Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Bispecific Antibodies in Lymphoma

Tycel Jovelle Phillips
Associate Professor University of Michigan
Rogel Cancer Center
Ann Arbor, MI 48130

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Disclosures

- Research Funding:
  - Genentech
  - Abbvie
  - Bayer
  - BMS
  - Incyte
- Advisory Board: Abbvie, Genentech, Kite, ADC Therapeutics, Bayer, Incyte, Eli Lilly, Beigene, Astra Zeneca, BMS
- I will be discussing non-FDA approved indications during my presentation.

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Outline

- Outcomes in relapsed/refractory (R/R) lymphoma
- Initial “off the shelf” Bispecific T-cell engager
  - Blinatumomab
- CD20/CD3 agents
  - Mosunetuzumab
  - Glofitamab
  - Epcoritamab
  - Odronextamab
  - Plamotamab
- Future directions

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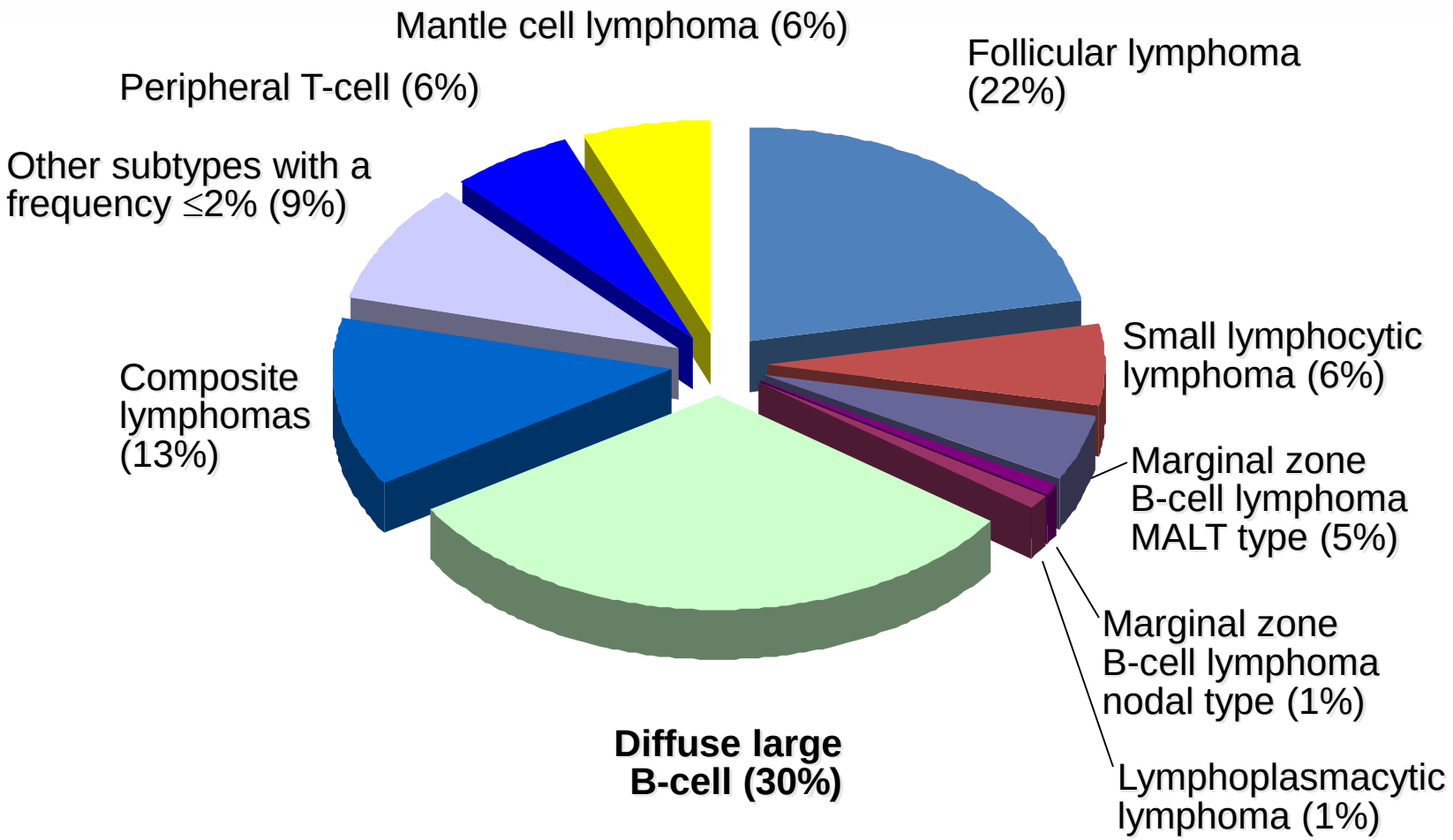
Frequency of NHL Subtypes in Adults



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Background

- Outcomes variable amongst different subtypes but overall trend is progressively worse with more lines of therapy irrespective of subtype.
- Treatment have historically been dominated by multi-agent cytotoxic chemotherapy but despite utilizing agents with different mechanisms of action (MOA); for the most part all agents induce response by inhibiting DNA replication.
  - As such induces chemotherapy resistance.

[1]Ruan et al. abstract 704 ASH 2020

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Background

- Diffuse Large B-Cell Lymphoma (DLBCL) is the most common lymphoma accounting for over 30% of diagnosed cases of non-Hodgkin lymphoma (NHL).
  - Outcomes especially poor in those with primary refractory disease[1].
- Follicular lymphoma is the most common indolent lymphoma about 20% of diagnosed cases of NHL.
  - Poor outcomes in those who relapse within 24 months of primary immuno-chemotherapy[2].
- Similar patterns noted in other NHL subtypes[3, 4].

[1]Crump et al. *Blood* 2017 130 (16): 1800–1808.
[2]Casulo et al. J Clin Oncol. 2016 April 20; 34(12): 1430.
[3]Luminari et al. Blood 2019 Sep 5;134(10):798-801.
[4]Bond et al. *Blood* 2019 134 (Supplement_1): 753.

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- Recent research has focused on agents which have different MOA compared to chemotherapy.
  - Given data has demonstrated that allogeneic T-cells can cure lymphoma including those typically deemed incurable research has focused on safer alternatives that won't induce deadly complications of this treatment such as Graft vs. Host disease, veno-occlusive disorder, and infection.
  - This has included Chimeric Antigen Receptor T-Cell Therapy (CAR-T) and off the shelf products.

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Blinatumomab

- First “off the shelf” product utilized was blinatumomab.
  - This agent is a CD3/CD19 bispecific T-Cell engager.
  - Initial study evaluated patients with R/R NHL in an initial dose escalation followed by a phase 2 expansion
    - 76 patients enrolled (42 phase I and 35 were treated at phase II dose (60 ug/m^2/day).
    - Patients had a median of 3 prior lines of therapy

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Neuro-Toxicity

Table 2. Blinatumomab Dose Levels and DLTs (Dose Escalation Phase)

Dose Level	Highest Intended Dose ($\mu g/m^2$/day)	Patients (No.)	Patients With DLTs (No.)	Nature of DLT
1	0.5	3	0	
2	1.5	3 + 3	0	
3	5	3	0	
4	15*	7 + 6	1	Mental disorder due to general medical condition (grade 2)†
5	30‡	6	1	Metabolic acidosis due to grand mal seizure (grade 4)
6	60	4 + 3	0	
7	90	4	3	Encephalopathy (grade 3; n = 2); seizure and aphasia (grade 3; n = 1)

NOTE. Total number of patients was 42. Total number of patients with DLT was 5.
Abbreviation: DLT, dose-limiting toxicity.
*The first seven patients received an initial dose of 5 $\mu g/m^2$/day followed by intraindividual escalation to 15 $\mu g/m^2$/day. Three of the six patients were treated after a ramp-up dose escalation to the target dose within 24 hours followed by constant target dose administration. The remaining three patients received 15 $\mu g/m^2$/day constant dosing. Before protocol amendment to allow enrollment of patients with diffuse large B-cell lymphoma, one patient with follicular non-Hodgkin lymphoma that later transformed to diffuse large B-cell lymphoma was enrolled in this dose group (protocol deviation).
†Before protocol amendment, neurologic events of any grade were considered DLTs.
‡Three patients were treated after a ramp-up dose escalation to the target dose within 24 hours followed by constant target dose administration. Over-recruitment was permitted per the data review committee for further evaluation of the adverse event profile.

