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the MIRACLE of SCIENCE with SOUL

15th Annual California Cancer Consortium Conference – DLBCL: the latest and greatest

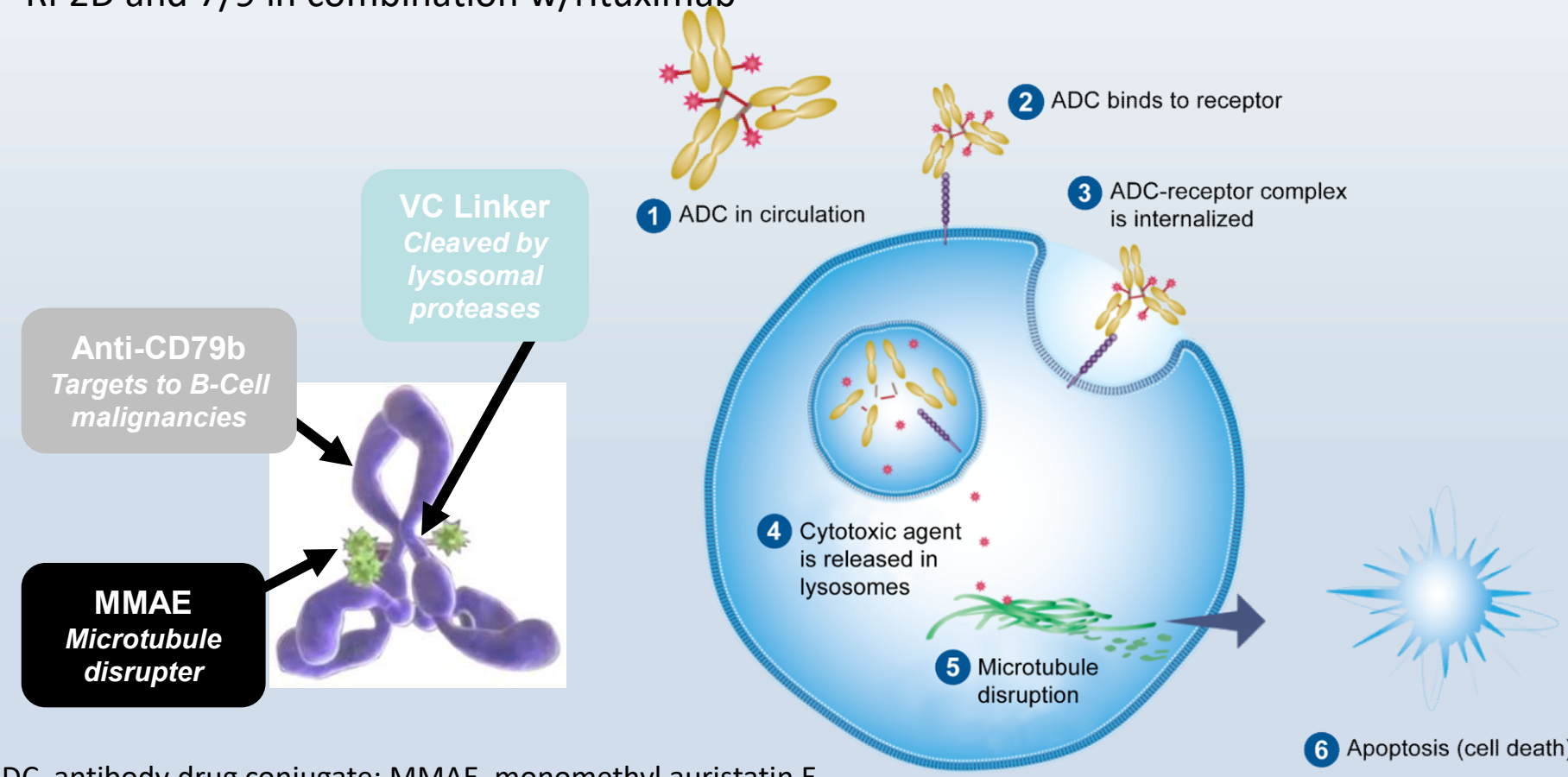
August 16-18, 2019, Pasadena, CA

Disclosures

- Advisory Board: Forty-Seven, Inc. Celltrion

Polatuzumab Vedotin (CD79b-ADC)

- ADC comprising potent microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker
- Single agent activity reported in 2015 by Morschhauser et al with 14/25 DLBCL pt at RP2D and 7/9 in combination w/rituximab



ADC, antibody drug conjugate; MMAE, monomethyl auristatin E

Polatuzumab Vedotin Combined with Obinutuzumab for Patients with Relapsed or Refractory Non-Hodgkin Lymphoma: Preliminary Safety and Clinical Activity of a Phase Ib/II Study

Tycel Phillips[1], Mark Brunvand[2], Andy Chen[3], Oliver Press[4], James Essell[5], Annalisa Chiappella[6], Catherine Diefenbach[7], Surai Jones[8], Jamie Hirata[8], Ian Flinn[9]

[1]Department of Internal Medicine, Division of Hematology and Oncology, University of Michigan Medical School, Ann Arbor, MI; [2]Colorado Blood Cancer Institute, Denver, CO; [3]Oregon Health and Science University, Portland, OR; [4]Fred Hutchinson Cancer Research Center, Seattle, WA;[5]Oncology Hematology Care, Inc, Cincinnati, OH; [6]Azienda Ospedaliera Universitaria Città della Salute e dellaScienza di Torino, Torino, Italy; [7]New York University School of Medicine/NYU Perlmutter Cancer Center, NewYork, NY; [8]Genentech, Inc., South San Francisco, CA; [9]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN

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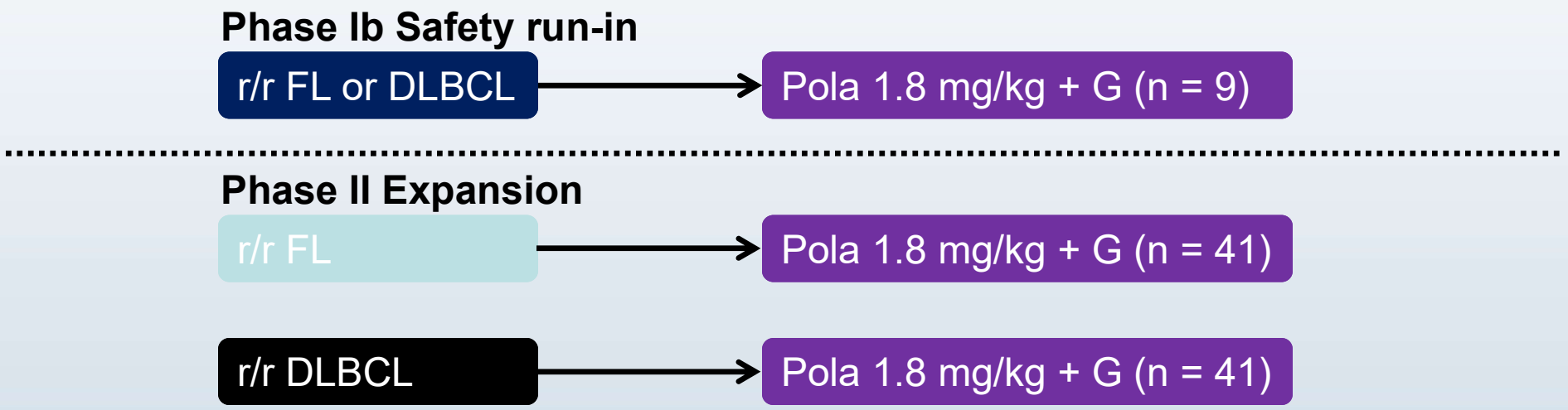
ROMULUS study

- Open label phase Ib/II study in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL)
- Previously reported results showed clinical activity for polatuzumab vedotin (Pola) 2.4 mg/kg + rituximab (RTX) in patients with R/R DLBCL and FL treated until progression[1]
- Pooled analysis comparing Pola doses (2.4 mg/kg vs 1.8 mg/kg) and duration of treatment (8 cycles vs treatment to progression) suggested tolerability may be improved with 1.8 mg/kg and ≤ 8 cycles treatment[2]

1. Morschhauser ASH 2014; 2. Advani ASCO 2015; 3. Herter et al. 2013; 4. Mössner et al. 2010

ROMULUS Study Design (G-containing Cohorts)



- **Pola (1.8 mg/kg, Day 2 in cycle 1; Day 1 in subsequent cycles)**
- **G (1000 mg, Days 1, 8 and 15 in cycle 1; Day 1 in subsequent cycles)**
- **For total of eight 21-day cycles**

Primary endpoint

- Evaluation of antitumor activity based on PET-CT at end of treatment by Lugano criteria

PET-CT, positron emission tomography–computed tomography
https://www.clinicaltrials.gov/ct2/show/NCT01691898.

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Patient Baseline Characteristics

Characteristics	FL (N=41)	DLBCL (N=45)
Median age, yr (range)	65 (43–82)	70 (27–84)
Sex, n (%)		
Male	25 (61)	25 (56)
Female	16 (39)	20 (44)
Baseline ECOG PS, n (%)		
0	19 (46)	9 (21)
1	22 (54)	30 (68)
2	–	5 (11)
International Prognosis Index, n (%)[a]		
0		2 (5)
1		3 (7)
2	–	14 (33)
3		10 (23)
4		11 (26)
5		3 (7)
Bulky disease[b], n (%)	6 (15)	11 (24)

[a]For DLBCL only; only available in 5 FL patients
[b]Defined as presence of baseline tumor ≥ 7.5 cm in largest dimension

Data Cut-Off: 26 JUL 2016

ECOG PS, Eastern Cooperative Oncology Group Performance Status; yr, years

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Patient Baseline Characteristics (Contd)

Characteristics	FL (N=41)	DLBCL (N=45)
Number of prior systemic therapies, median (range)	3 (1–8)	2 (1–7)
Prior transplant, n (%)	6 (25)	5 (11)
Prior rituximab, n (%)	40 (98)	44 (98)
Rituximab refractory[a], n (%)	10 (24)	27 (60)
Median time from prior treatment, months, (range)	9 (0.6–122.6)	2.5 (0.2–53.8)
Refractory to last prior treatment[b], n (%)	17 (42)	34 (76)

[a]Defined as progression or relapse within 6 months among patients whose last prior regimen contained rituximab
[b]Defined as progression or relapse within 6 months of last prior treatment

Details of Therapy Delivered

	FL (N=41)	DLBCL (N=45)
Median duration of follow-up, mo (range)	4.6 (0.4–15.4)	2.8 (0.1-11.8)
Median cycles received, (range)	7 (0–8)	4 (0–8)
Median time on study treatment, mo (range)	4.4 (0–6.0)	2.1 (0–5.7)
Treatment modifications, n (%)		
Treatment discontinuation for AE	5 (12)	5 (11)
Dose reductions	5 (12)	3 (7)
Treatment delays	10 (24)	11 (24)

