ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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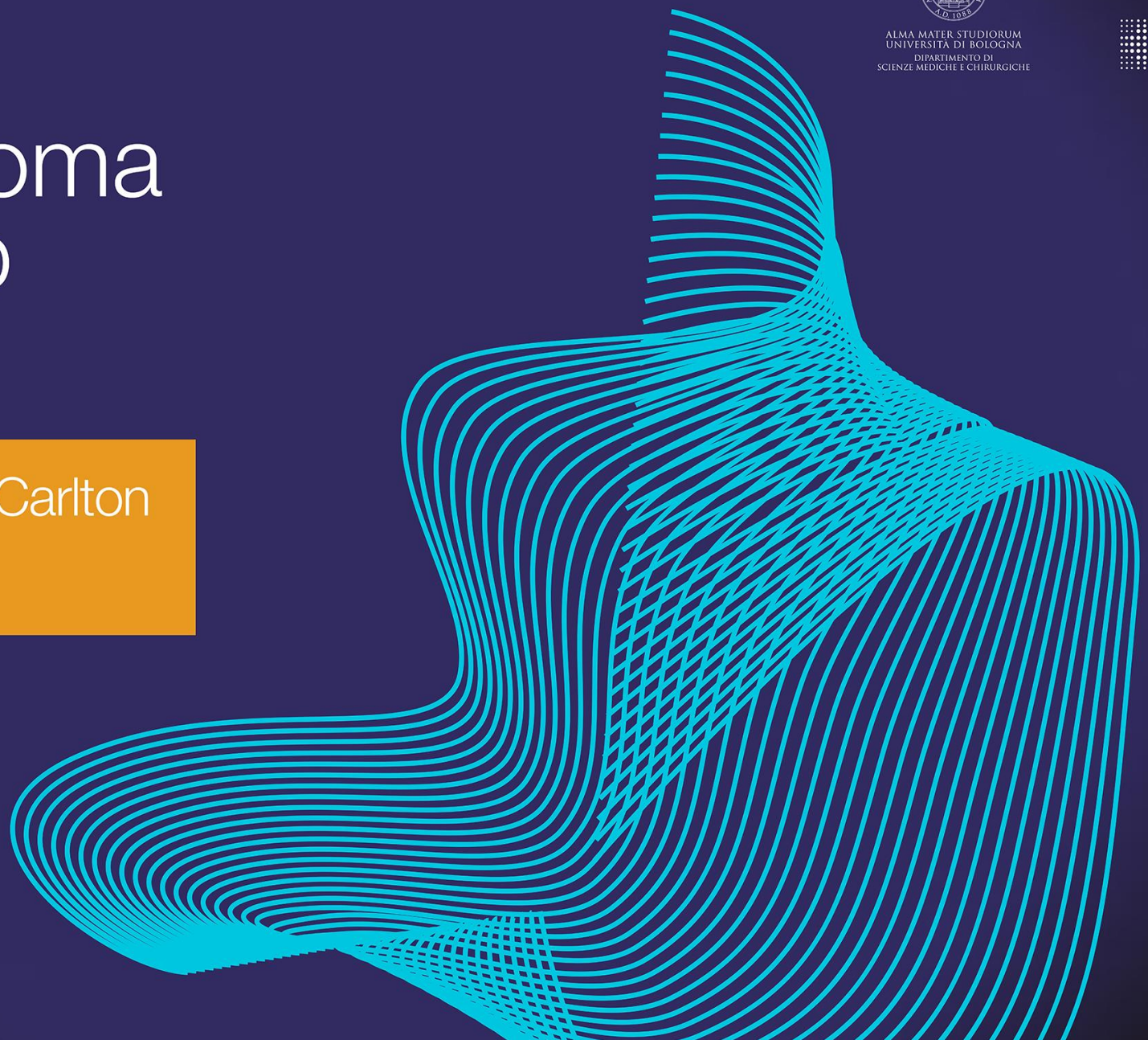
Aggressive Lymphoma Workshop



Bologna, Royal Hotel Carlton

May 8-9, 2023

President: **Pier Luigi Zinzani**

Use of Mosunetuzumab in Aggressive B Cell Lymphoma

Elizabeth Budde, M.D., Ph.D.

City of Hope National Cancer Center

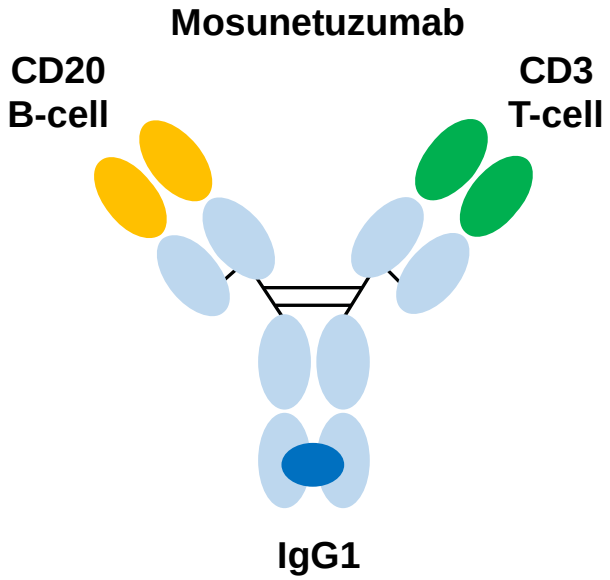
Disclosures

Disclosures of Name Surname

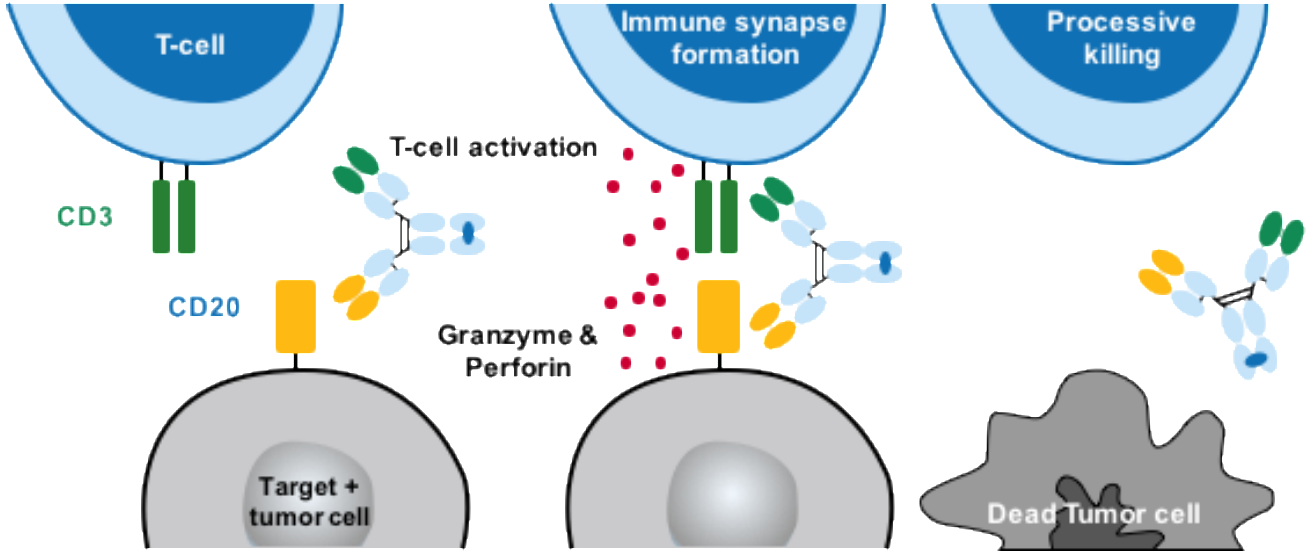
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AstraZeneca	x					x	
Amgen	x						
ADC Therapeutics						x	
Roche			x			x	
Merck	x						
Mustang Therapeutics	x						
Abbive						x	
Gilead						x	
Nurix						x	