- Most common DLT was neurologic complications (neuro tox).
- Study was amended during the escalation to evaluate different administration strategies to reduce incidence of neuro tox.
- Introduced “step up dosing” and steroid prophylaxis

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Efficacy

Table 5. Clinical Response

	Dose ($\mu g/m^2$/day)	No. of Patients	No. of Responses						
			CR	CRu	CR/CRu	PR	ORR CR + CRu + PR, n (%)	SD	PD
Response at highest actual dose received*	0.5, 1.5	9	0	0		0	0 (0)	4	5
	5	7†	0	0		0	0 (0)	4	2
	15	15†	1	0		2	3 (20)	7	4
	30	6†	1	0		0	1 (17)	2	2
	60	35†	8	5		11	24 (69)	5	5
	90	4†	1	0		1	2 (50)	1	0
Response at target dose*									
By histology									
FL	60	15			6	6	12 (80)		
MCL	60	7			3	2	5 (71)		
DLBCL‡	60§	11			4	2	6 (55)		
Other	60	2			0	1	1 (50)		
By early relapse status‖									
Early relapse	60	19			5	5	10 (53)		
No early relapse	60	16			8	6	14 (88)		

Abbreviations: CR, complete response; CRu, unconfirmed complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

*During the first treatment period only (not including consolidation treatment).

†One patient did not have a response assessment. Five patients had no response data available (MCL, n = 4; FL, n = 1) but were included in the statistical response analysis calculations.

‡Three patients with DLBCL did not receive the target dose (study termination before dose step to target dose, n = 2; one patient was treated in the 30 $\mu g/m^2$/day dose group).

§One patient received 30 $\mu g/m^2$/day.

‖Early relapse: end of last chemotherapy less than 12 months before blinatumomab treatment start. No early relapse: end of last chemotherapy 12 months or more before blinatumomab treatment start.

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Conclusion

- Blinatumomab demonstrated promising efficacy but did demonstrate issues with neuro-toxicity as well as potential mechanisms for overcoming this AE.
- Overall limited utilization in lymphoma related to burdensome mechanism of administration.
- Given its short serum half-life, blinatumomab is administered as a continuous intravenous infusion. With ramp up hospitalization is required at some centers until final dose if reach.
- Double step (5 mg/m^2/day, days 1 to 7; 15 mg/m^2/day, days 8 to 14; then 60 mg/m^2/day).

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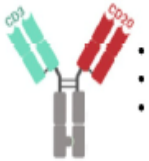
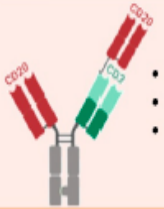
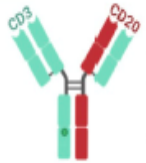
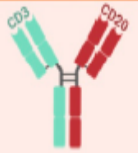
Conclusion continued

- Infused for 4 to 8 weeks followed by an additional 4-week consolidation treatment phase at the respective initial dose if patient with response.
- All in all this has helped with the development of agents with a longer half life

Bi-Specific Antibody	Targets	Design	Ig Fragment Formats	Ref.
blinatumomab	CD19 x CD3		• two murine scFv joined by a glycine-serine linker • monovalent CD19 and monovalent CD3 binding • cloned from anti-CD19 (clone HD37) and anti-CD3 (clone L2K-07) murine mAbs	1, 2, 3
mosunetuzumab	CD20 x CD3		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	4
glofitamab	$(CD20)_2$ x CD3		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	5
odronextamab	CD20 x CD3		• fully human IgG4-based heterodimeric antibody • monovalent CD20 and monovalent CD3ε binding • Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding • common κ light chain from anti-CD3ε mAb	6
epcoritamab	CD20 x CD3		• humanized mouse IgG1-based heterodimeric antibody • monovalent CD20 and monovalent CD3 binding • IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield	7

Ig, immunoglobulin; scFv, single-chain variable fragment; mAb, monoclonal antibody; Fc, fragment crystallizable; FcγR, Fc gamma receptor

[1]Dufner V, *et al.* Blood Adv (2019) 3:2491; [2]Goebeler ME, *et al.* J Clin Oncol (2016) 34:1104; [3]Viardot *et al.* Blood (2016) 127(11):1410; [4]Schuster SJ, *et al.* ASH 2019, Plenary Abstract 6; [5]Hutchings M, *et al.* ASH 2020, Abstract 403; [6]Bannerji R, *et al.* ASH 2020, Abstract 400; [7]Hutchings M, *et al.* ASH 2020, Abstract 406

Table from Schuster Hematological Oncology. 2021;39(S1):113– 116

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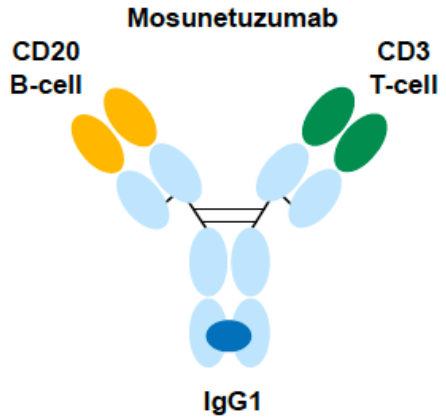
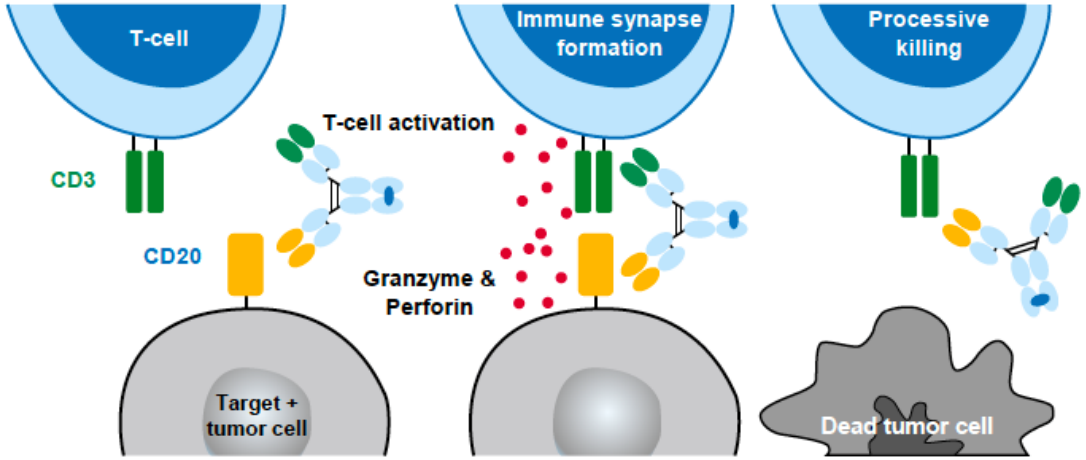
Mosunetuzumab