AE, adverse event; mo, months

Grade 3 or 4 Adverse Events (≥ 5% across cohorts)

	FL (N=41)	DLBCL (N=45)	Total (N=86)
Any grade 3-4 AEs, n (%)	20 (48.8)	26 (57.8)	46 (53.5)
Neutropenia	7 (17.1)	10 (22.2)	17 (19.8)
Infections	6 (14.6)	6 (13.3)	12 (14)
Anemia	3 (7.3)	3 (6.7)	6 (7)
Thrombocytopenia	1 (2.4)	4 (8.9)	5 (5.8)

- Neutropenia was most common grade 3–4 treatment emergent adverse event
- Febrile neutropenia reported in 2 patients with DLBCL
- No treatment discontinuations were for neutropenia
- No clear pattern for the infections, with some bacterial and some viral infections

Peripheral Neuropathy (per SMQ)[a]

	FL (N=41)	DLBCL (N=45)
History of prior PN, n (%)	15 (37)	16 (36)
Ongoing PN at Study Entry, n (%)[b]	13 (32)	16 (36)
All Grades, n (%)	17 (42)	11 (24)
Grade 2, n (%)	7 (17)	7 (16)
Median time to Onset, mo. (Q1–Q3)		
First PN Event	2.3 (0.7–2.8)	1.5 (1.3–4.1)
Grade 2 PN Event	3.9 (2.8–4.5)	2.1 (2.1–4.2)
Led to Pola Discontinuation, n (%)	2 (4.9)	2 (4.4)
Led to Pola Dose Reduction, n (%)	5 (12.2)	3 (6.7)

- At time of data cut off, 14 patients experienced Grade 2 PN
  - 11 ongoing (3 of 11 discontinued treatment)
  - 3 recovered within 19-23 days after dose reduction

[a]Peripheral neuropathy = System organ class term
[b]All Grade 1 per protocol eligibility criteria

SMQ, Standardized MedDRA Queries

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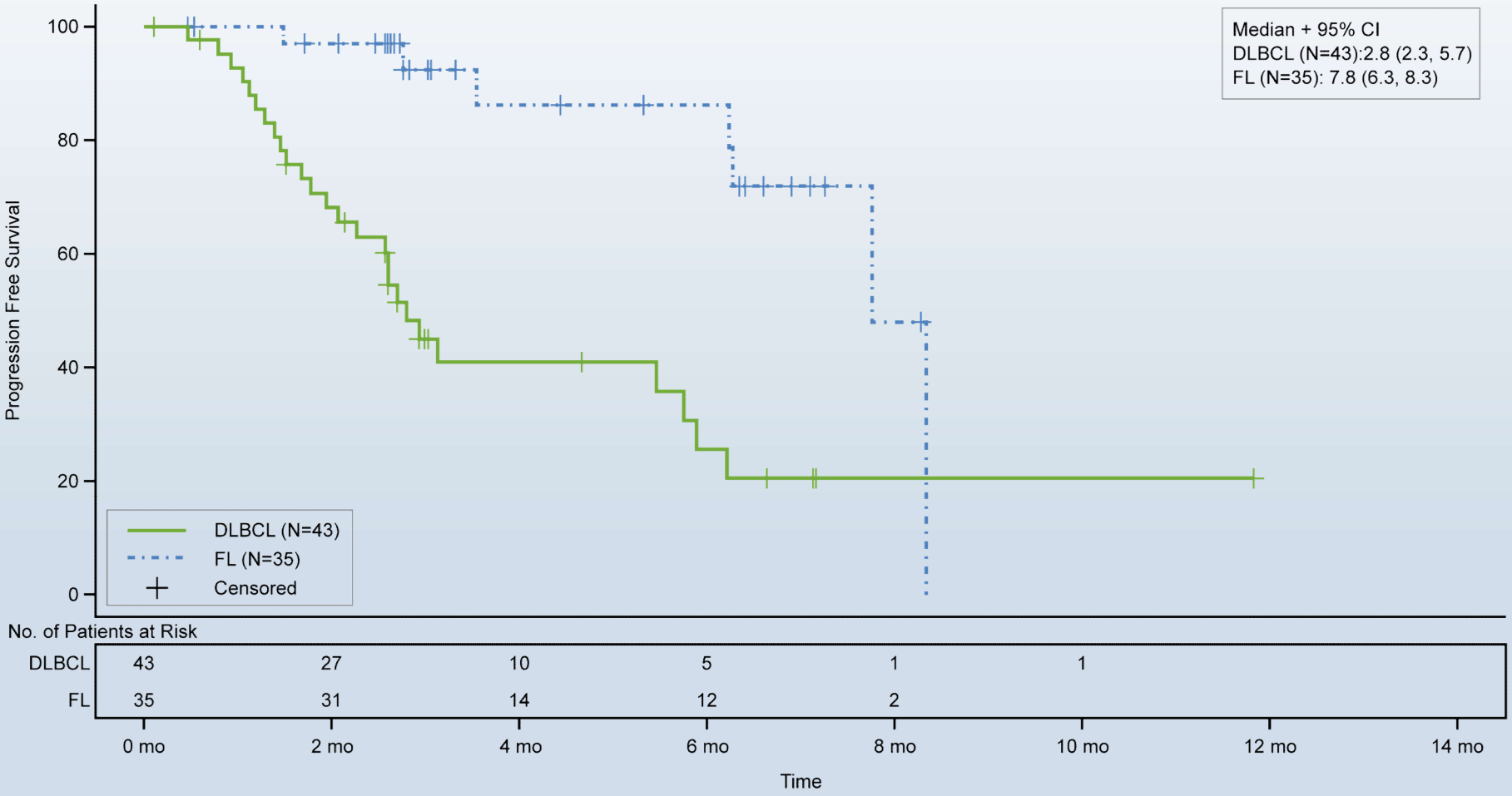
Investigator-Assessed Best Responses by Lugano Criteria[a]

	FL (N=35)	DLBCL (N=43)
Objective response, n (%)	**24 (69)**	**17 (40)**
Complete Response	11 (31)	9 (21)
[90% CI]	[19–47]	[11–34]
Partial Response	13 (37)	8 (19)
[90% CI]	[24–52]	[10–31]
Stable disease, n (%)	4 (11)	0
Progressive disease, n (%)	1 (3)	18 (42)
Unable to evaluate, n (%)	6 (17)[b]	8 (19)[c]

[a]Patients who received ≥1 dose of study treatment; assessment per Lugano Criteria (Cheson 2014)
[b]No Pola dose due to IRR from G, taken off-study (n=2); no PET assessment (n=2); taken off-study due to neutropenia before assessment (n=1); fatal pneumonia before assessment (n=1)
[c]Died before assessment (n=1); PD not by PET (n=4); not assessed due to hospitalization / taken off study (n=2); W/D consent / not dosed (n=1)

Progression Free Survival



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Conclusions

- Early results from ongoing study show that novel combination of Pola (1.8 mg/kg with fixed duration of ≤ 8 cycles) plus G has acceptable safety profile
  - Most AEs were Grade 1–2
  - Peripheral neuropathy was not a major issue
- Evidence of clinical activity in r/r FL or DLBCL pts who were heavily pretreated or refractory to last prior regimen
  - Best objective response (by Lugano criteria) observed in 69%of FL
  - Median PFS of 7.8 months in FL patients

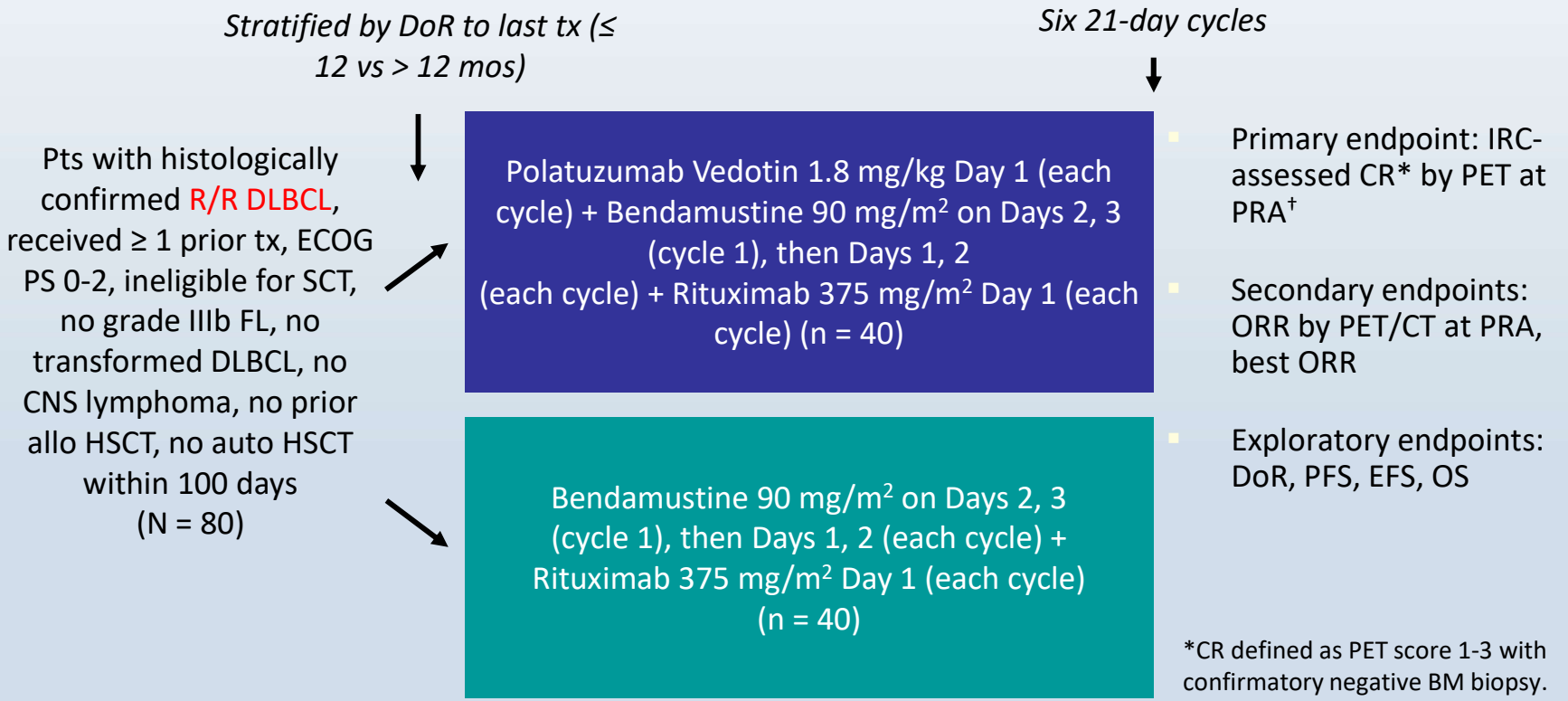
Polatuzumab Vedotin + BR in R/R DLBCL: Background

- Durable responses and acceptable safety profile reported in phase Ib/II study of PV addition to BR or BG in transplantation-ineligible pts with R/R DLBCL and FL[4]
  - Among pts with R/R DLBCL, ORR of 50% with PV + BR and ORR of 57% to 83% with PV + BG
- Current analysis evaluated efficacy and safety of PV addition to BR vs BR alone in phase II cohorts of transplantation-ineligible R/R DLBCL pts[5]

1. Friedberg JW. Hematology Am Soc Hematol Educ Program. 2011;2011:498-505. 2. Dornan D, et al. Blood. 2009;114:2721-2729. 3. Polson AG, et al. Blood. 2007;110:616-623. 4. Matasar M, et al. EHA 2017. Abstract S468. 5. Sehn LH, et al. ASH 2017. Abstract 2821.