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

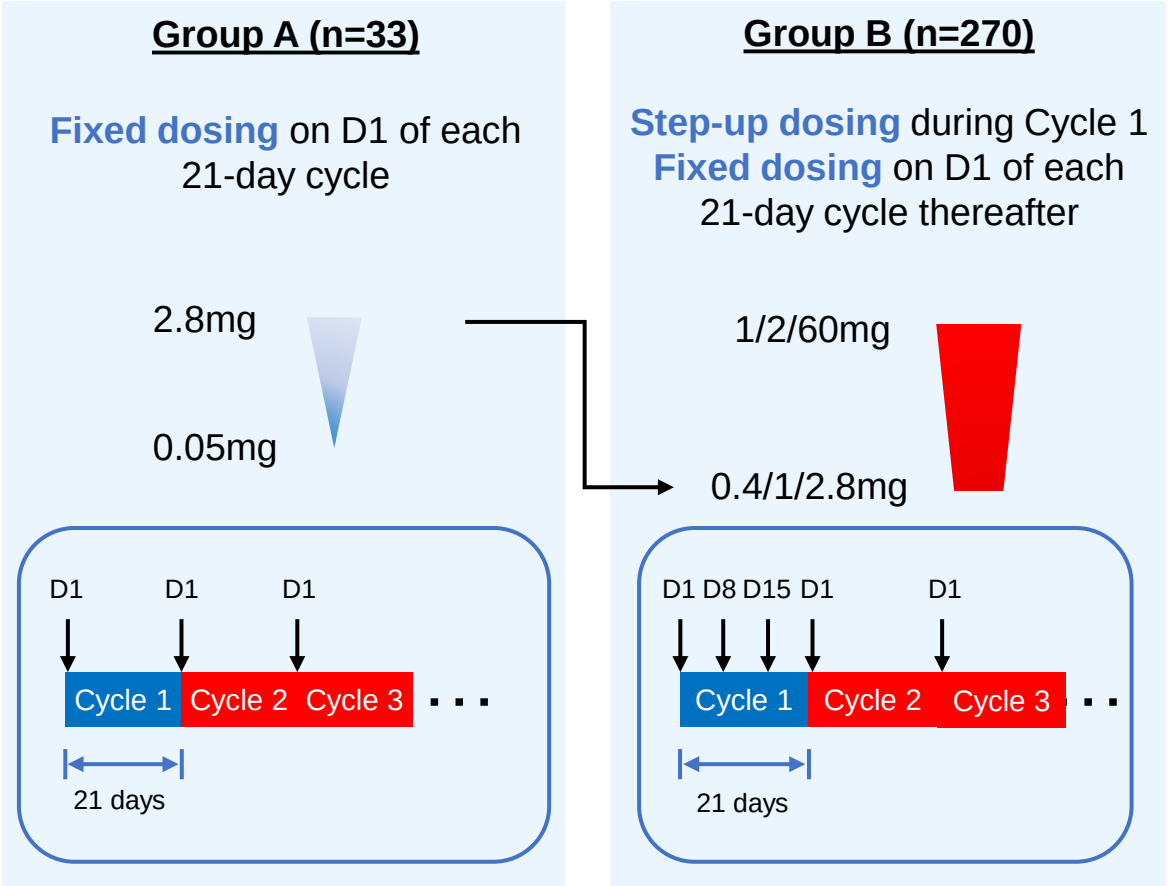


ADCC, antibody-dependent cell-mediated cytotoxicity

Sun et al. Sci Transl Med 2015

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

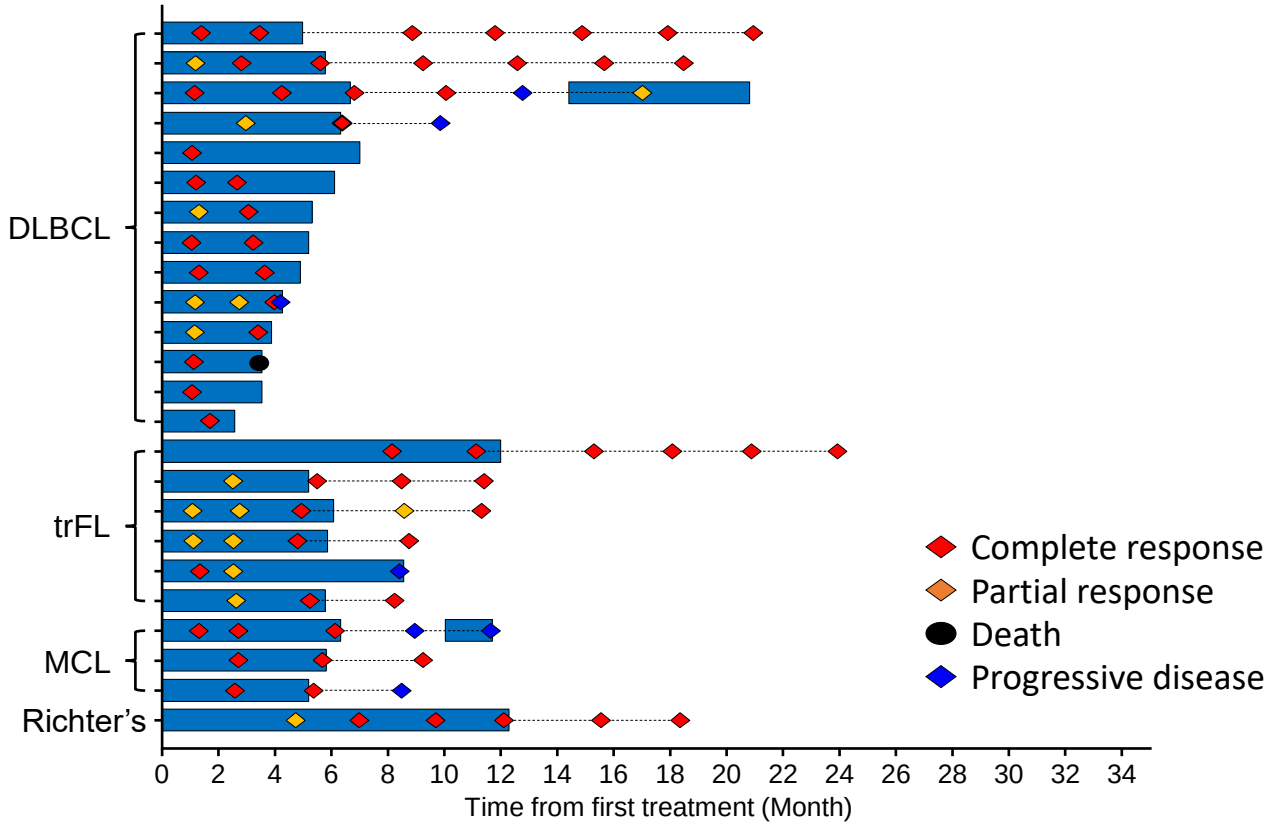
CCOD (clinical cut-off date): Aug 9, 2019; *safety evaluable pts; [†]n=268, as two pts did not have data entered by CCOD; [‡]no response (PR or CR) or PD within ≤6 months of treatment; trFL, transformed FL;

