to understand resistant mechanism, further improve efficacy, reduce toxicities, reduce cost, and expand indications.

Thank you!

- Elizabeth Budde, MD, PhD

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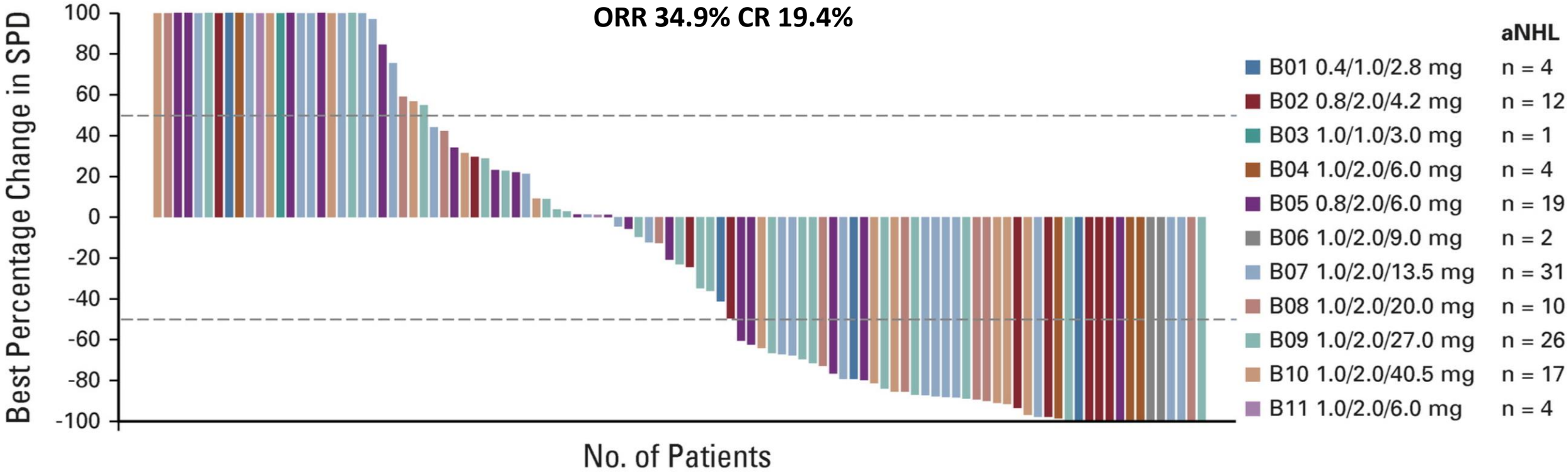
Mosunetuzumab in aNHL: Efficacy Result from GO29781

aNHL: DLBCL, tFL, HGL, MCL, Richter's



Budde et al. JCO 2022

What have we learned?

- CAR T therapy has changed the outcome of patients with hematologic malignancies.
- Different CAR T design and products are associated with distinct safety profiles. Clinical expertise and infrastructure are needed to deliver CAR T safely, effectively, and to regulatory standard.
- Bispecific antibodies have demonstrated promising activity (including in patients with CAR T) and exhibited favorable safety profile.
- Ongoing effects (clinical trials, preclinical studies) aim to further improve efficacy, reduce toxicities, reduce cost, and expand indications.