Polatuzumab Vedotin + BR in R/R DLBCL: Study Design

- Analysis of phase II randomized R/R DLBCL cohorts from multicenter, open-label phase Ib/II trial



*CR defined as PET score 1-3 with confirmatory negative BM biopsy.
†PRA at 6-8 wks after either cycle 6, Day 1 or last dose of tx.

Sehn LH, et al. ASH 2017. Abstract 2821.

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Polatuzumab Vedotin + BR in R/R DLBCL: Baseline Characteristics

Characteristic, n (%)	PV + BR (n = 39)	BR (n = 39)
Median age, yrs (range)	67 (33-86)	71 (30-84)
Male	27 (69.2)	25 (64.1)
ECOG PS 2	6 (15.4)	8 (20.5)
Bulky disease ≥ 7.5 cm	9 (23.1)	15 (38.5)
Ann Arbor stage III/IV	33 (84.6)	35 (89.7)
Extranodal involvement	26 (66.7)	29 (74.4)
IPI score 3-5 at enrollment	21 (53.8)	28 (71.8)
Median no. prior therapy lines (range) ▪ 1/2/≥ 3	2 (1-7) 11 (28.2)/14 (35.9)/14 (35.9)	2 (1-5) 13 (33.3)/9 (23.1)/17 (43.6)
Refractory to last tx	29 (74.4)	32 (82.1)
DoR to last tx ≤ 12 mos	31 (79.5)	33 (84.4)
Prior anti-CD20 agents	38 (97.4)	39 (100)

Sehn LH, et al. ASH 2017. Abstract 2821.

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Polatuzumab Vedotin + BR in R/R DLBCL: Response

- Median follow-up per reverse Kaplan-Meier: PV + BR, 11.1 mos; BR, 10.9 mos

Response, %	PV + BR	BR	*P* Value
IRC-assessed OR (CR + PR) at PRA	45	17.5	.008
▪ CR	40	15	.012
Investigator-assessed OR (CR + PR) at PRA	47.5	17.5	.004
▪ CR	42.5	15	.007
Investigator-assessed best objective response	70.0	32.5	--
▪ CR	57.5	20.0	
Pts achieving OR per PET/CT at PRA by cell of origin*			
▪ Activated B-cell	91	67	--
▪ Germinal center B-cell	60	20	
Median DoR, mos	8.8	3.7	

Sehn LH, et al. ASH 2017. Abstract 2821.

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Polatuzumab Vedotin + BR in R/R DLBCL: Survival

- OS favored PV + BR in subgroups stratified by BL characteristics

Outcome, Mos	PV + BR	BR	Stratified HR (95% CI)	*P* Value
Median OS	11.8	4.7	0.35 (0.19-0.67)	.0008
1-yr OS, %	48	24	--	--
Median PFS	6.7	2.0	0.31 (0.18-0.55)	< .0001
Median EFS	6.0	2.0	--	--

stratified by DoR

Adjustment Factor(s)	Pts, n	HR (95% CI) for PV + BR vs BR	*P* Value
ECOG PS (≥ 2 vs < 2) and bulky disease (yes vs no)	78	0.41 (0.21-0.77)	.006
Stage (III/IV vs I/II) and bulky disease (yes vs no)	80	0.38 (0.20-0.72)	.003
ECOG PS (≥ 2 vs < 2) and no. prior tx lines (≥ 2 vs 1)	78	0.38 (0.20-0.73)	.004
IPI score (≥ 3 vs < 3)	80	0.39 (0.21-0.75)	.004

Sehn LH, et al. ASH 2017. Abstract 2821.

Polatuzumab Vedotin + BR in R/R DLBCL: Safety

AE, n (%)	PV + BR (n = 39)	BR (n = 39)
Pts with ≥ 1 AE	39 (100)	38 (97.4)
Grade 5*	7 (17.9)	7 (17.9)
Serious AE	20 (51.3)	20 (51.3)
Serious AE in ≥ 3% pts		
▪ Infections	8 (20.5)	10 (25.6)
▪ Febrile neutropenia	4 (10.3)	2 (5.1)
▪ Neutropenia	0	3 (7.7)
▪ Pyrexia	4 (10.3)	1 (2.6)
Peripheral neuropathy	15 (38.5)	NR
▪ Grade 2	7 (17.9)	
Grade 3/4 AE	33 (84.6)	26 (66.7)
Grade 3/4 AE in ≥ 10% of pts		
▪ Neutropenia	18 (46.2)	14 (35.9)
▪ Febrile neutropenia	4 (10.3)	2 (5.1)
▪ Thrombocytopenia	13 (33.3)	8 (20.5)
▪ Anemia	10 (25.6)	5 (12.8)
▪ Infections	7 (17.9)	7 (17.9)

Pt Disposition, n (%)	PV + BR (n = 39)	BR (n = 39)
Completed all tx	18 (46.2)	7 (17.9)
Median no. cycles completed (range)	5 (1-6)	3 (1-6)
D/c due to PD/lack of efficacy	7 (17.9)	21 (53.8)
D/c due to death	0	1 (2.6)
D/c due to AE	13 (33.3)	6 (15.4)
▪ Due to PN	1 (2.6)	--
Study drug modification or interruption due to AE	21 (53.8)	17 (43.6)
▪ PV reduction due to PN	2 (2.1)	--

*Grade 5 AEs during tx in PV + BR arm: pulmonary edema, massive hemoptysis, pneumonia; in BR arm, pneumonia, sepsis, septic shock, cerebrovascular accident. During follow-up in PV + BR arm: distributive shock, pneumonia, herpetic encephalitis, renal failure (all in setting of PD); in BR arm: multiple organ dysfunction and cerebral hemorrhage (both in setting of PD), unexplained death.

Polatuzumab Vedotin + BR in R/R DLBCL: Conclusions

- Addition of polatuzumab vedotin to BR was associated with a significantly increased response rate in R/R DLBCL pts vs BR alone
  - CR by IRC at PRA (primary endpoint): 40% vs 15% (P = .012)
    - Preliminary biomarker data suggested that PV + BR improved response rates in pts with activated B-cell or germinal center B-cell subtypes
  - PV addition associated with improved DoR, EFS, PFS, and OS
    - Median OS with PV + BR vs BR: 11.8 vs 4.7 mos (HR: 0.35; P = .0008)
    - OS benefit with PV + BR was consistent across subgroups and after adjusting for BL characteristics in multiple Cox regression models
- Investigators conclude that polatuzumab vedotin addition to BR associated with clinically meaningful responses, prolonged survival, and acceptable safety profile in transplantation-ineligible R/R DLBCL pts

Polatuzumab vedotin Combined with Bendamustine and Rituximab or Obinutuzumab in R/R FL or R/R DLBCL: Preliminary Results of a Phase Ib/II Study

Alex F. Herrera,[1] Matthew J. Matasar,[2] Sarit Assouline,[3] Manali Kamdar,[4] Amitkumar Mehta,[5] Isabelle Fleury,[6] Won Seog Kim,[7] Tae Min Kim,[8] Francesc Bosch,[9] John Radford,[10] Lilian Bu,[11] Wan-Jen Hong,[12] Laurie H. Sehn[13]

[1]City of Hope, Duarte, CA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Jewish General Hospital, Montreal, Canada; [4]University of Colorado, Denver, CO; [5]Department of Medicine, University of Birmingham, Birmingham, AL; [6]Department of Hematology, Maisonneuve-Rosemont Hospital and University of Montreal, Montreal, Canada; [7]Samsung Medical Center, Seoul, South Korea; [8]Seoul National University Hospital, Seoul, South Korea; [9]Hospital Universitari Vall d'Hebron, Barcelona, Spain;[10]The University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [11]Roche, Shanghai, China; [12]Genentech, Inc., South San Francisco, CA; [13] Centre for Lymphoid Cancer, BC Cancer Agency, Vancouver, Canada