Response rates and duration in aggressive NHL (Mosun)

	N*	ORR, n (%)	CR, n (%)
Aggressive NHL	124	46 (37.1%)	24 (19.4%)
DLBCL/trFL ≥ 2 lines	98	37 (37.8%)	20 (20.4%)
• Refractory to anti-CD20	88/98	32 (36.4%)	18 (20.5%)
• With prior ASCT	32/98	17 (53.1%)	11 (34.3%)

- Increased efficacy in pts with higher exposure to mosunetuzumab, as measured by CD20 receptor occupancy (RO%)

Time on treatment and duration of response among aggressive NHL complete responders



- 17 CR pts (70.8%) remain in remission (up to 16 months off treatment)

*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

Li et al. ASH 2019 P-1285; Shuster et al. ASH 2019

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

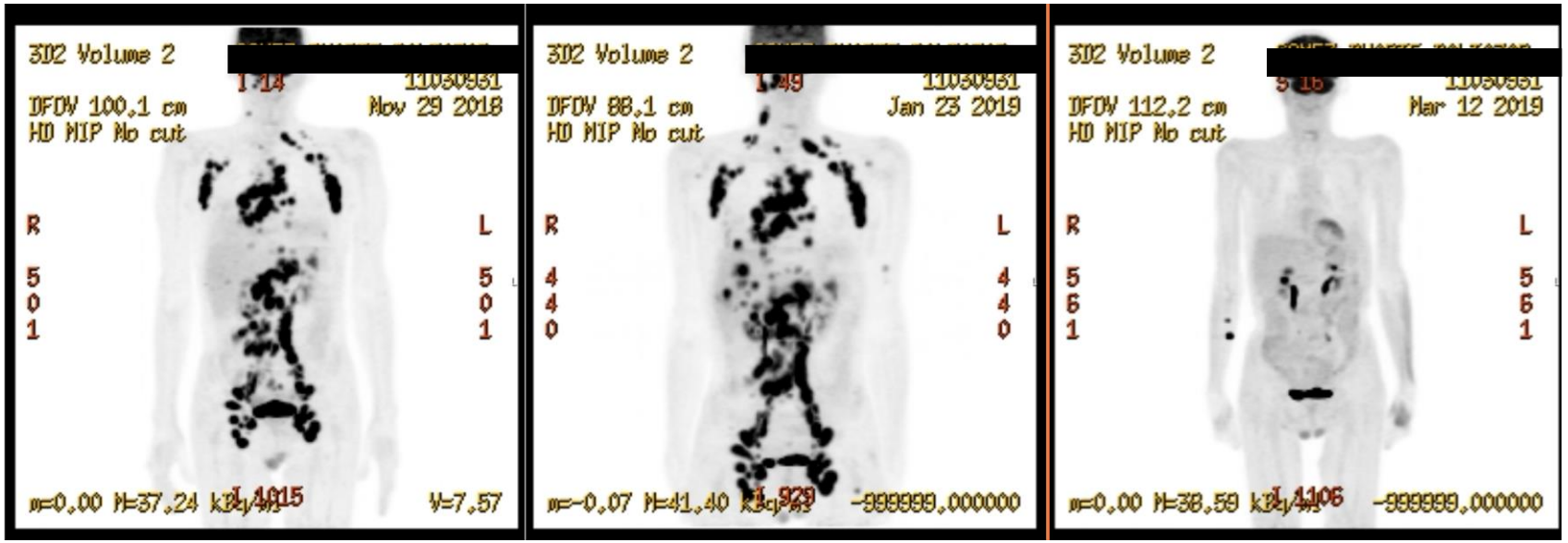
D0 Axi-cel

IRB#15391
D1C1 Mosun/TDB

Pre Axi-Cel, Day -7

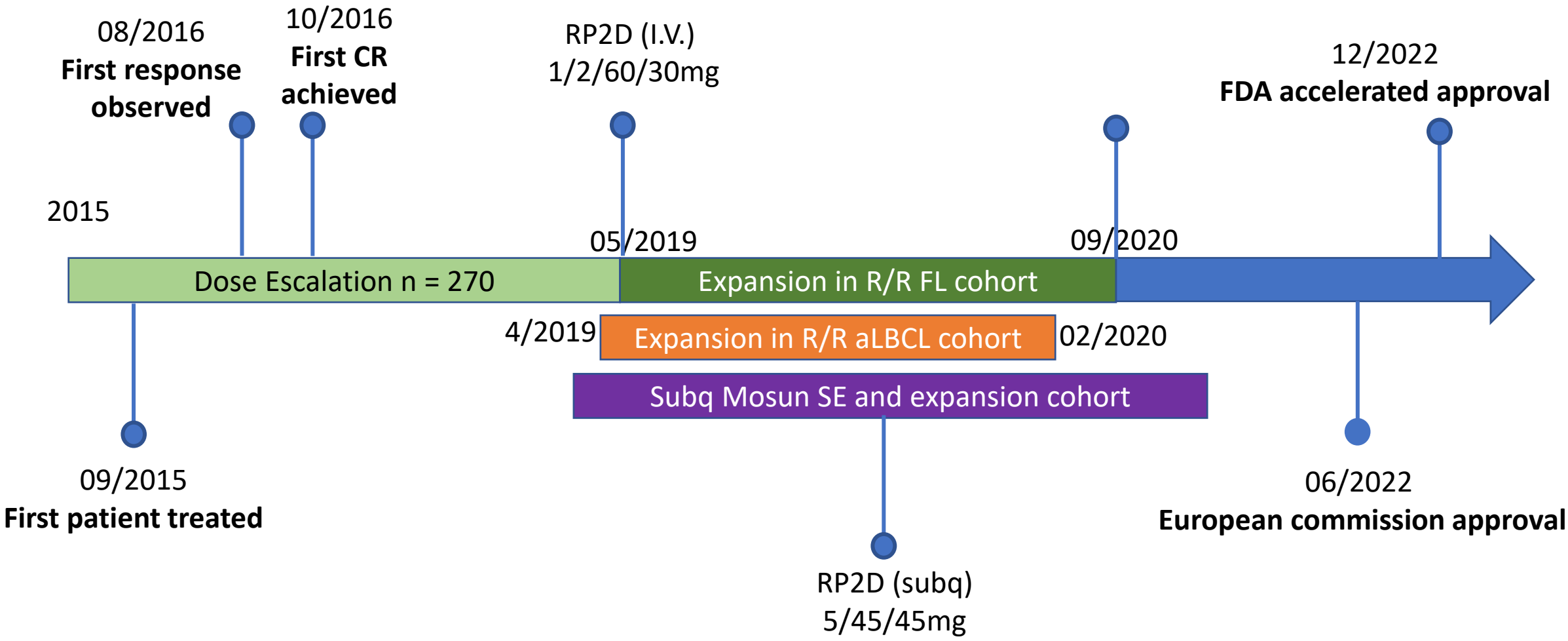
Post Axi-Cel D+38

D37 Mosun/TDB



Mosunetuzumab in relapsed/refractory B-NHL

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



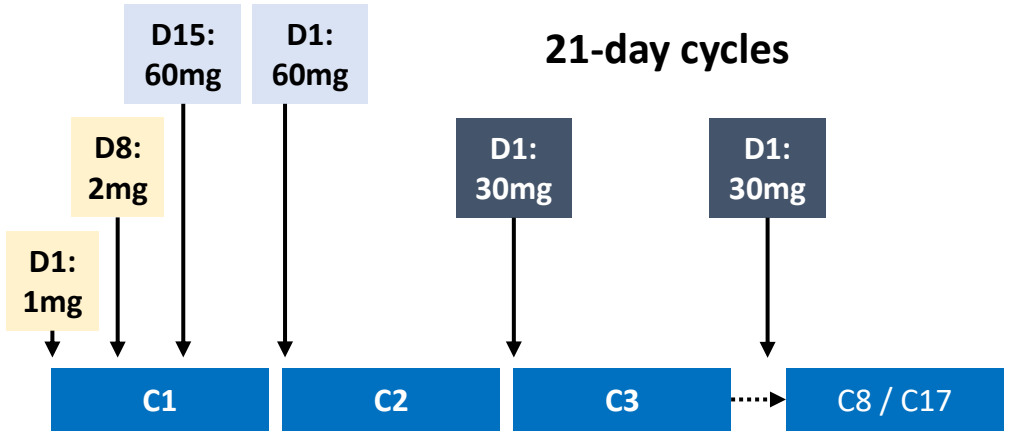