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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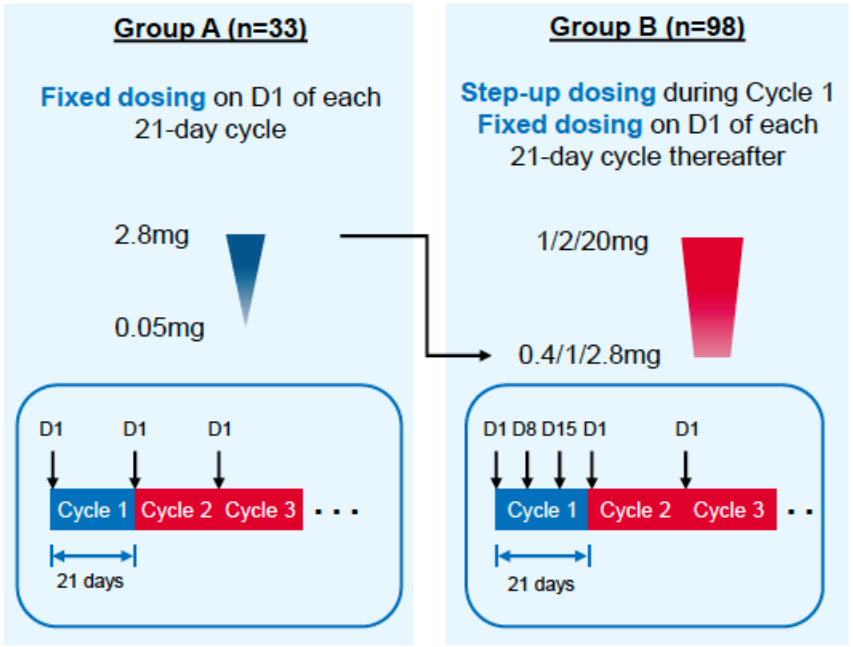
Step Up Dosing

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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AE summary

Step-up dosing during Cycle 1 enabled continued dose escalation with no worsening of toxicity profile

Patients, n (%)	Group A (n=33) [Max dose: 2.8 mg, Range: 0.05–2.8 mg]	Group B (n=98) [Max dose: 20.0 mg, Range: 0.4–20.0 mg]	All patients (n=131) [Max dose: 20.0 mg; Range: 0.05–20.0 mg]
Any AE	32 (97.0%)	92 (93.9%)	124 (94.7%)
Treatment-related AE*	24 (72.7%)	58 (59.2%)	82 (62.6%)
Grade ≥3 AE†	16 (48.5%)	56 (57.1%)	72 (55.0%)
Grade ≥3 treatment-related AE	7 (21.2%)	27 (27.6%)	34 (26.0%)
Neutropenia^	2 (6.1%)	13 (13.3%)	15 (11.5%)
Hypophosphatemia	2 (6.1%)	5 (5.1%)	7 (5.3%)
Anemia	1 (3.0%)	3 (3.1%)	4 (3.1%)
Serious AE, excluding lymphoma progression‡	7 (21.2%)	26 (26.5%)	33 (25.2%)
AE leading to withdrawal from treatment	1 (3.0%)	3 (3.1%)	4 (3.1%)
Grade 5 AE, excluding lymphoma progression‡	1 (3.0%)	2 (2.0%)	3 (2.3%)‡

Data cut-off date: 17 August 2018. No MTD established for either Group A or B.
*Relationship between each AE and study treatment determined by investigator assessment; †Occurring in ≥10% of patients in any group;
^Includes AE terms 'neutropenia' and 'neutrophil count decreased'; ‡Deaths due to macrophage activation syndrome/HLH (n=1), Candida sepsis (n=1), and disease-related large intestine perforation (n=1). 9 deaths occurred within 90 days of last mosunetuzumab administration due to malignant disease progression.

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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

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

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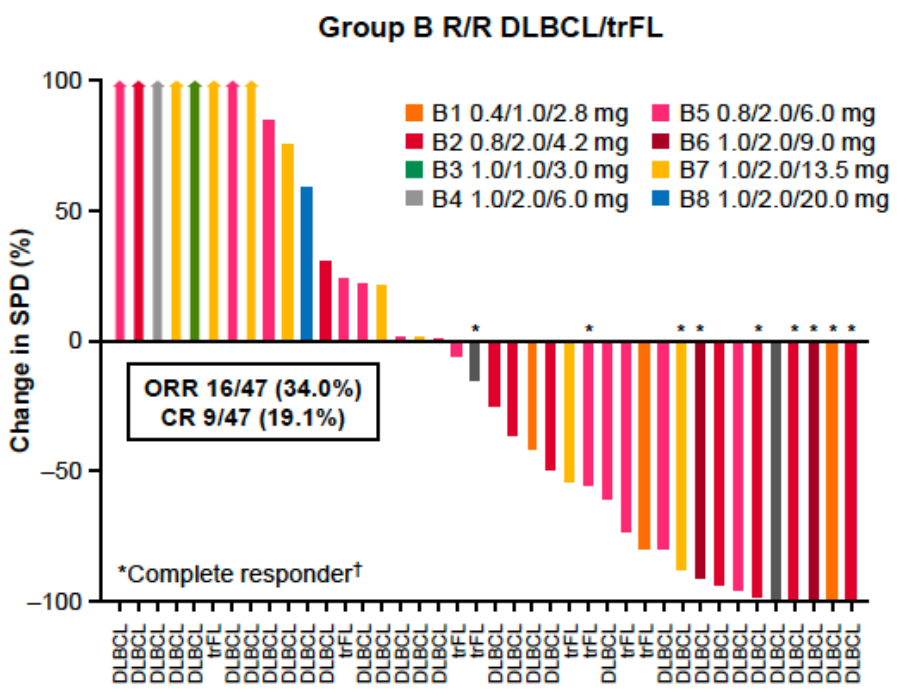
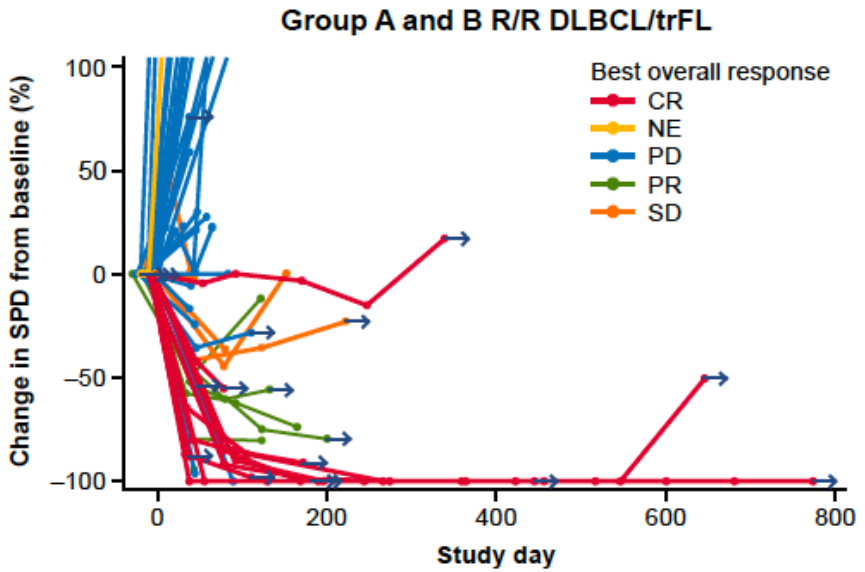
Efficacy of mosunetuzumab in R/R DLBCL/trFL

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)