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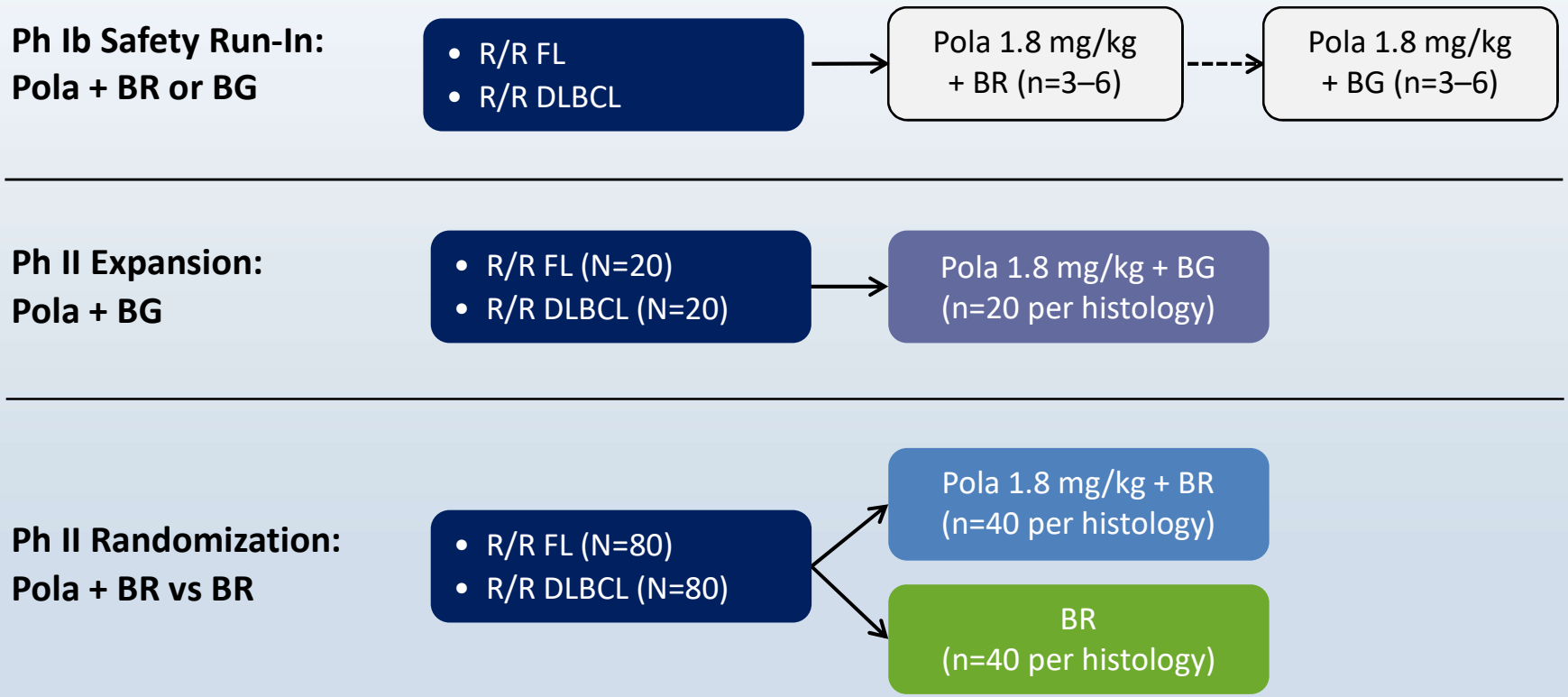
GO29365: Introduction

- Preliminary data are presented from:
  - Phase Ib safety run-in for Pola + BR or BG in R/R FL and R/R DLBCL
  - Phase II expansion for Pola + BG in R/R DLBCL

Study Design



R (375 mg/m^2) D1 of each cycle or G (1000 mg) D1, D8, D15 in cycle 1 then D1 of each subsequent cycle plus B (90 mg/m^2) D2 and D3 in cycle 1 then D1 and D2 in each subsequent cycle. Pola (1.8 mg/kg) D2 of cycle 1, then D1 of each subsequent cycle. FL: Tx administered every 28 das x 6 cycles. DLBCL: Tx administered every 21 days x 6 cycles.

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Baseline Characteristics

Characteristic	Phase Ib: Safety Run-In				Phase II: Expansion
	R/R FL		R/R DLBCL		R/R DLBCL
	Pola + BR (N=6)	Pola + BG (N=6)	Pola + BR (N=6)	Pola + BG (N=6)	Pola + BG (N=20)
Median age (range)	68 (54–73)	63.5 (42–73)	65 (58–79)	71 (53–84)	65.5 (30–86)
ECOG PS, n (%)					
0	3 (50)	3 (50)	2 (33)	1 (17)	5 (21)
1	3 (50)	3 (50)	4 (67)	4 (67)	12 (57)
2	0	0	0	1 (17)	3 (14)
Median # of prior therapies (range)	2 (1–3)	3 (1–3)	2 (1–2)	2 (1–4)	3 (1–5)
Refractory to last prior tx n, (%)	3 (50)	2 (33)	5 (83)	4 (67)	17 (85)
FLIPI1, n (%)					
Low (0–1)	0	1 (17)	N/A	N/A	N/A
Intermediate (2)	4 (67)	1 (17)			
High (3–5)	2 (33)	4 (67)			
FLIPI2, n (%)					
Low (0–1)	0	1 (17)	N/A	N/A	N/A
Intermediate (2)	4 (67)	2 (33)			
High (3–5)	2 (33)	3 (50)			
IPI, n (%)					
Low (0–1)	N/A	N/A	1 (17)	1 (17)	3 (15)
Low-intermediate (2)			4 (67)	1 (17)	2 (10)
High-intermediate/high (3–5)			1 (17)	4 (67)	15 (75)

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Best Objective Response by PET/CT

	Pola + BR	Pola + BG	Pola + BR/BG
R/R FL	N=6	N=6	N=12
ORR, n (%)	6 (100)	6 (100)	12 (100)
CR	5 (83)	5 (83)	10 (83)
PR	1 (17)	1 (17)	2 (17)
R/R DLBCL	N=6	N=26**	N=32
ORR, n (%)	3 (50)	16 (61)	19 (59)
CR	2 (33)	10 (38)	12 (39)
PR	1 (17)	6 (23)	7 (22)***
SD, n (%)	0	2 (8)	2 (6)
PD, n (%)	2 (33)	4 (15)	6 (19)
Missing or UE, n (%)	1 (17)	4 (15)	5 (16)

*Response assessment according to modified Lugano 2014 criteria (if available);
**Includes Phase Ib and Phase II expansion pts who received Pola + BG;
***1 pt achieved a CMR by PET scan but did not have a confirmatory bone marrow biopsy

SMART START: Ibrutinib, Lenalidomide, and Rituximab in DLBCL: Background

- Rituximab: commonly used in R-CHOP to treat DLBCL
- Lenalidomide: IMiD approved for MM, MDS, MCL, and FL, with single-agent activity in relapsed ABC DLBCL[1]
- Ibrutinib: BTK inhibitor approved for MCL, CLL/SLL, WM, and MZL, with single-agent activity in relapsed ABC DLBCL[2]
- Phase II study of RLI in relapsed/refractory non-GCB DLBCL: 55% ORR, median DoR of 9 mos[3]
- Current Smart Start trial designed to determine efficacy of RLI before and then with chemotherapy in patients with newly diagnosed non-GCB DLBCL[4]

1. Wilson. Nat Med. 2015;21:922. 2. Hernandez-Ilizaliturri. Cancer. 2011;117:5058.
3. Ramchandren. ASH 2018. Abstr 402. 4. Westin. ASCO 2019. Abstr 7508.

Smart Start: RLI + Chemotherapy in High-Risk, Newly Diagnosed non-GCB DLBCL

- Single-center, nonrandomized phase II study

Patients with high-risk, newly diagnosed non-GCB DLBCL by Hans IHC, PS 0-2 (N = 60)*

→

Cycles 1-2

RLI†
Rituximab IV over 4-6 hrs Day 1
Lenalidomide 25 mg/day x 10 days
Ibrutinib 560 mg/day x 21 days
(n = 58)

→

Cycles 3-8

RLI + EPOCH‡ or CHOP §
Q21D x 6 cycles

‡EPOCH selected by investigator preference considering high ki-67, high IPI, bulky mass, etc.

§ July 2018: ibrutinib dosing with chemotherapy amended to 420 mg for patients > 65 yrs (n = 9).

- Primary endpoints: ORR at end of 2 cycles of RLI alone, CR after 2 cycles RLI and 6 cycles RLI plus chemotherapy
- Secondary endpoints: ORR, PFS, OS, safety of lenalidomide + ibrutinib + chemotherapy; CR rate with RLI + CHOP and RLI + EPOCH
- Follow-up: every 3 mos for 1 yr, then every 4 mos for another yr

1. Wilson. Nat Med. 2015;21:922. 2. Hernandez-Ilizaliturri. Cancer. 2011;117:5058.
3. Ramchandren. ASH 2018. Abstr. 4. Westin. ASCO 2019. Abstr 7508.

Smart Start: Baseline Characteristics

Characteristic	Patients (N = 60)
Median age, yrs (range)	63.5 (29-83)
▪ > 70 yrs, %	28
Female, %	50
Median IPI score, %	3
▪ Very good (0/1)	16.7
▪ Good (2)	31.7
▪ Poor (3-5)	51.7
Ki-67 > 80%, %	77
▪ > 90%	49
Stage III-IV, %	65
Double-expressor (MYC, BCL2 per IHC), %	54 (n = 19/35)
Double hit (MYC, BCL6 per FISH), %	2.7 (n = 1/37)

Westin. ASCO 2019. Abstr 7508.

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Smart Start: Adverse Events

Adverse Event Category	Patients (N = 60)
Most common all-grade AEs	~ 45%-50%: nausea, peripheral sensory neuropathy, diarrhea, oral mucositis ~ 30%-35%: anemia, thrombocytopenia, rash, neutropenia
Most common grade 3/4 AEs	~ 20%-30%: Anemia, thrombocytopenia, neutropenia, febrile neutropenia ~ 10%: rash
Other AEs in < 25% of patients	~ 20%-25%: Dyspnea, nonneutropenic fever, vomiting ~ 5%: atrial fibrillation, syncope
Grade 5 events (1 each)	Febrile neutropenia, CNS aspergillosis

Westin. ASCO 2019. Abstr 7508.

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Smart Start: Response Rates

Response, %	2 Cycles RLI (n = 58)	2 Cycles RLI + 2 Cycles RLI With CT (n = 56)	End of Treatment (n = 49)	ITT Population (N = 60)
ORR	86	100	100	98.0
▪ CR	36	73	96	92.3
▪ PR	50	27	4	5.8
SD	7	--	--	--
MR	5	--	--	--
PD	2	--	--	1.9

Westin. ASCO 2019. Abstr 7508.