GO29781 (Mosunetuzumab): Single-arm, Phase II expansion in patients with R/R DLBCL and ≥2 prior therapies (N=88)

Key inclusion criteria

- aLBCL (DLBCL, tFL, HGL)
- ECOG PS 0–1
- ≥2 prior regimens, including
  - ≥1 anti-CD20 Ab
  - ≥1 anthracycline
- No requirement of CD20+

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

Bartlett et al. Blood Adv 2023

Data cut off: 3.15.2021

Patient population

n	*N= 88*
Median age, years (range)	**66.5 (24–96)**
Male	60 (68.2%)
ECOG PS 1 at baseline	57 (64.8%)[†]
Aggressive NHL subtype	
DLBCL	65 (73.9%)
trFL	23 (26.1%)
Cell-of-origin	
GCB	49 (55.7%)
Non-GCB	29 (33.0%)
Unknown	10 (11.4%)
Myc and BCL2 and or BCL6 translocation	17 (19.3%)
Median prior systemic therapies, n (range)	**3 (2–13)**[†]
Prior CAR-T therapy	26 (29.5%)
Prior autologous SCT	15 (17.0%)
Refractory[‡] to last prior therapy	70 (71.9%)
Refractory[‡] to prior anti-CD20 therapy	77 (87.5%)
Refractroy to prior CAR T therapy	18/26 (69.2%)

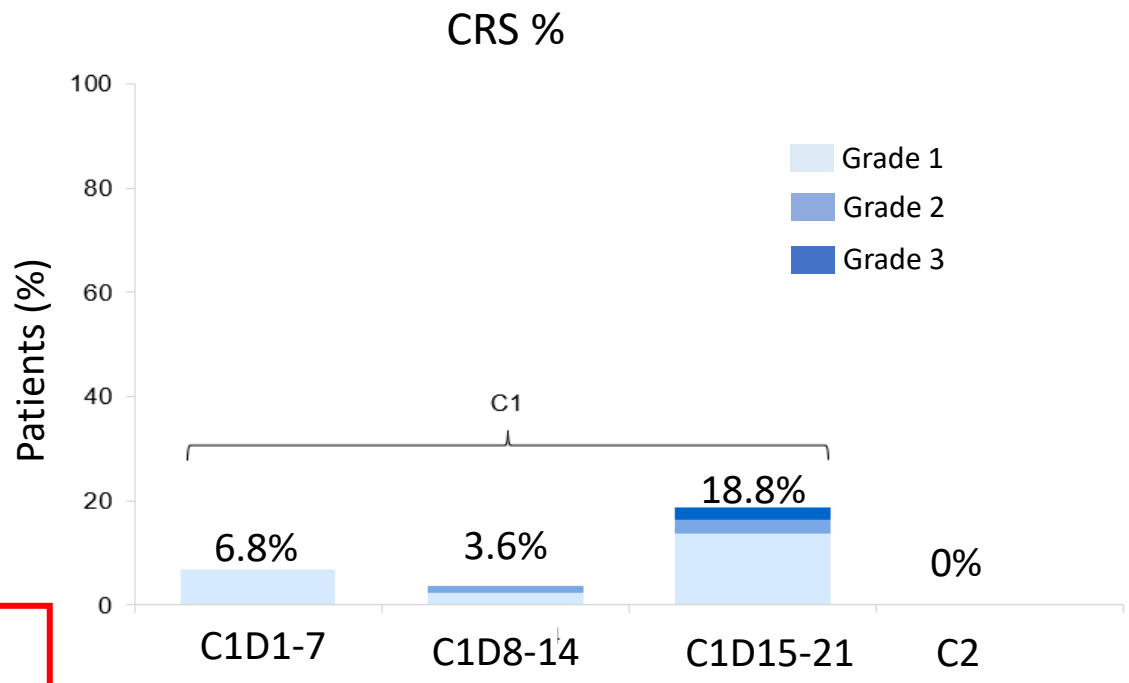
[‡]no response (PR or CR) or PD within ≤6 months of treatment