Data cut-off date: 17 August 2018

†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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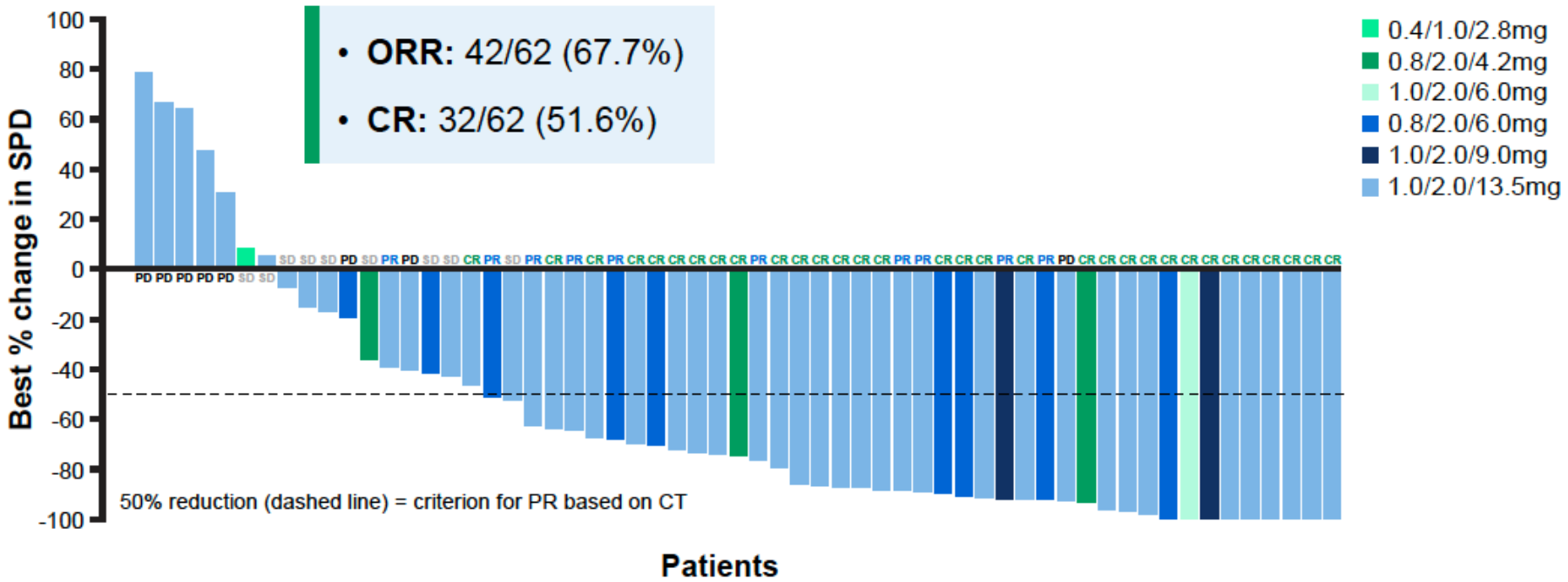
Mosunetuzumab antitumor activity in patients with R/R FL across dose levels



Assessment of higher dose levels is ongoing

SPD, sum of product diameter

1. Cheson BD, et al. J Clin Oncol 2007; 25(5):579–86.

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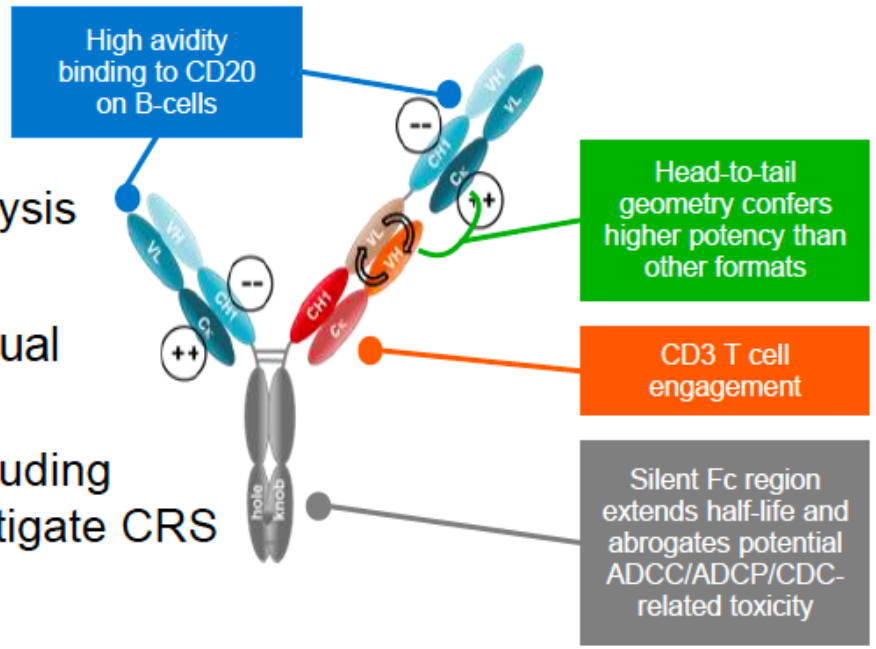
Glofitamab

Background

- Patients with R/R B-cell NHL need better treatment options with less toxicity
- CD20-TCB (RG6026; RO7082859)
  - Humanized bispecific mAb targeting CD20 and CD3
  - Induces rapid T cell activation, proliferation and cytokine release, leading to target cell lysis
  - 2:1 (CD20:CD3) format offers
    - Undiminished activity in presence of residual aCD20 from previous lines of therapy
    - Ability to combine with other aCD20s, including obinutuzumab pre-treatment to control/mitigate CRS



ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; CRS, cytokine release syndrome; TCB, T cell bispecific

Bacac et al. Clin Canc Res 2018

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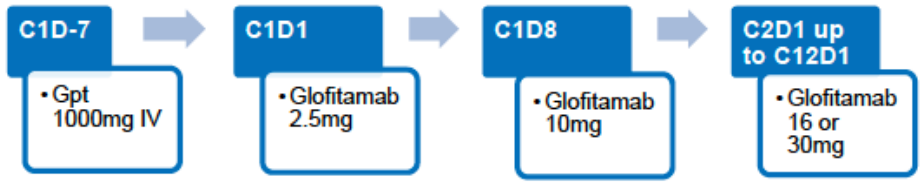
Dosing

NP30179 (NCT03075696): an ongoing Phase I dose-escalation and expansion study in R/R NHL

Treatment schedule

- 1000mg Gpt 7 days prior to glofitamab administration
- Glofitamab IV step-up doses on C1D1 and D8 and at target dose from C2D1 (2.5/10/16mg or 2.5/10/30mg)
- Cycle 1 was 14-days long; glofitamab was given Q3W thereafter for up to 12 cycles



Clinical cut-off date: August 03, 2020

MTD, minimum tolerated dose; OBD, optimal biological dose; RP2D, recommended Phase II dose.

Key inclusion criteria

- Age ≥18 years
- CD20+ B-cell R/R NHL
- ≥1 prior therapy
- ≥1 measurable lesion
- Adequate haematological and liver function
- ECOG PS ≤1

Primary objectives

- Evaluate safety, tolerability, PK, and anti-tumor efficacy (Lugano criteria)[1]
- Determine MTD/OBD and RP2D

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

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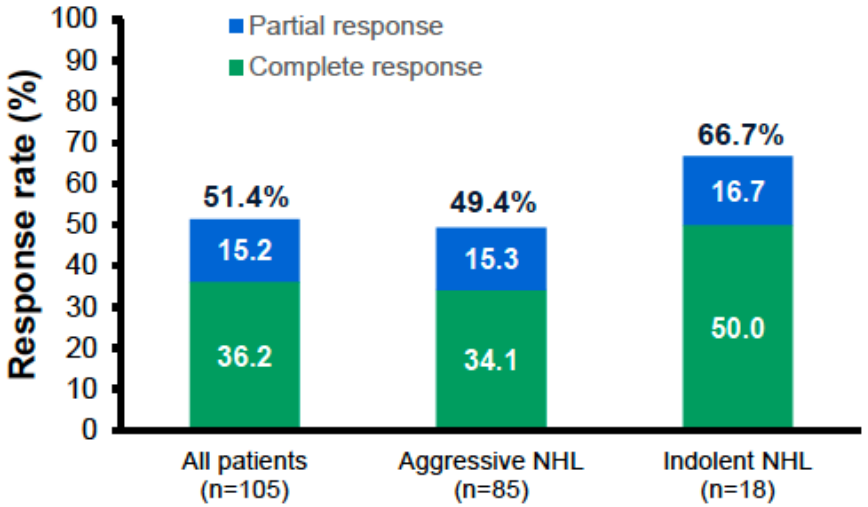
Efficacy