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Smart Start: Survival

Survival Category, Days	Patients (N = 60)
Median TTP[1]	Not reached (range: 32-938) 3 progression events
Median OS[1]	Not reached (range: 74-938)

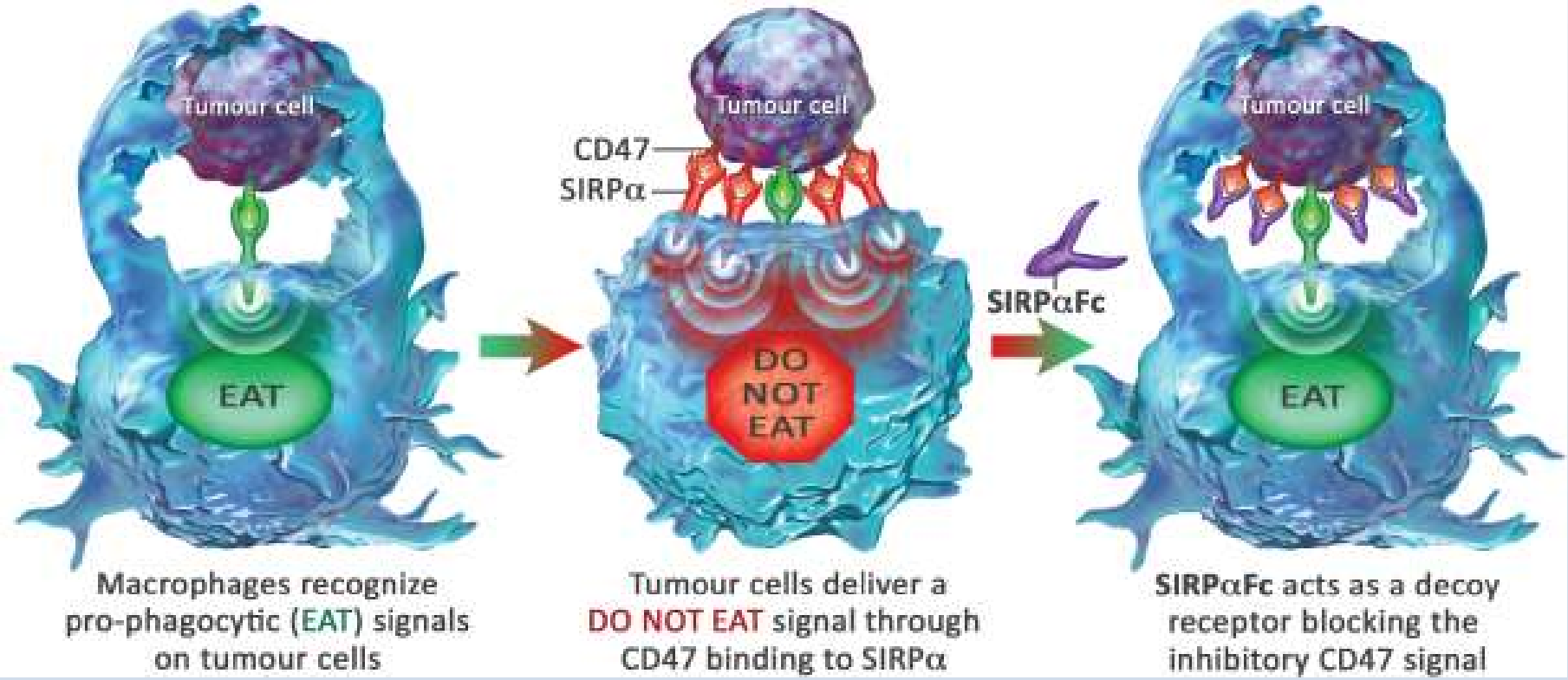
- TTP with RLI prolonged compared with historical results for R-CHOP ± ibrutinib[2] and R-CHOP + lenalidomide[3] (*not statistical comparisons)*
- PFS of 94% at 1 yr for patients with double-expressor DLBCL (n = 19) prolonged compared with historical results for DA-EPOCH-R,[4] R/G-CHOP + venetoclax,[5] R-CHOP + bortezomib[6] (*not statistical comparisons)*

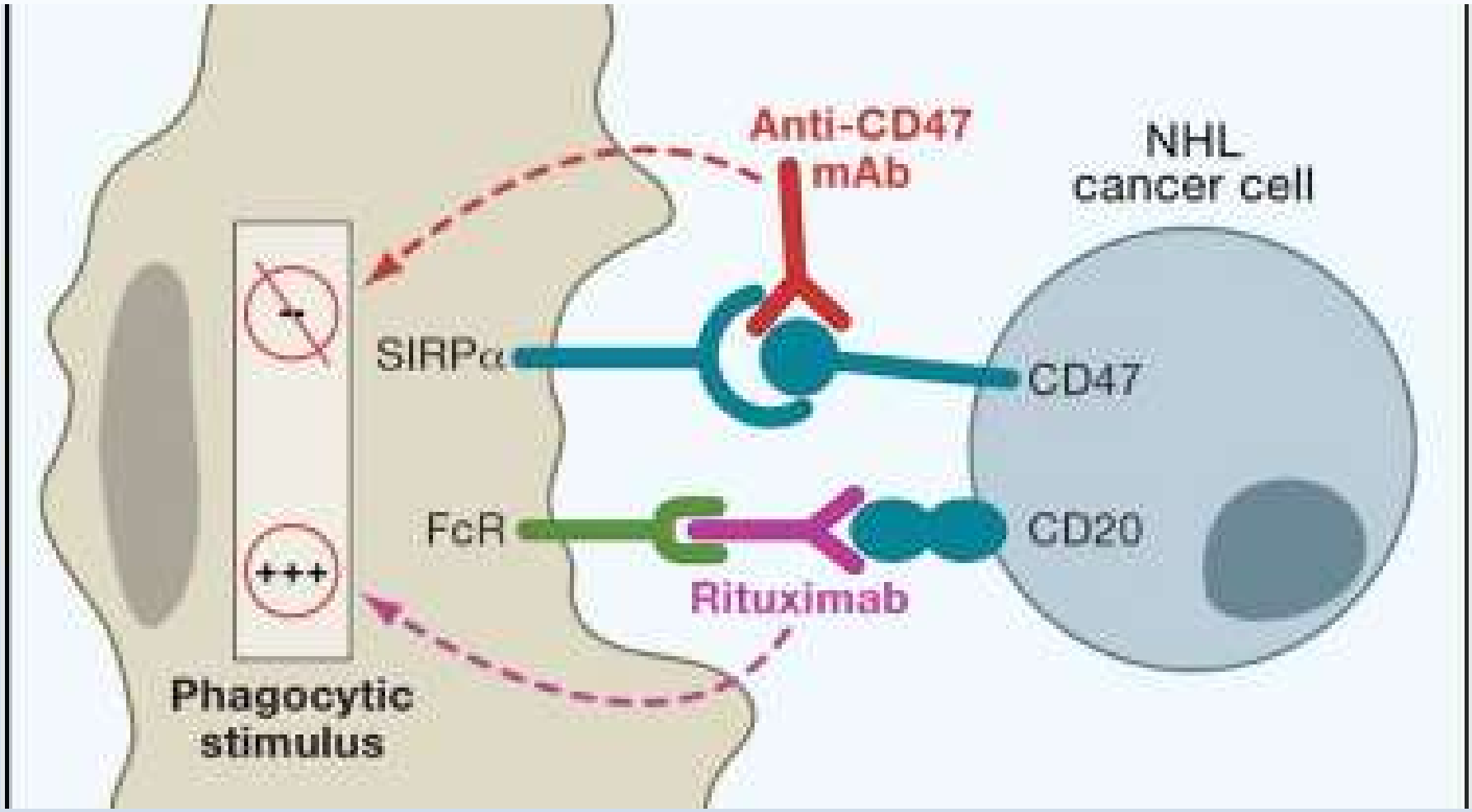
1. Westin. ASCO 2019. Abstr 7508. 2. Nowakowski. JCO. 2014;33:251. 3. Younes. JCO. 2019;37:1285.
4. Bartlett. JCO. 2019;[Epub]. 5. Morschhauser. ASH 2018. Abstr 782. Davies. Lancet Oncol. 2019;20:649.

Smart Start: Conclusions

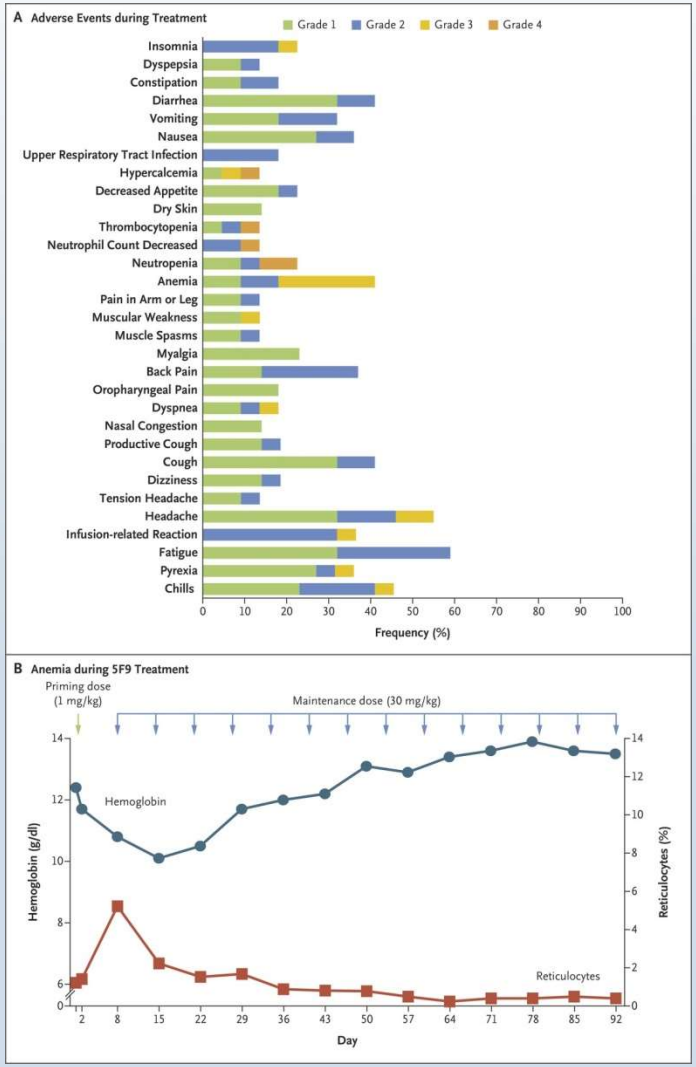
- In patients with non-GCB DLBCL, the use of RLI followed by RLI + chemotherapy produced high response rates and prolonged survival times, which compare favorably with historical results
  - RLI before chemotherapy: 86%
  - RLI + chemotherapy: 96%
  - 1-yr PFS/OS: 96%
- Investigators suggest value in pursuing additional studies of combinations of novel agents, with or without chemotherapy, in DLBCL

CD47: Don't Eat Me!




Anti-CD47
mAb
NHL
cancer cell
SIRPα
CD47
FcR
CD20
Rituximab
Phagocytic
stimulus

Adverse Events Due to Hu5F9-G4 (5F9), Rituximab, or Both and On-Target Anemia Effect of 5F9.