Bartlett et al. Blood Adv 2023

Adverse event overview: manageable safety profile

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

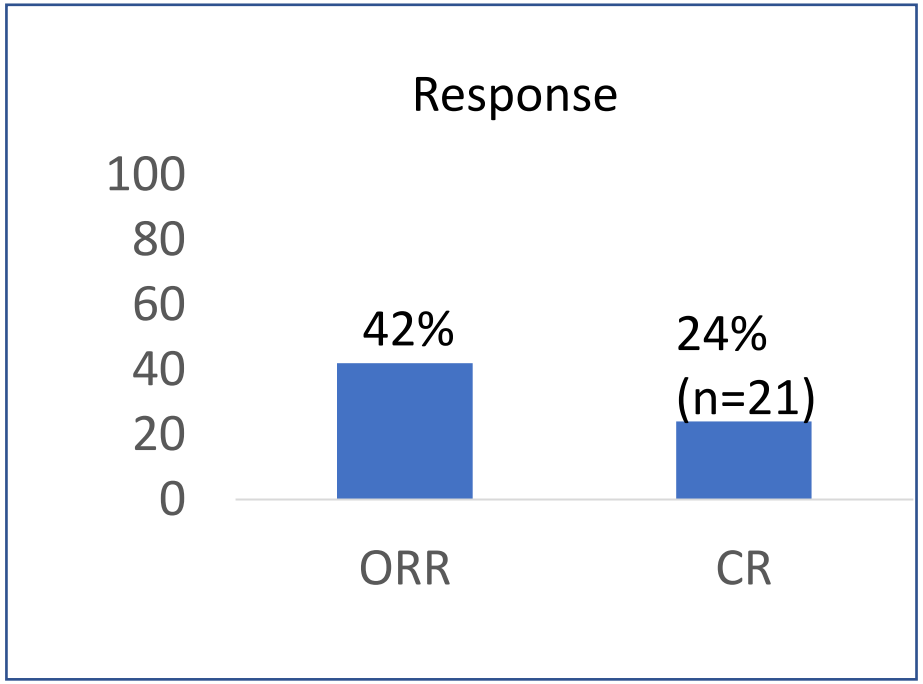
N (%)	N=88
Grade 5 (fatal) AE*	3 (3.4)†
M related	1 (1.1)
AE leading to M discontinuation	4 (4.5)
M related	2 (2.3)
Most common AEs (≥20%)	
Neutropenia	24 (27.3)
CRS	23 (26.1)
Fatigue	23(26.1)
Rash	19 (21.6)
CRS (any Grade)*	
Grade 1	18 (20.5)
Grade 2	3 (3.4)
Grade 3	2 (2.3)
ICANS any grade	2 (2.3)
Grade 1	2 (2.3)



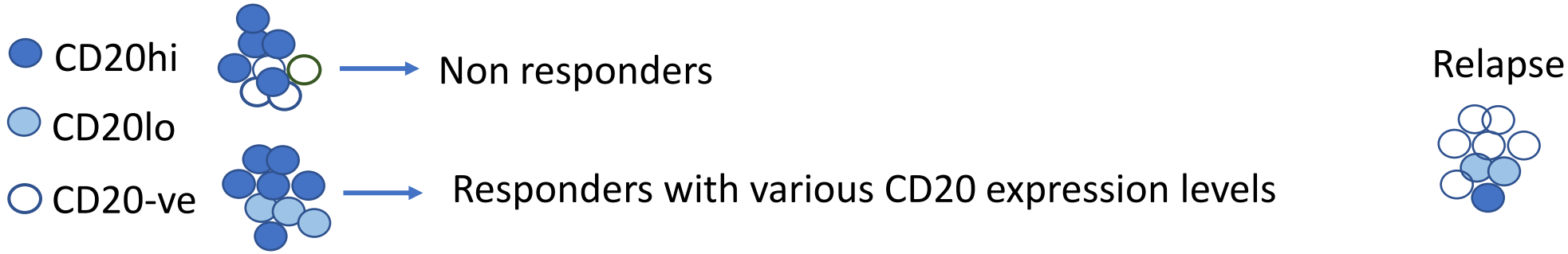
- **The majority of AEs were low Grade;**
- **all CRS & NT resolved.**

Mosunetuzumab monotherapy in relapsed/refractory DLBCL

GO29781: aLBCL expansion cohort

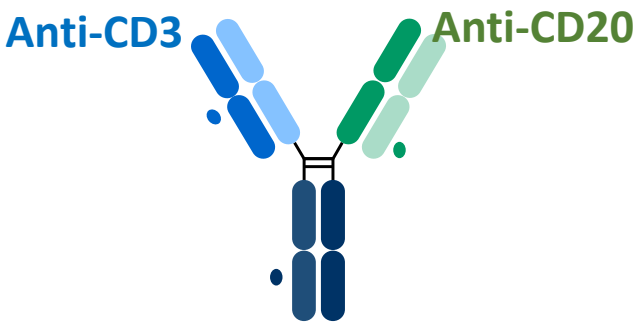


Outcomes	By IRF
Median time to 1st response, months (range)	1.4 (1.1-11.5)
Median time to first CR, months (range)	2.8 (1.1-17.5)
Duration of response; Median, months (95% CI)	7.0 (4.2-NE)
Duration of CR , Median, months (95% CI)	NE (9.0-NE)
PFS, Median, months (95% CI)	3.2 (2.2-5.3)
OS, Median, months (95% CI)	11.5 (9.0-16.4)