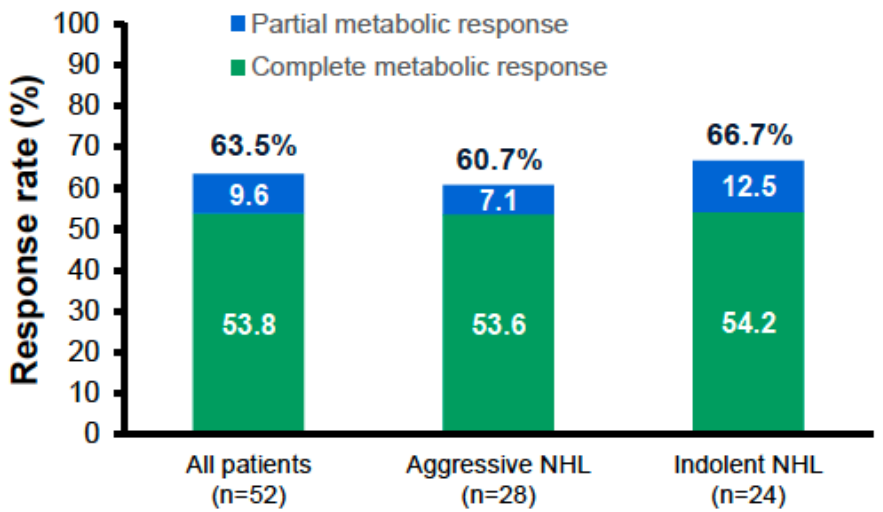
High response to glofitamab was maintained with step-up dosing

- Complete response was usually achieved early, at first or second response assessment (C3 or C6*)

Glofitamab ≥10mg fixed dosing (10, 16, 25, 10/16mg)[1]



Glofitamab step-up dosing 2.5/10/16mg or 2.5/10/30mg



*Cycle 3: ~44 days after obinutuzumab pretreatment, Cycle 6: ~107 days after obinutuzumab pretreatment.
Efficacy population includes all patients who have been on study long enough to have their first mandatory response assessment (Lugano criteria). Patients with missing or no response assessment are included as non-responders. Two aNHL and six iNHL patients did not have a response assessment reported at time of CCOD.

1. Dickinson M, et al. 25th EHA Congress, June 11–14, 2020 (Presentation S241).

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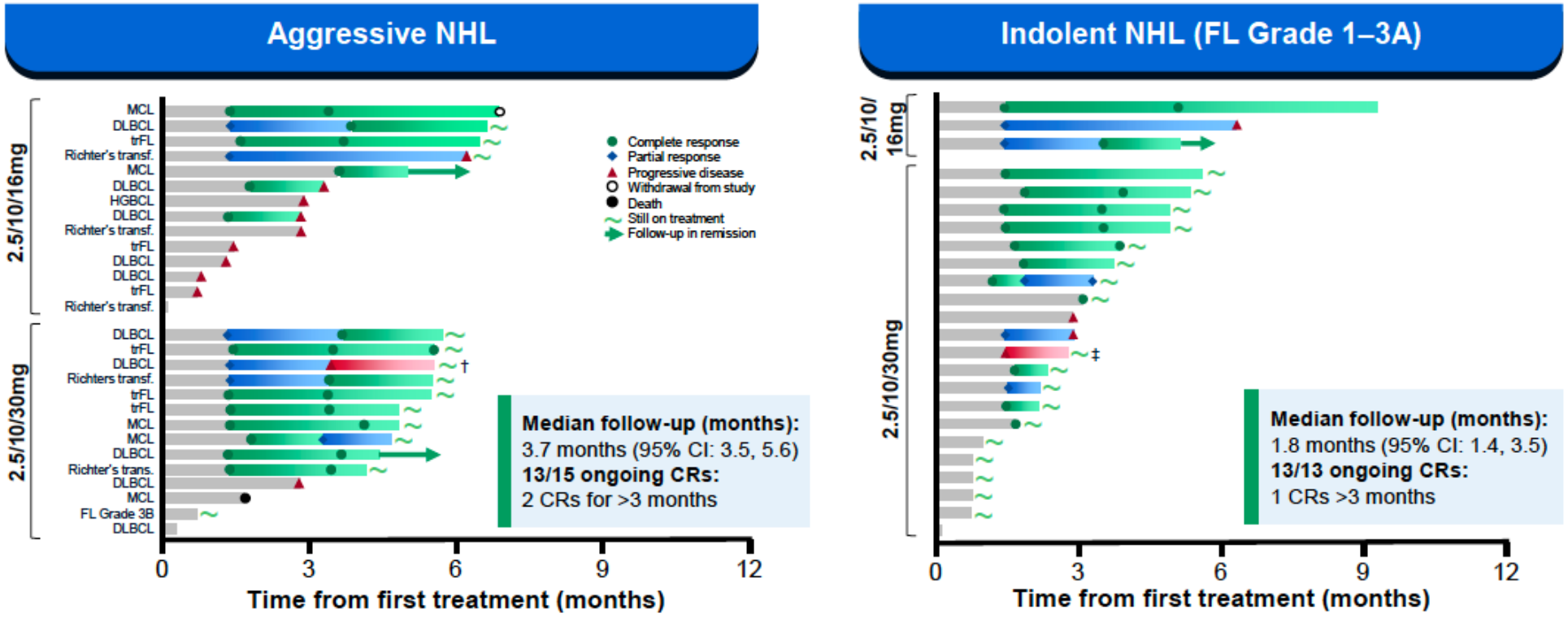
Time on initial treatment and response*

- Most patients have ongoing responses



*Efficacy population includes all patients who have been on study long enough for the first mandatory response assessment. Two aNHL and six iNHL patients did not have a response assessment reported at time of CCOD.
†Patient had paradoxical response with PD in one lesion. ‡Patient had paradoxical response, biopsy confirmed HL.

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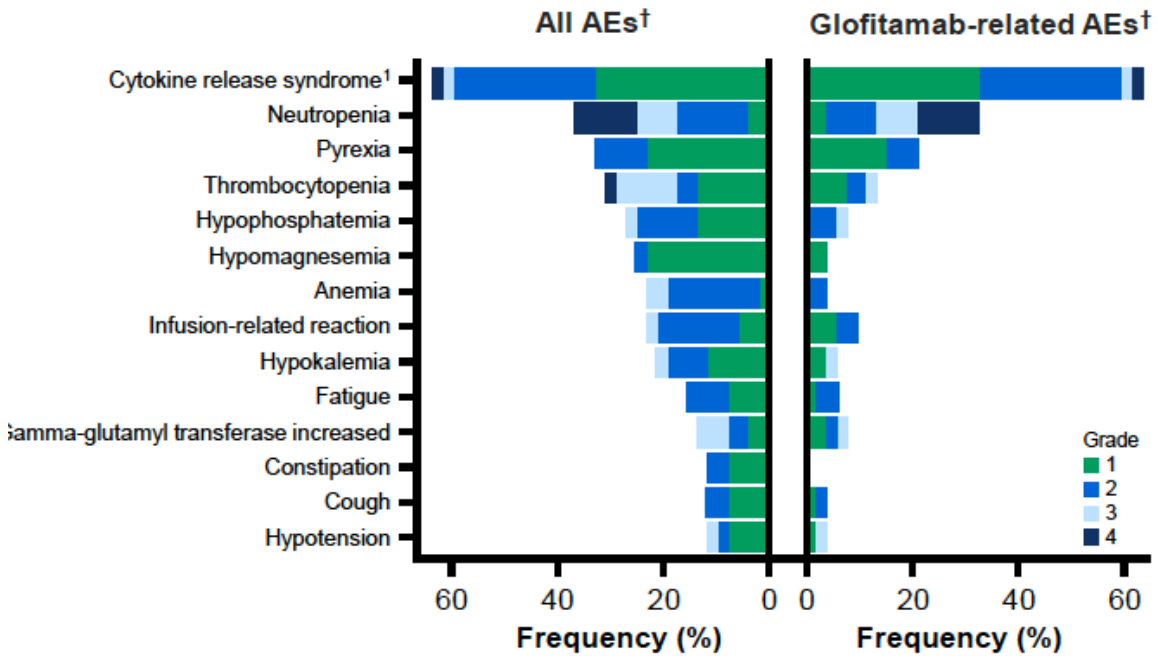
Adverse events* observed with step-up dosing