Advani R et al. N Engl J Med 2018;379:1711-1721

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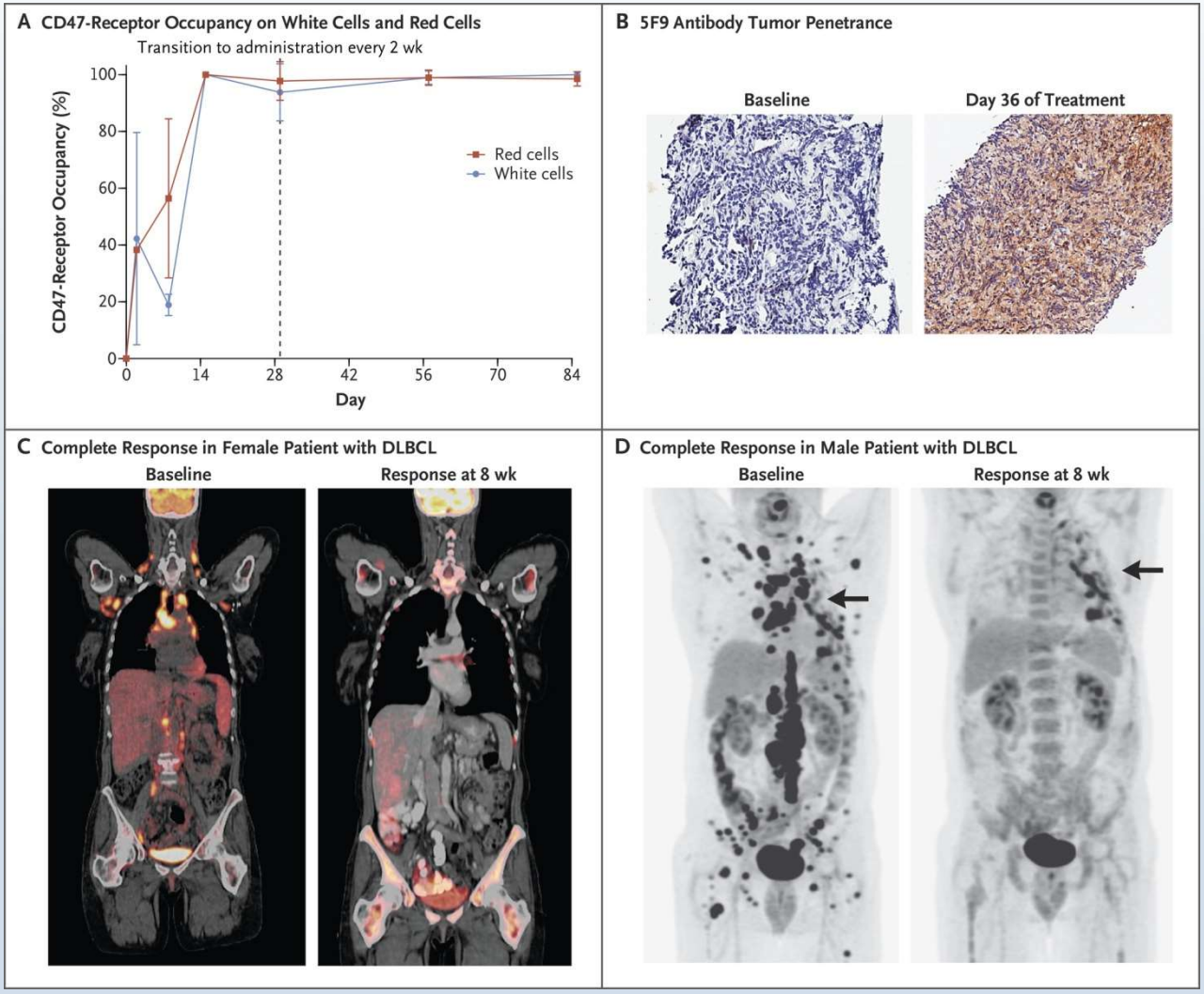
Pharmacodynamic Data on CD47-Receptor Occupancy, Tumor Penetrance, and Responses in Two Patients.



Advani R et al. N Engl J Med 2018;379:1711-1721

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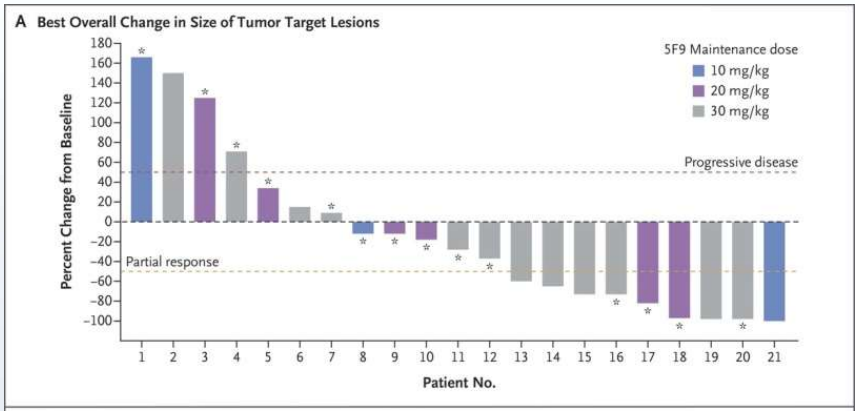
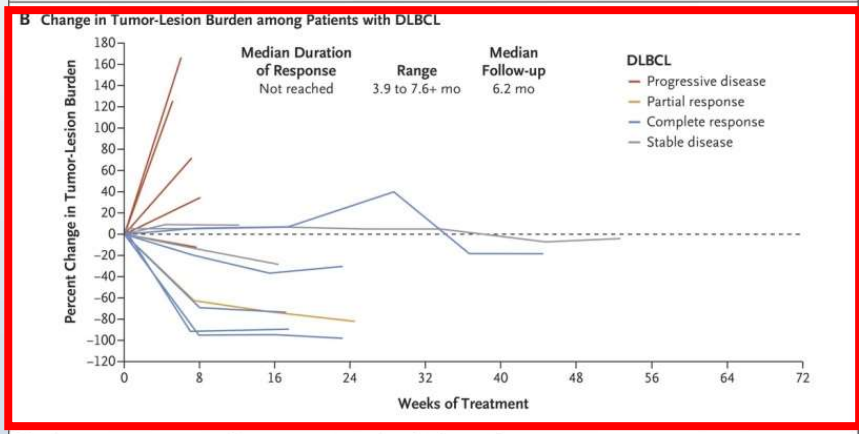
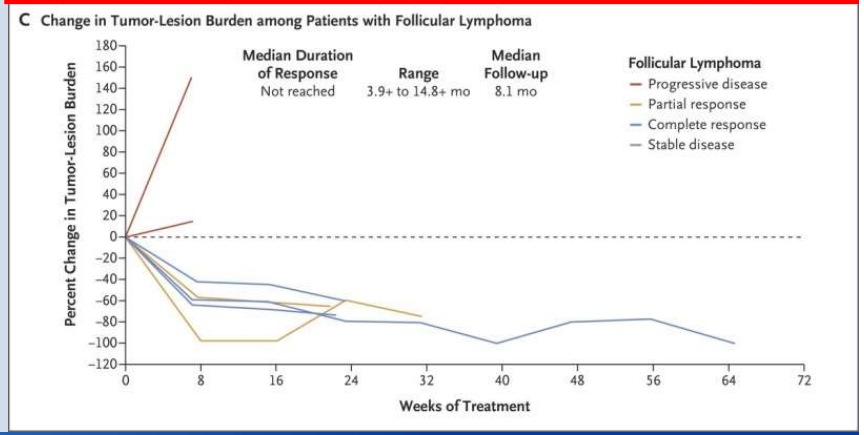
Change in Tumor-Lesion Size and Duration of Responses with 5F9 and Rituximab.







Advani R et al. N Engl J Med 2018;379:1711-1721

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Clinical Responses to Combination Therapy with 5F9 and Rituximab.

Table 2. Clinical Responses to Combination Therapy with 5F9 and Rituximab.*

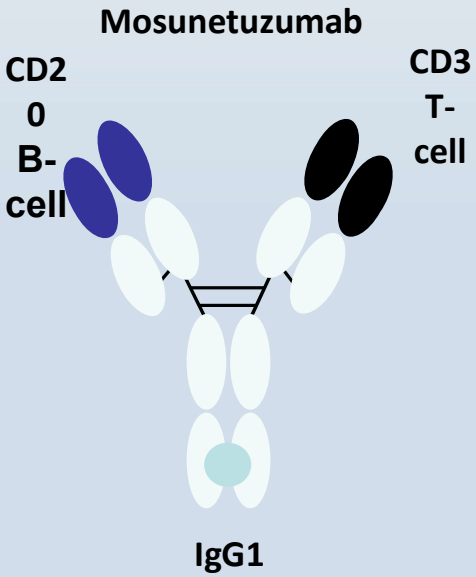
Response	All Patients (N=22)	Patients with DLBCL (N=15)	Patients with Follicular Lymphoma (N=7)
Objective response	11 (50)	6 (40)	5 (71)
Complete response	8 (36)	5 (33)	3 (43)
Partial response	3 (14)	1 (7)	2 (29)
Stable disease	3 (14)	3 (20)	0
Progressive disease	8 (36)	6 (40)	2 (29)
Disease control	14 (64)	9 (60)	5 (71)

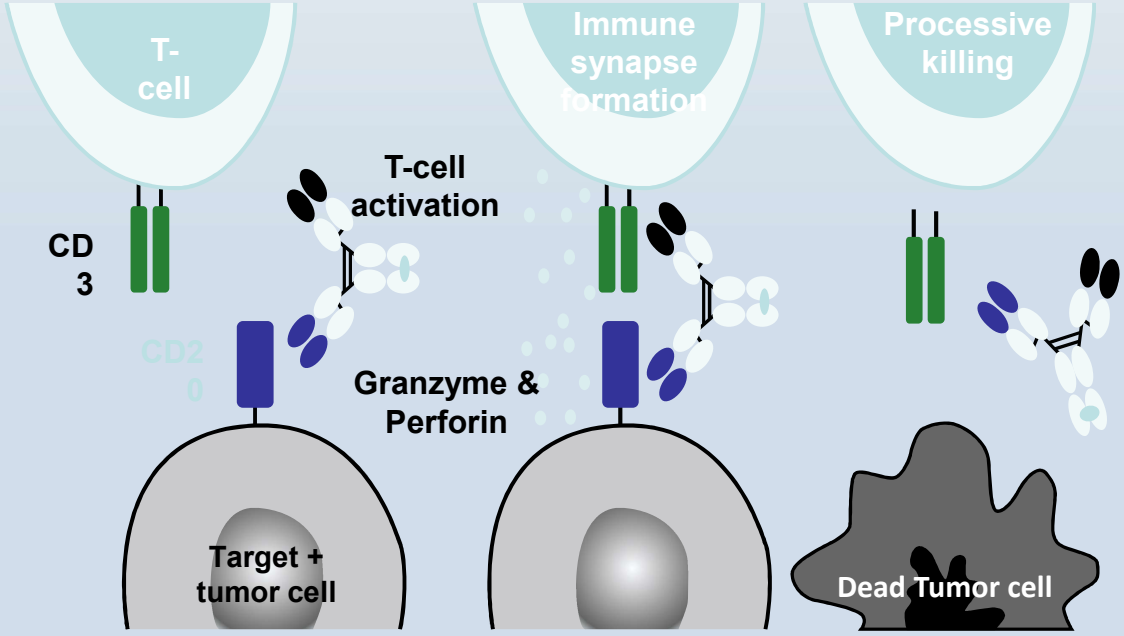
* Objective response was defined as a complete or partial response. Disease control was defined as a complete response, partial response, or stable disease.