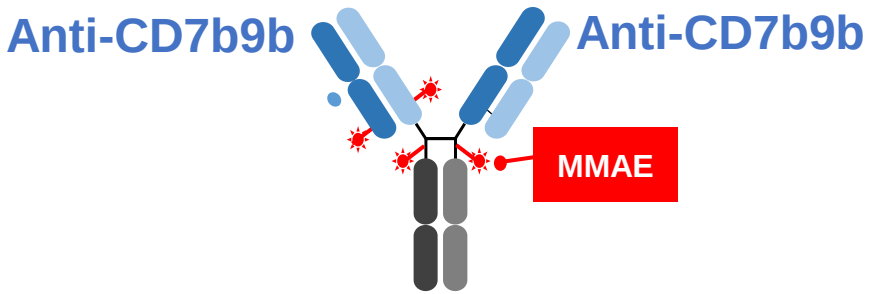


GO40516: Mosunetuzumab + Polatuzumab for aggressive B-NHL

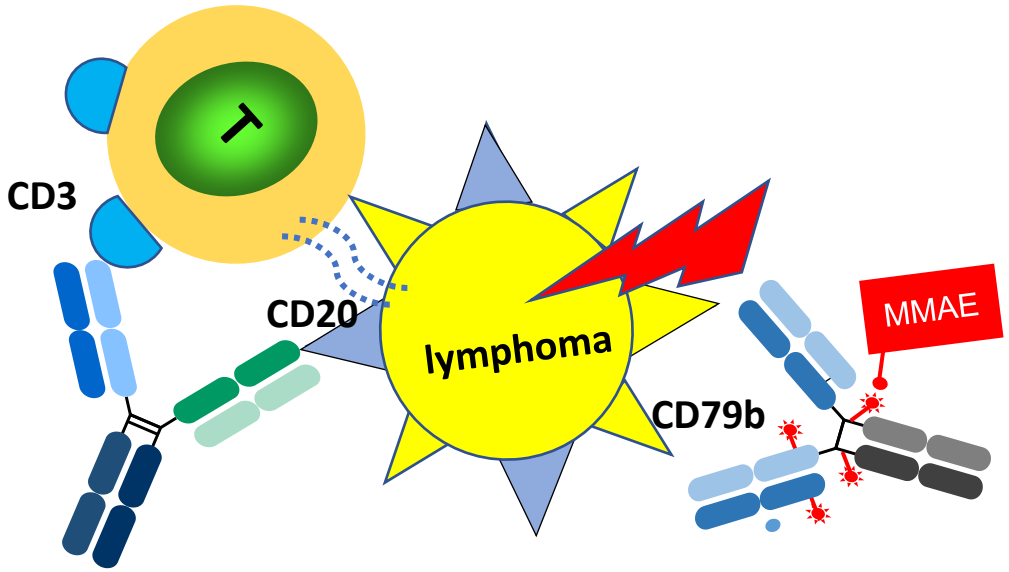
- **Phase Ib/II study (NCT03671018)**[5->] evaluating M-Pola combination in R/R aBNHL



Mosunetuzumab



Polatuzumab vedotin



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. ASH 2021

Study overview: mosunetuzumab+polatuzumab

- 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

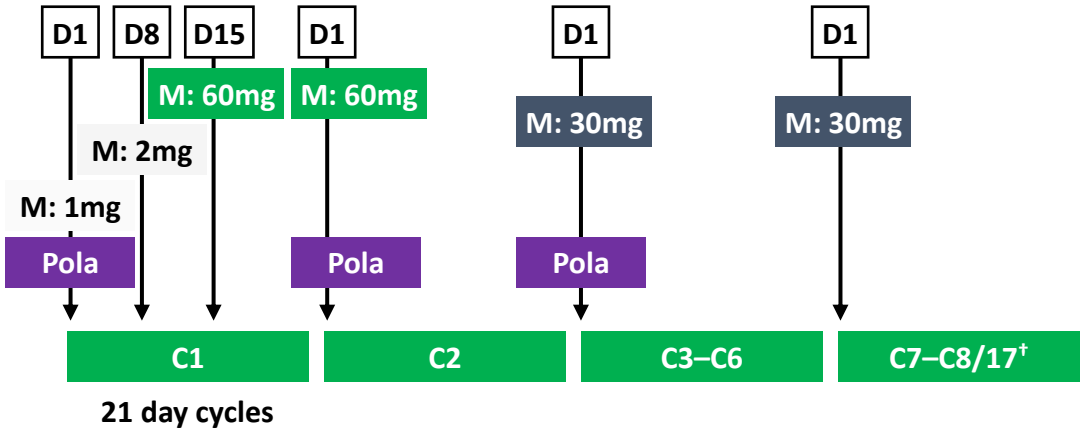
M-Pola administration in Phase II expansion*

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)



Budde et al. ASH 2021

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)

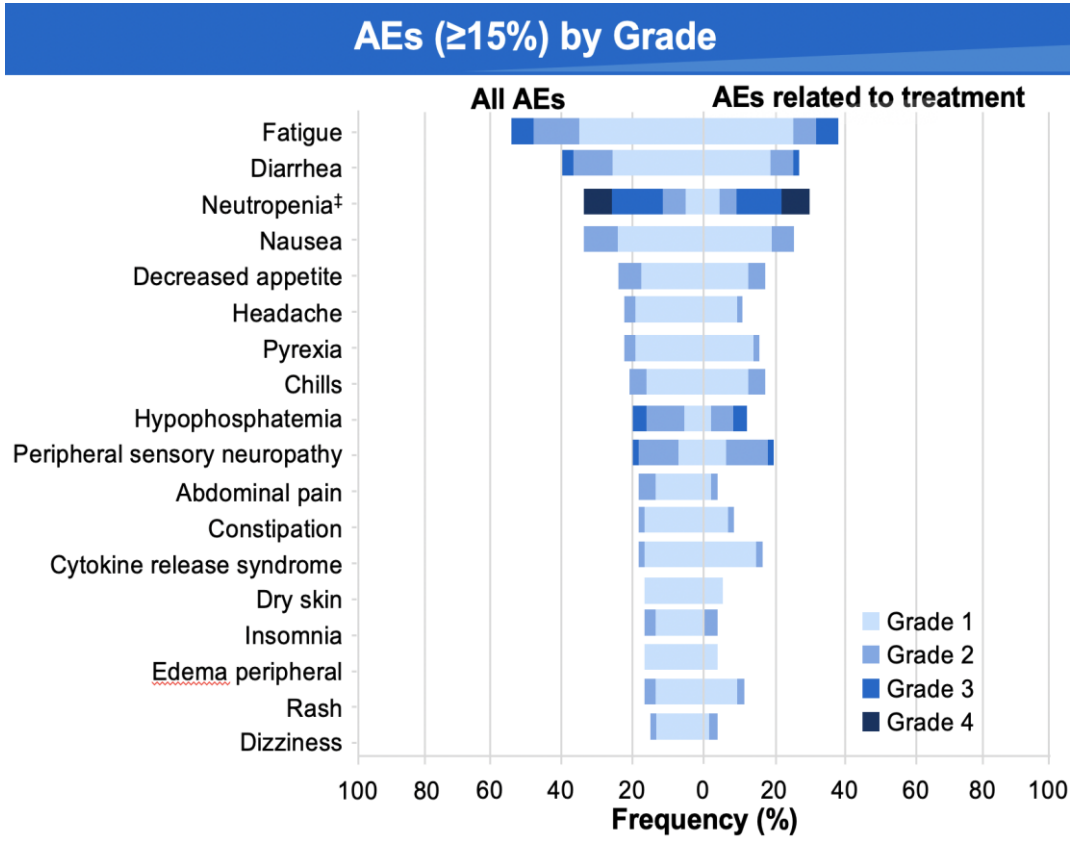
Cut-off date: March 15, 2021

*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)