n (%)	All patients (N=52)
Any AE	51(98.1)
Treatment related	46 (88.5)
Serious AE	31 (59.6)
Treatment related	28 (53.8)
Grade 3–4 AE	29 (55.8)
Treatment related	18 (34.6)
Grade 5 (fatal) AE	0
AE leading to treatment discontinuation‡	2 (3.8)
Treatment related	2 (3.8)

*Investigator-reported AEs coded using MEDRA v22.1.†Grade 1–4 AEs with an incidence of ≥10% or a NCI-CTCAE grade of 5.
‡Includes neutropenia in 1 patient (Grade 4), and colitis (Grade 4) and sepsis (Grade 3) in 1 patient.

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

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Adverse events of special interest with step-up dosing

Adverse event, n (%)	All patients (N=52)	Comments
Cytokine release syndrome (CRS)[1]		• CRS events were confined to C1 and C2. Median time to CRS from the first glofitamab dose was 14.23 hrs with median duration of 28.7 hrs
All grade	33 (63.5)	
Grade 1	17 (32.7)	
Grade 2	14 (26.9)	• One patient with FL experienced a grade 3 CRS after 2.5mg dose (achieved CR; on treatment) and one patient with MCL experienced grade 4 CRS after the 30mg dose (experienced PD)
Grade 3	1 (1.9)	
Grade 4	1 (1.9)	• Tocilizumab was used to manage CRS in 8 (15.4%) patients
		• Three patients were admitted to ICU, eight patients received low-flow oxygen, three patients received single vasopressors and one patient required mechanical ventilation
Neutropenia*		• Neutropenia lead to treatment discontinuation in one patient
All grade	20 (38.5)	
Grade ≥3	11 (21.2)	• One patient experienced neutropenic infection (1.9%)
Febrile neutropenia	2 (3.8)	

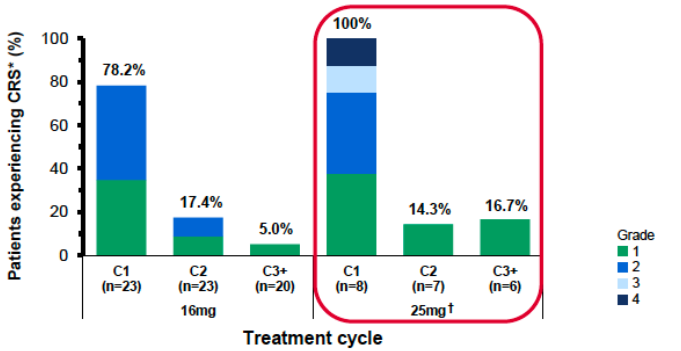
*Includes the preferred terms neutropenia and neutrophil count decreased.

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

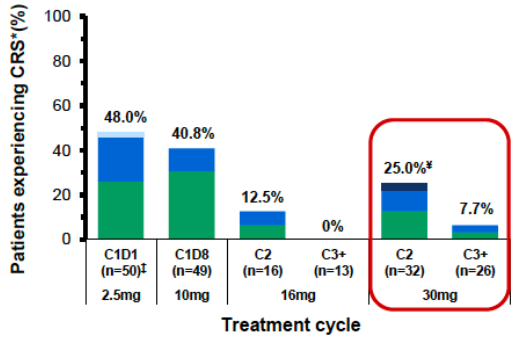
CRS[1] frequency/severity: step-up dosing allows administration of a high target dose of glofitamab

- While the overall CRS rates were similar between the fixed-dosing and step-up dosing cohorts, step-up dosing reduced the frequency of high-grade CRS (Grade ≥2; 36.3% in the ≥10mg fixed-dosing versus 30.7% in the step-up dosing cohort)

Glofitamab ≥10mg fixed dosing (16 and 25mg)[2]



Glofitamab step-up dosing 2.5/10/16mg or 2.5/10/30mg



*Multiple occurrences of CRS are counted at the highest grade. †Based on observed events, 25mg as first C1 dose on fixed-dosing schedule was determined to exceed maximum tolerated dose. ‡Two patients had not reached their first dose of glofitamab at CCOD. ¥Patient who experienced Grade 4 CRS received 30mg glofitamab as part of step-up dosing following a long treatment delay.

1. Lee DW, et al. Blood 2014;124(S2):188–95.
2. Dickinson M, et al. 25th EHA Congress, June 11–14, 2020 (Presentation S241).

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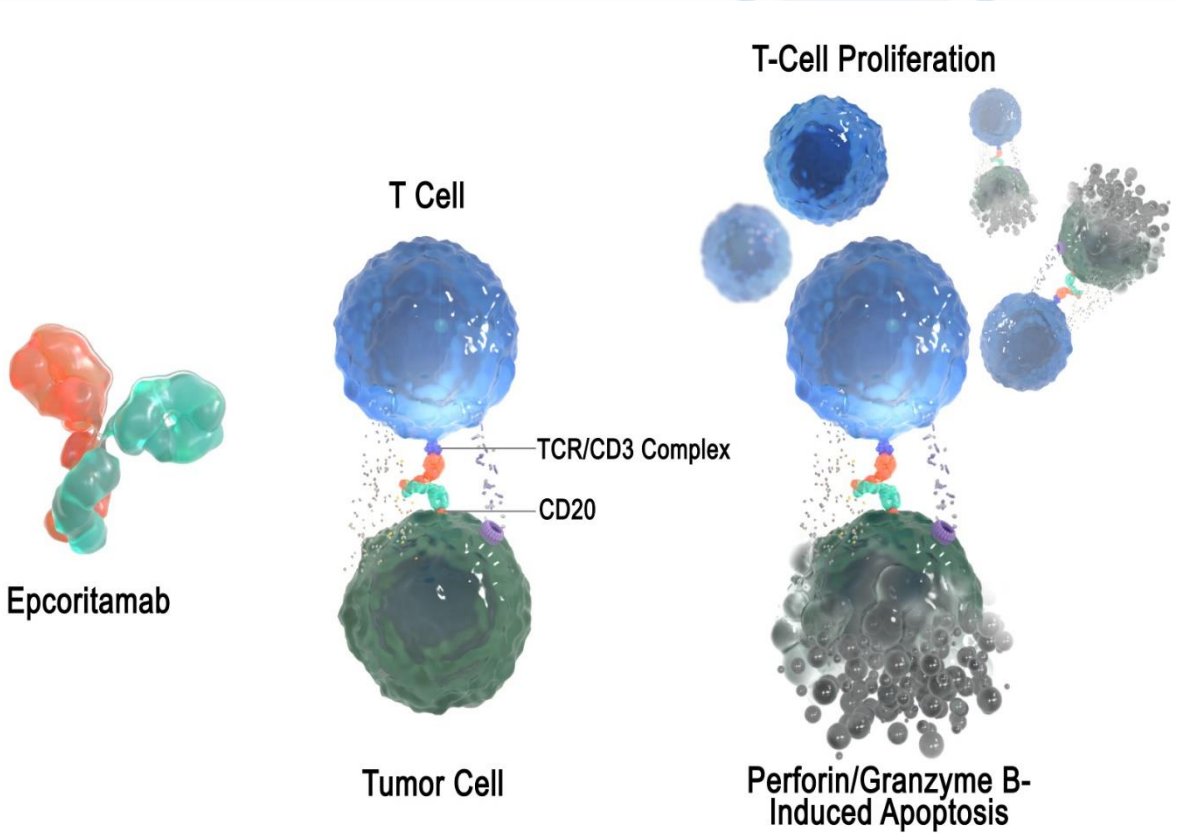
Epcoritamab in B-cell non-Hodgkin Lymphoma