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

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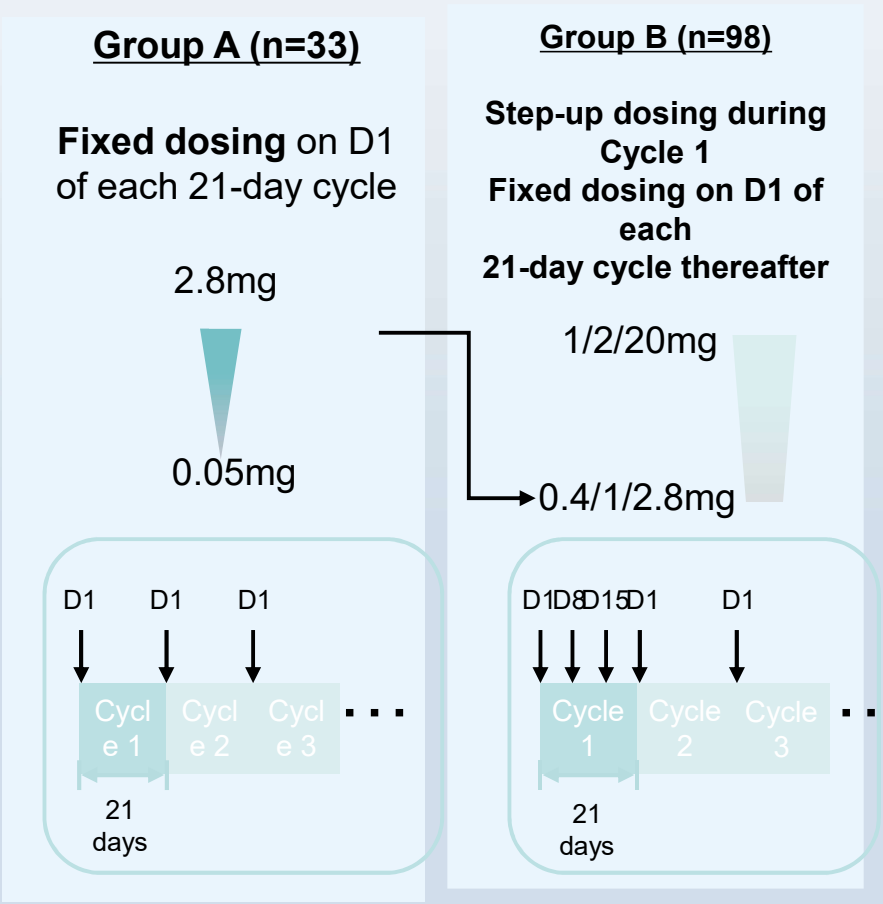
GO29781: study design

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



- **Patient population:**
  - dose escalation: R/R NHL
  - dose expansion: R/R FL, MCL, DLBCL/trFL
- **Administration:**
  - intravenous, administered in out-patient setting except with first maximal dose in dose escalation
  - initial treatment: eight cycles, up to 17 cycles allowed
- **Primary outcome measures:**
  - MTD
  - tolerability
  - pharmacokinetics
  - best objective response, as per revised International Working Group response criteria (Cheson BD, et al. 2007)

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

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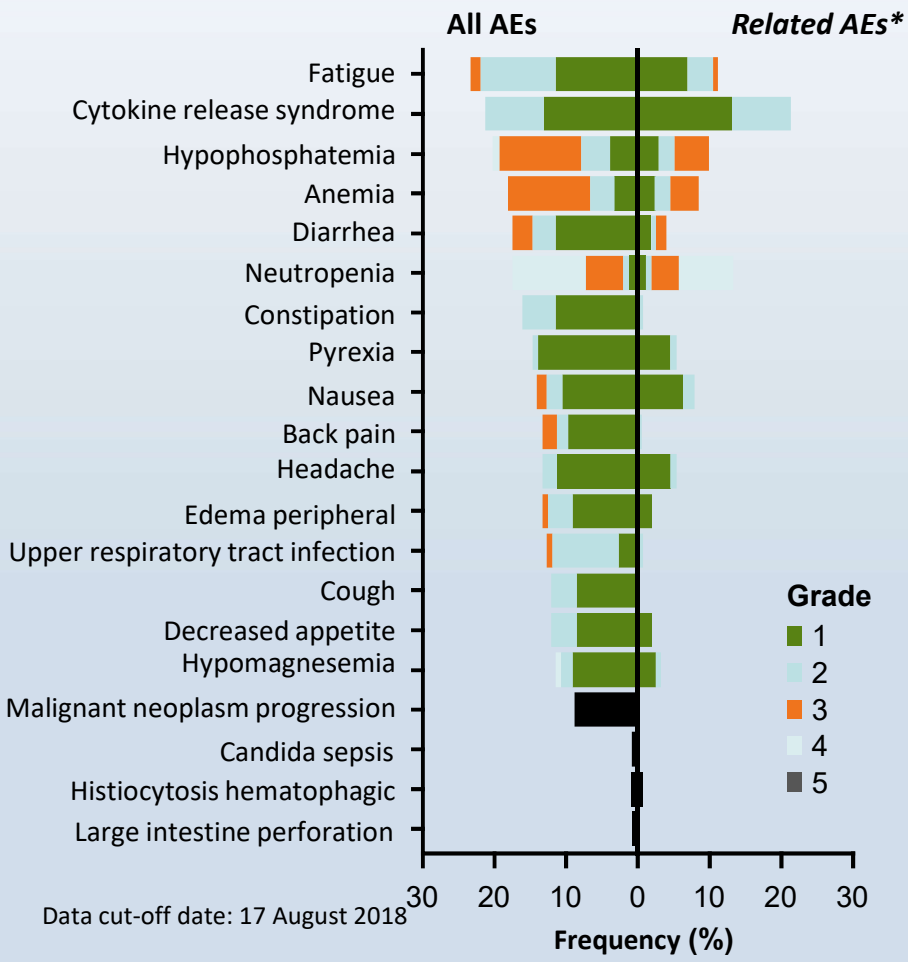
Treatment-emergent AEs

Group A and B; N=131; maximum single dose: 20 mg

AEs with ≥10% incidence or Grade 5 AE



Data cut-off date: 17 August 2018

* Related AEs per investigator assessment

- Majority of AEs were grade 1 or 2
- Most treatment-related AEs were transient and reversible
  - 19% of events resolved within 24h; median duration 4 days (range 1–144 days)
- Median time to onset for all AEs: 18 days (i.e. during cycle 1)
- No evidence of cumulative or chronic toxicity

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AEs of special interest

n, (%)	All safety-evaluable (N=131)	Description
CRS (Lee criteria[1])	30 (22.9%)	• Majority during cycle 1; median duration 2 days (range 0–19) • Two patients treated with tocilizumab • 40/41 (98%) events resolved
Grade 1–2	30 (22.9%)	
Grade ≥3	0	
Neurologic AEs[†]	64 (48.9%)	• Most common: headache (15.3%), dizziness (9.9%), insomnia (9.2%) • Grade 3: seizure (HLH); confusion and hepatic encephalopathy; post-herpetic neuralgia (n=1 each)
Grade 1–2	61 (46.6%)	
Grade ≥3	3 (2.3%)	
Treatment-related (any grade)[‡]	27 (20.6%)	
Treatment-related (Grade ≥3)[‡]	1 (0.8%)	
Neutropenia[*]	25 (19.1%)	• Responsive to G-CSF; 37/41 (90%) events resolved • No concurrent Grade ≥3 infections reported
Grade 1–2	3 (2.3%)	
Grade ≥3	22 (16.8%)	
Febrile neutropenia	4 (3.1%)	

[*]Includes AE terms 'neutropenia' and 'neutrophil count decreased'. Febrile neutropenia events were deemed unrelated to mosunetuzumab by investigator; [†]defined as all AEs occurring in either the SOC nervous system disorders or SOC psychiatric disorders. [‡]per investigator assessment; Data cut-off date: 17 August 2018

Lee DW, et al. Blood. 2014;124:188-195

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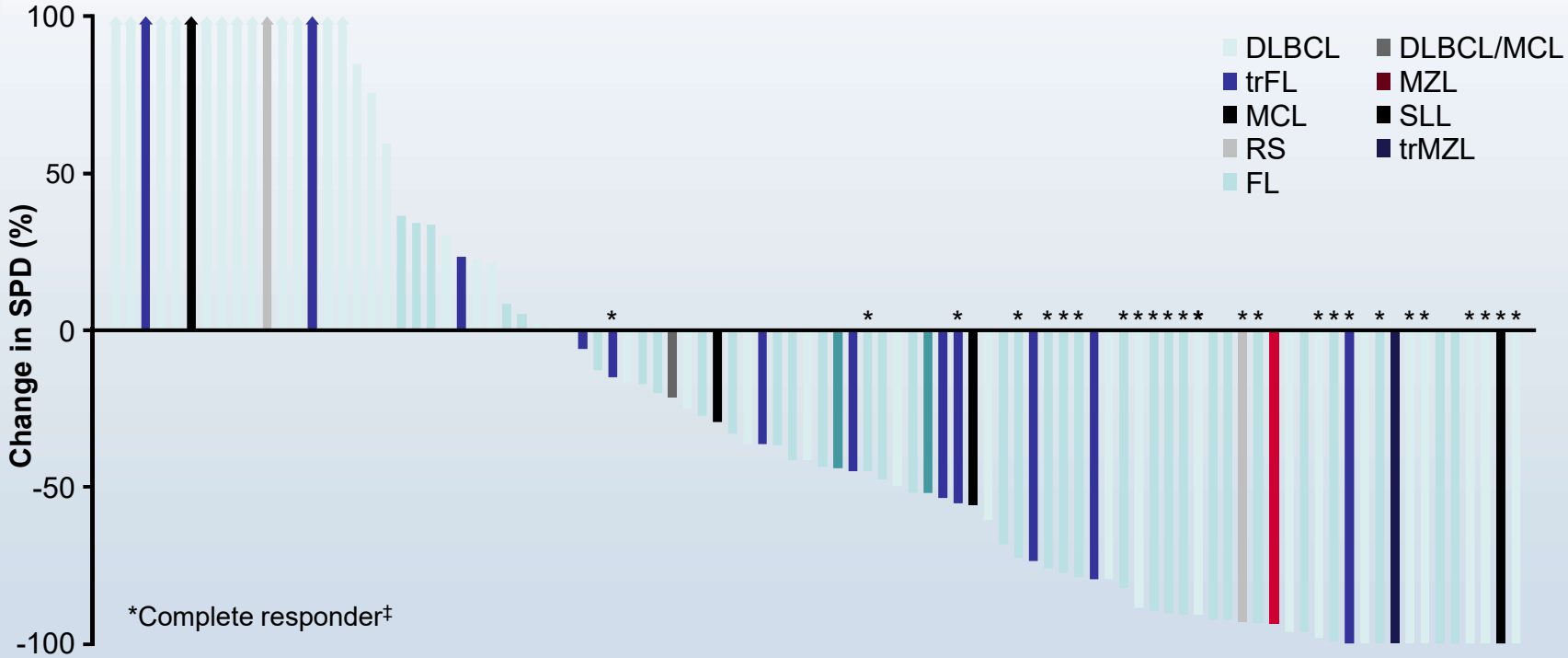
Mosunetuzumab exhibits anti-tumor activity in multiple histologies