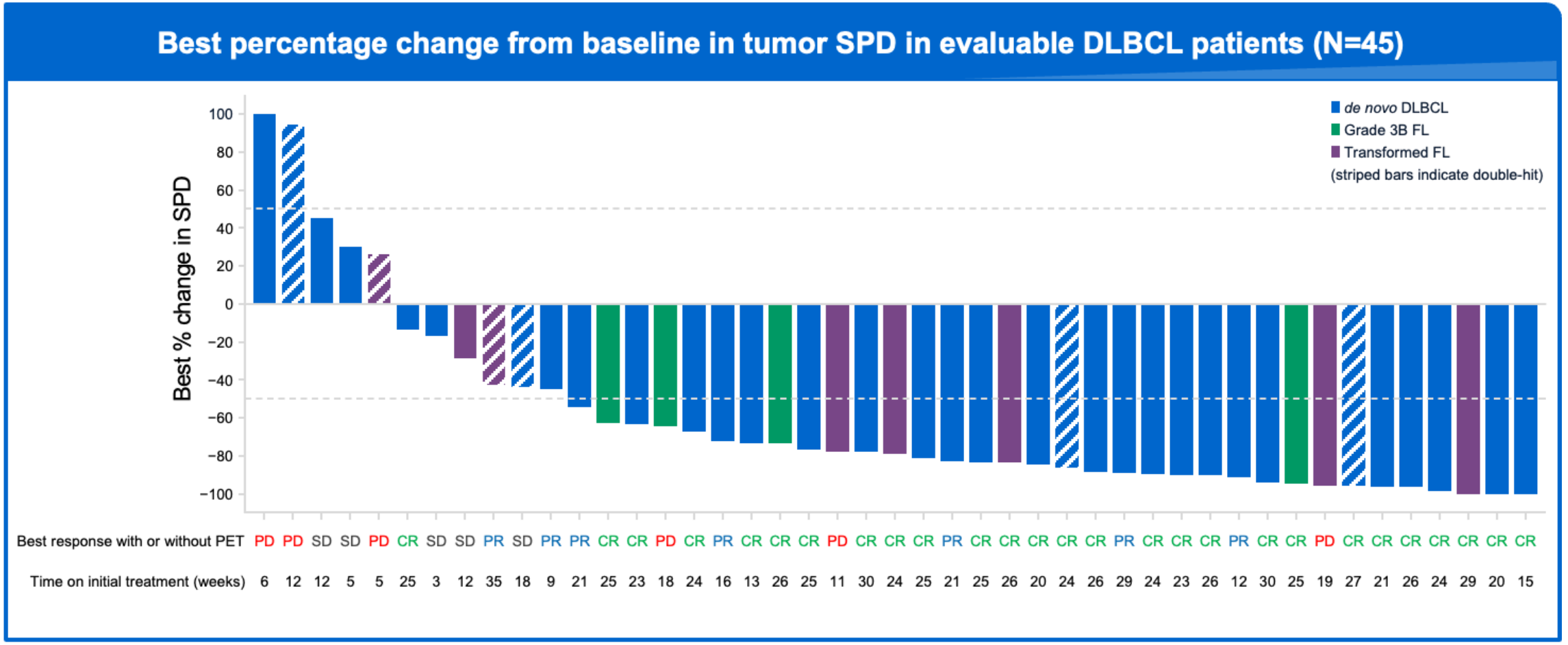
N (%)	N=63
Grade 5 (fatal) AE*	3 (4.8)†
M-Pola related	1 (1.6)
AE leading to M discontinuation	5 (7.9)
M related	3 (4.8)
AE leading to Pola discontinuation	8 (12.7)
Pola related	6 (9.5)
CRS (any Grade)*	11 (17.5)
Grade 1	10 (15.9)
Grade 2	1 (1.6)
Grade 3	0
ICANS any grade	5 (7.9)
Grade 3-4	2 (3.2)



- **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;

Anti-tumor efficacy: Mosun + Pola



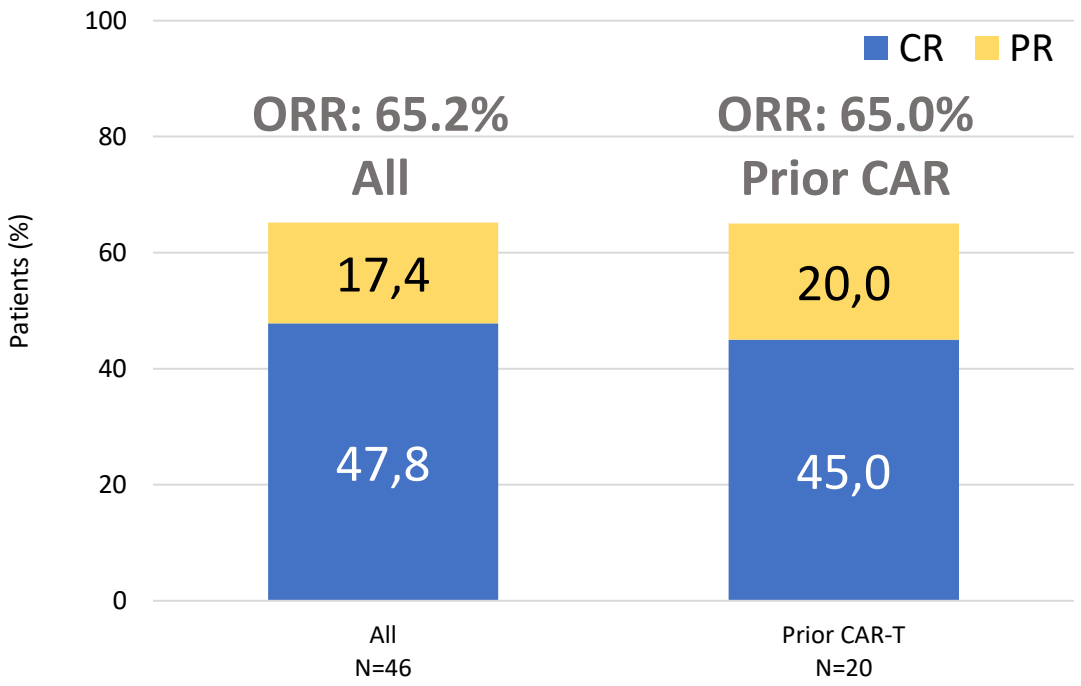
SPD, sum of product diameters

Budde et al. ASH 2021

Response in DLBCL patients*

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

Response in all DLBCL patients receiving mosunetuzumab at the RP2D (1/2/60/30mg) (N=46)