- Epcoritamab is a subcutaneous (SC) IgG1 bispecific antibody (bsAb) that binds CD20 and CD3, which harnesses the patient's immune system to induce T-cell–mediated killing of CD20-positive malignant B-cells[1]
- Epcoritamab key features:
  - SC formulation that allows more gradual increases and lower peaks in plasma cytokine levels as compared to an intravenous formulation, which may help mitigate cytokine release syndrome (CRS)
  - Potent T-cell–mediated killing even when CD20 expression levels are very low
  - Mutations to prevent off-target T-cell killing



1. Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625.

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EPCORE NHL-1 Study Design

Dose escalation*

Expansion Cohort

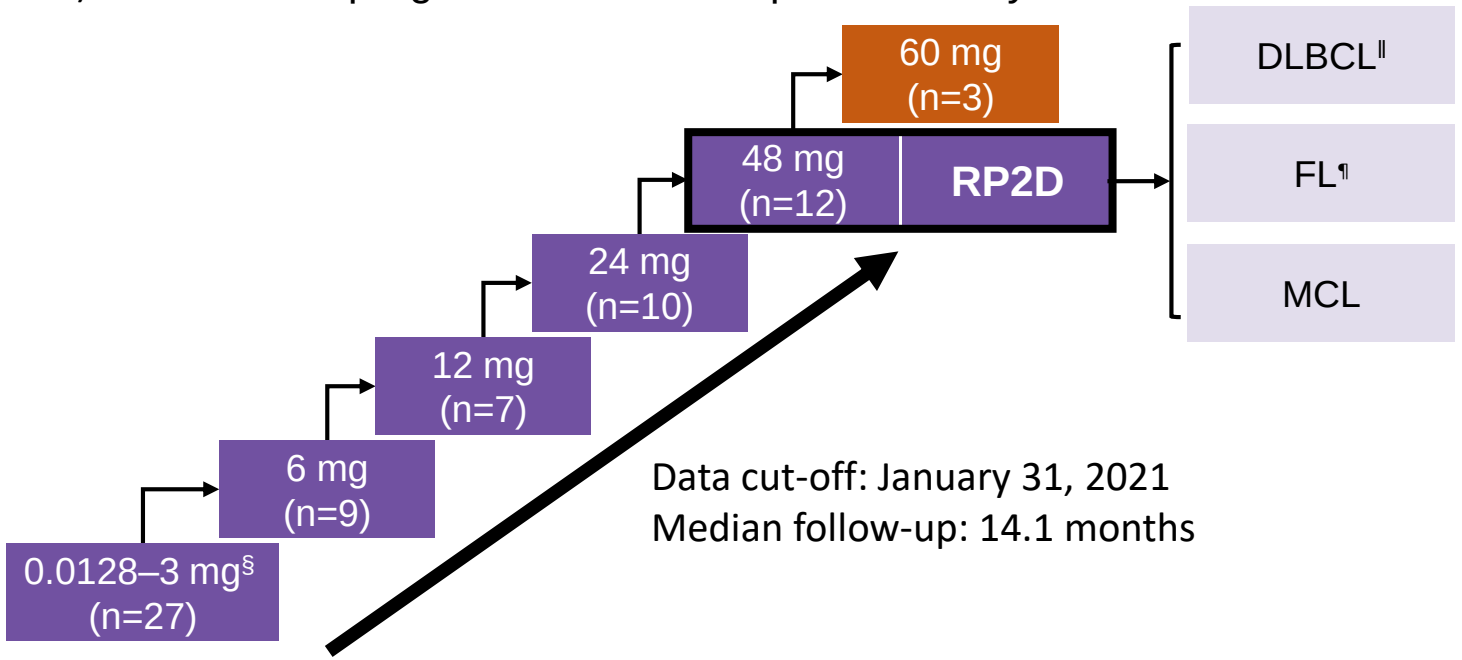
Flat-dose 1 mL SC epcoritamab administered in 28-day cycles
(q1w: Cycles 1–2; q2w: Cycles 3–6; q4w thereafter) until disease progression or unacceptable toxicity

Objectives

Primary
- MTD
- RP2D

Secondary
- Safety
- Anti-tumor activity

Inclusion criteria†
- Adults with R/R CD20+ B-NHL
- Prior treatment with anti-CD20 mAbs
- ECOG PS 0–2
- Measurable disease by CT, MRI, or PET/CT scan**; 6, 12, 18, 24, and every 24 weeks thereafter
- Adequate renal, liver, and hematologic function



To minimize the occurrence and severity of CRS, a priming dose (160 µg, Cycle 1 Day 1) and an intermediate dose (800 µg, Cycle 1 Day 8) of epcoritamab prior to the full dose (beginning on Cycle 1 Day 15), and premedication with corticosteroids, antihistamines, and antipyretics were used (during Cycle 1; as needed in Cycle 2)

*Modified Bayesian optimal interval design consisting of accelerated and standard titration. Accelerated titration includes single-patient cohorts; up to 2 patients may be added (at the currently investigated dose) to obtain additional PK/PD -biomarker data. †Patients previously treated with CAR-T cell therapy were allowed (protocol amended after study start). ‡CT or MRI scans: Weeks 6, 12, 18, 24, and every 12 weeks thereafter. PET scans not required in all patients. §Includes the following priming/final dose levels (mg): 0.004/0.0128, 0.0128/0.04, 0.04/0.12, 0.12/0.38, 0.04/0.76, 0.04/0.25/1.5, 0.04/0.5/3. ‖Includes patients with DLBCL or other aggressive histologies. ¶Includes FL or other indolent histologies

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Treatment Emergent Adverse Events (all cohorts)

Treatment-emergent AEs ≥20%, n (%)	AE Severity		
	Grade 1–2	Grade 3	Grade 4
Pyrexia	43 (63)	4 (6)	0
Cytokine release syndrome	40 (59)	0	0
Injection site reaction	32 (47)	0	0
Fatigue	26 (38)	4 (6)	0
Diarrhea	18 (26)	0	0
Hypotension	17 (25)	4 (6)	0
Dyspnea	16 (24)	0	1 (1)
Tachycardia	14 (21)	0	0
Anemia	7 (10)	9 (13)	0

Discontinuations
Most study drug discontinuations were due to progressive disease (n=46)
One patient discontinued therapy due to an unrelated fatal AE (COVID-19 pneumonia)
No patients discontinued therapy due to treatment-related AEs

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Adverse Events of Special Interest

Treatment-emergent AEs, n (%)	Epcoritamab Dose			Total (N=68)
	≥24 mg (n=53)	48 mg (N=12)	60 mg (n=3)	
Cytokine release syndrome				
Grade 1	15 (28)	4 (33)	1 (33)	20 (29)
Grade 2	15 (28)	4 (33)	1 (33)	20 (29)
Grade 3	0	0	0	0
Neurological symptoms				
Grade 1	2 (4)	0	0	2 (3)
Grade 2	0	0	0	0
Grade 3	2 (4)	0	0	2 (3)
Tumor lysis syndrome				
Grade 3	0	1 (8)	0	1 (1)