Group A+B patients treated at ≥ 1.2 mg dose (primary response population)†



First responses observed in Group A at doses ≥1.2 mg

Complete responses observed in DLBCL, trFL, FL, RS, MCL, MZL

- Data cut-off date: 17 August 2018.
  †Patients who have response data available at any time; ‡CR, assessed by the investigator with or without PET, marked for efficacy-evaluable patients (when SPD data available).
- CR, complete response; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; RS, Richter transformation; SLL, small lymphocytic lymphoma; SPD, sum of the product diameters; tr, transformed

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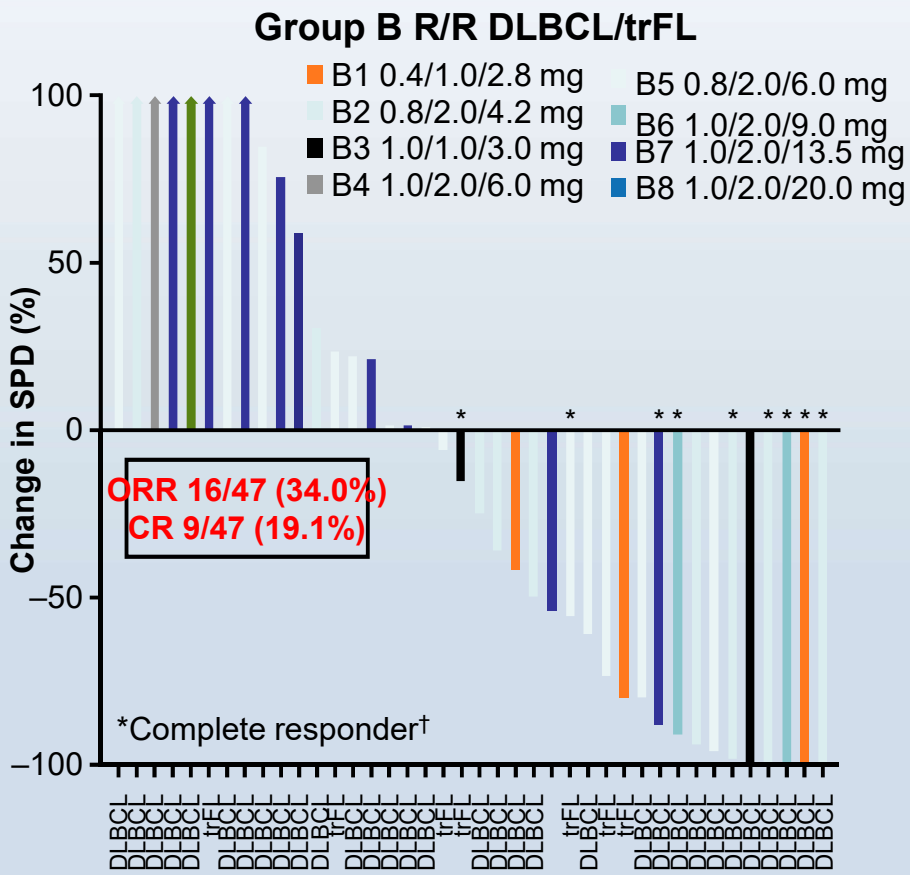
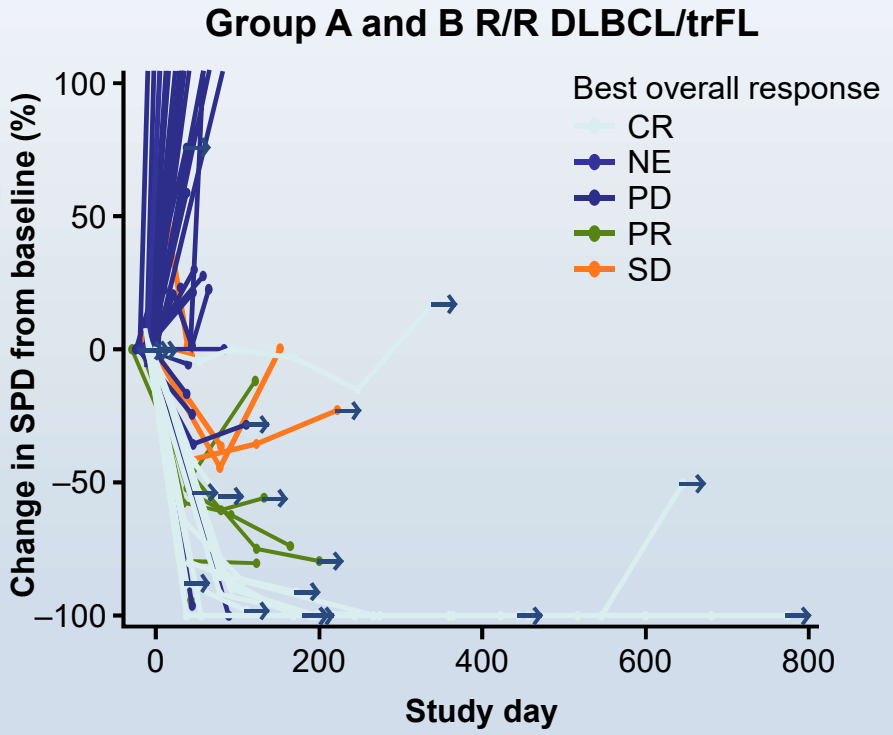
Efficacy of mosunetuzumab in R/R DLBCL/trFL

Early evidence of durable CR; re-treatment following relapse re-induced CR





- Median duration of CR: not reached
- Median duration of follow-up for CR: 298 days (range 46–816 days)

- CR, assessed by the investigator with or without positron emission tomography, marked for efficacy-evaluable patients (when SPD data available). tr, transformed

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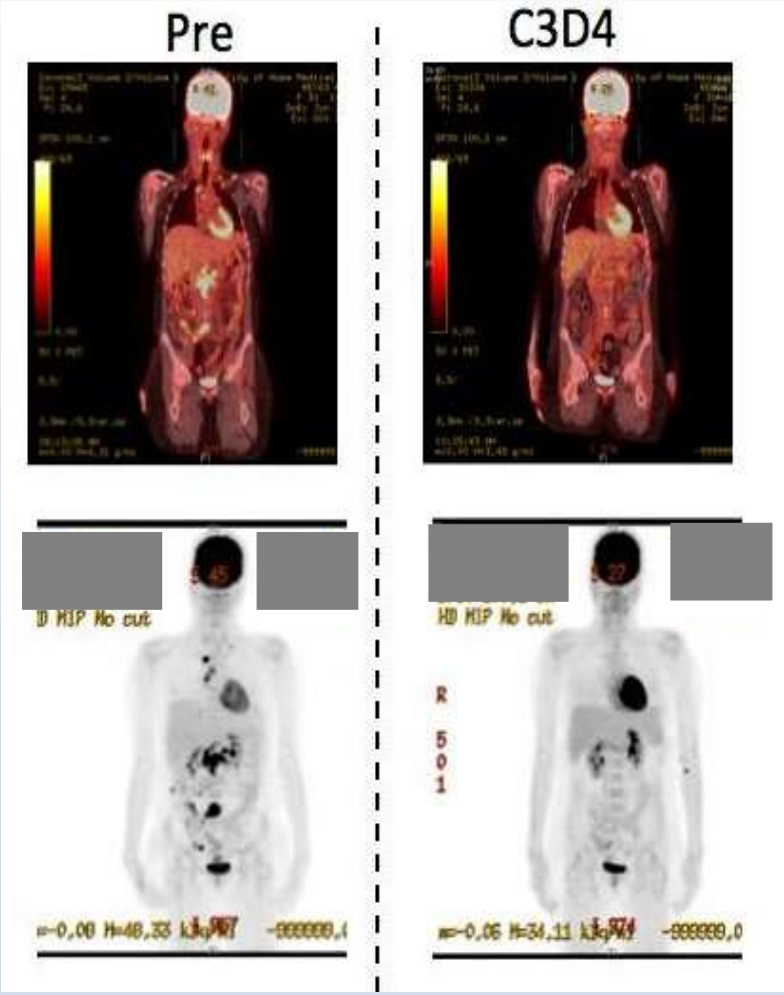
CR in a CAR-T-refractory patient with DLBCL



- Prior therapies included R-CHOP and R-ICE
- Patient subsequently received CD19 CAR-T in combination with PD-L1 blockade
  - CR achieved; disease relapsed within 4 months
  - Severe neurologic toxicity occurred (seizure)
- Mosunetuzumab administered as single-agent therapy (0.8/2.0/4.2 mg)
  - CR achieved after 3 cycles
  - No CRS or neurologic AEs except Gr 1 headache
  - Allogeneic stem cell transplant pursued after 4 cycles of mosunetuzumab
  - No evidence of disease relapse after 1 year in remission

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Conclusions

- Mosunetuzumab induces durable CR in late-line R/R indolent and aggressive NHL
  - Pharmacodynamic activation of peripheral T-cells confirms MOA
  - Clinical activity observed with intermittent (q3W) dosing and limited treatment duration
- Favorable safety profile
  - Cycle 1 step-up dosing appears to mitigate toxicity
  - MTD not reached
  - Most AEs during cycle 1; mild, transient and reversible; no evidence of cumulative or chronic toxicity
  - Low rate of treatment discontinuation due to AEs
  - No Grade 3 CRS
  - Low frequency (0.8%) of Grade 3 neurotoxicity related to mosunetuzumab
- Single-agent dose and schedule continues to be optimized
- Combinations with chemotherapy, atezolizumab, and polatuzumab vedotin under investigation