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

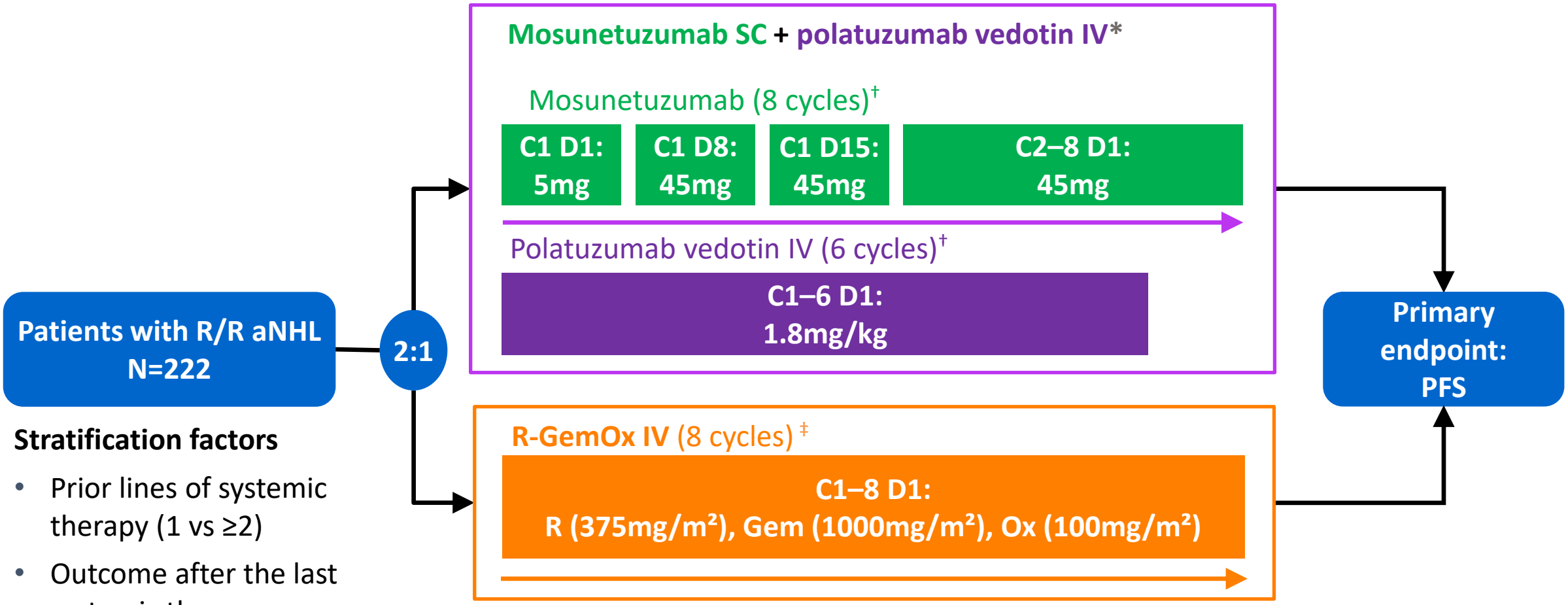
- Of 29 patients who achieved CR, 28 (96.6%) remained in CR and 1 (3.4%) had PD
  - the patient with PD subsequently received retreatment and achieved a CR

- Phase 2 pivotal cohort completed

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

Budde et al. ASH 2021

SUNMO (NCT05171647)
a randomized, open-label, multicenter, global Phase III trial



Stratification factors

- Prior lines of systemic therapy (1 vs ≥2)
- Outcome after the last systemic therapy (relapsed vs refractory)

Mosunetuzumab: 1st line DLBCL

GO40554 (NCT03677154): an ongoing Phase 1

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

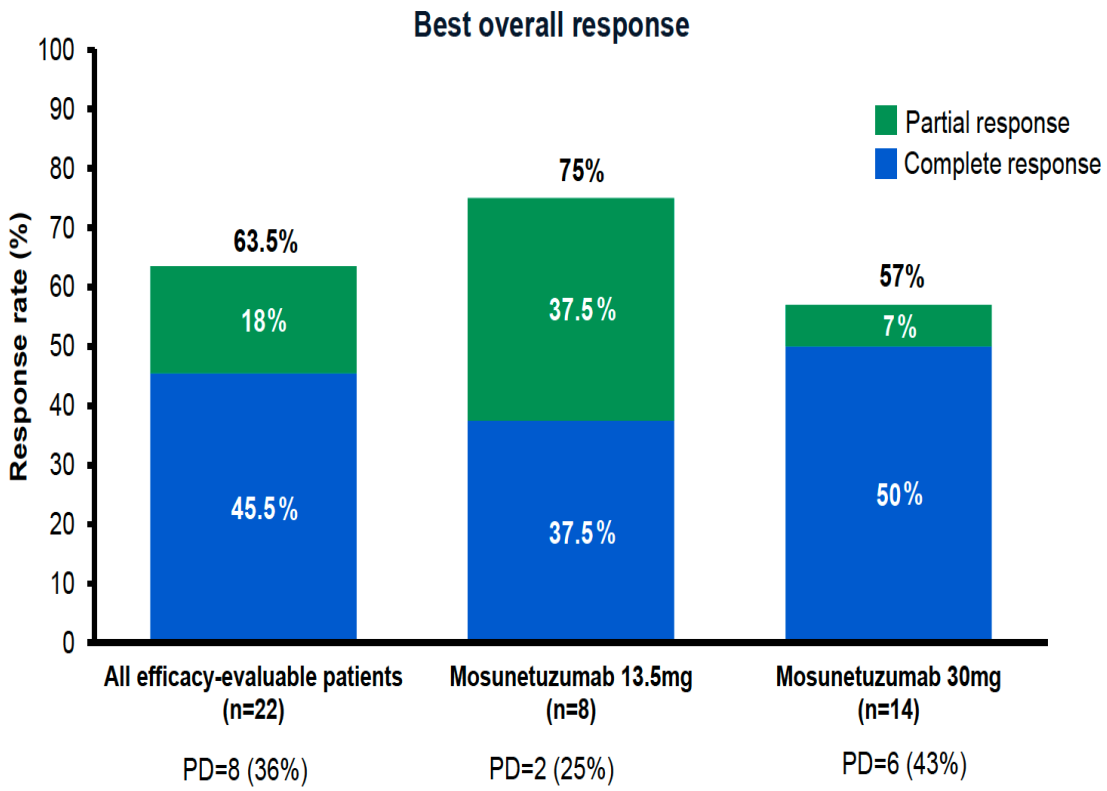
Key inclusion criteria

- 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

Mosunetuzumab in relapsed/refractory DLBCL

	Regimens
First line	Mosun or Mosun+pola (NCT03677154): Elderly unfit (NCT05207670) Mosun + CHOP or CHP-pola (NCT03677141)
Second line	Mosun+platinum based chemo (DHAX or ICE) NCT05464329: Transplant eligible Mosun monotherapy (NCT05412290): Post transplant consolidation
Third line	Mosun+pola (NCT03671018, phase II); NCT05171647 (phase III) Mosun+ lonca-T (NCT05672251) Mosun+pola + CAR T (NCT05260957) CAR T (PR+SD), randomized to Mosun, pola, M+P, or SOC (SWOG, NCT05633615) CAR T followed by Mosun (NCT04889716) Mosun+ CELMoDs (NCT05169515) Mosun+pola+tafasitmab+lenalidomide (NCT05615636) Mosun+atezolizumab (NCT02500407, terminated) Mosun + tiragolumab (NCT05315713) Mosun_GemOX (NCT04313608)

Conclusions

- Mosunetuzumab leads to meaningful remissions in B cell lymphomas.

- Mosunetuzumab is expanding its clinical development in earlier line use and in combinational
- use for aBCL.

  favorable attributes (outpatient use, fixed treatment duration, and favorable safety profile)

- Understanding the mechanism of action, mechanism of resistance, evolution of tumor and its microenvironment are essential to guide the rational design of therapeutic regimens using BsAbs.