- Majority of CRS events occurred in Cycle 1
- Neurotoxicity was limited and transient (median [range] 1.5 [<1–3] days) and manageable with standard therapy
- There were no cases of febrile neutropenia or treatment-related deaths

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Responses to epcoritamab was seen across B-NHL histologies

Response*	R/R DLBCL†		R/R FL	R/R MCL‡
	12-60 mg	48-60 mg	12-48 mg	0.76-48 mg
Evaluable patients	22§	11§	5‖	4**
ORR, n (%) ¶	15 (68)	10 (91)	4 (80)††	2 (50)
CR	10 (46)	6 (55)	3 (60)	1 (25)
PR	5 (23)	4 (36)	1 (20)	1 (25)
SD, n (%)	1 (5)	0	0	1 (25)
PD, n (%)	5 (23)	0	1 (20)	0

Represents the modified response-evaluable set. *Data are not shown for 23 patients with R/R DLBCL and 6 patients with FL who received <12 mg doses and for 6 additional patients with other R/R B-NHL histologies. †Includes 3 patients who received 60-mg dose before RP2D was determined. ‡3 patients had blastoid/pleomorphic MCL; 1 had unknown histology. §Excludes 1 patient who discontinued before first assessment due to COVID-19. ‖Excludes 1 patient who discontinued before first assessment due to cardiac bypass surgery. ¶Response rates are based on number of evaluable patients (defined as patients with ≥1 post-baseline disease assessment or who died without a post-baseline disease assessment). **Includes 1 patient who died before assessment. ††6/10 patients had response evaluation by PET scans (not mandatory until recent protocol amendment).

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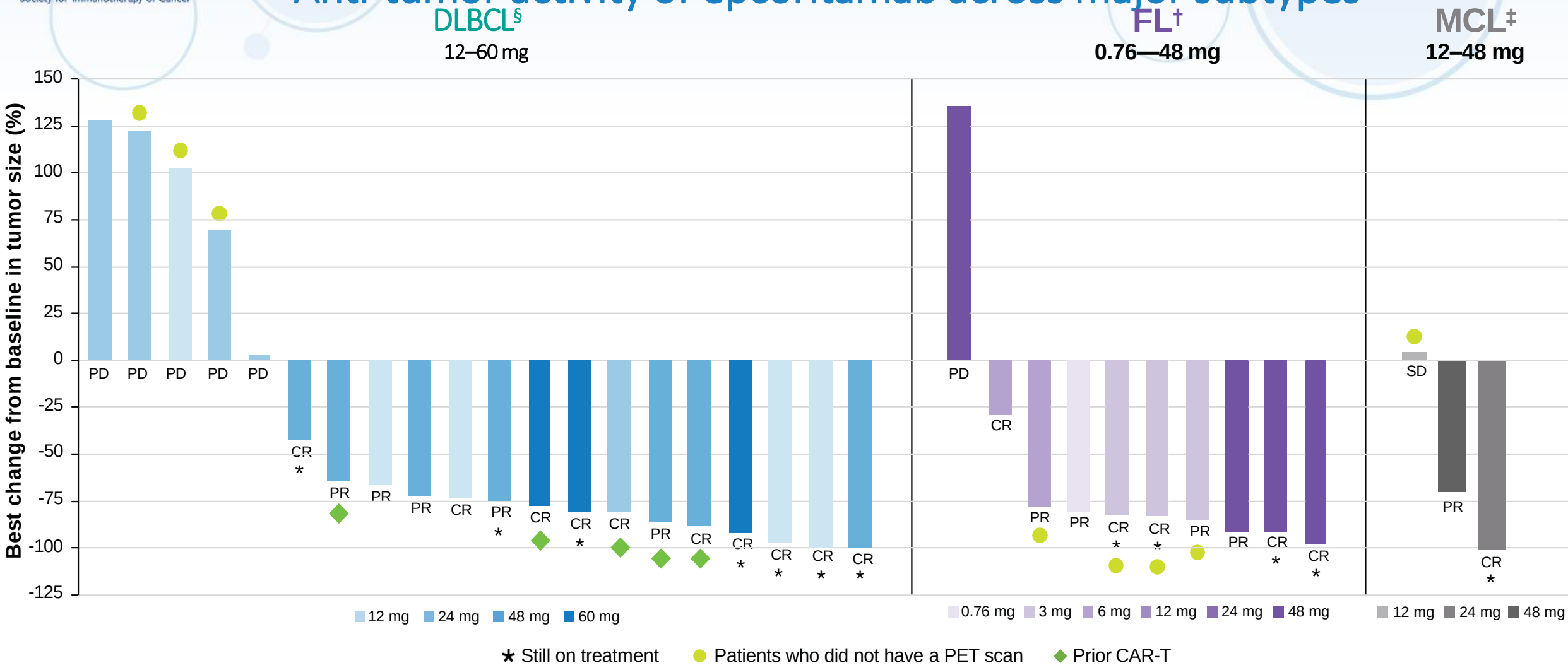
Anti-tumor activity of epcoritamab across major subtypes



Data are shown for the modified response-evaluable population. §Excludes 2 patients with DLBCL; 1 patient died before receiving the first post-baseline evaluation due to COVID019 and 1 patient did not have measurable disease based on CT scan evaluation at the time of enrollment. †Excludes 1 patient who discontinued before first assessment due to coronary artery bypass graft surgery. ‡Excludes 1 patient with MCL who died before post-baseline assessment.

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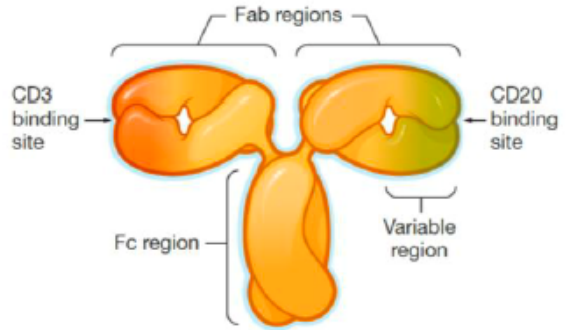
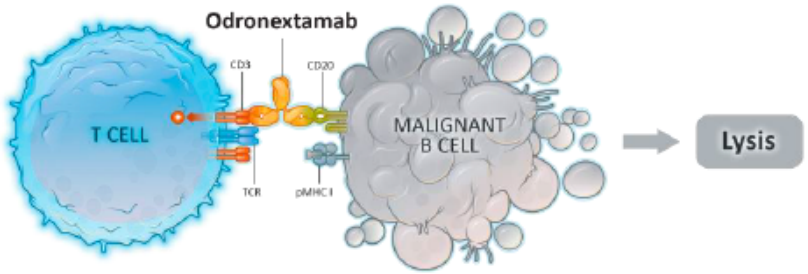
Odronextamab

Introduction

Odronextamab bispecific antibody structure



Odronextamab mechanism of action



B-NHL, B-cell non-Hodgkin lymphoma; IV, intravenous; R/R, relapsed/refractory.

- Odronextamab (REGN1979) is a CD20 x CD3 bispecific antibody:
  - Binds to CD3 on T cells and CD20 on malignant B cells, triggering T-cell-mediated cytotoxicity independent of T-cell-receptor recognition[1,2]
- Off-the-shelf treatment for IV infusion
- Results from a first-in-human, Phase 1 study (NCT02290951; R1979-HM-1333) investigating odronextamab in patients with R/R B-NHL have been reported previously, and at ASH this year[3,4]
- Here, we report the study design of a potentially pivotal Phase 2, open-label, multi-cohort study designed to assess the antitumor activity and safety of odronextamab monotherapy in patients with R/R B-NHL (NCT03888105; R1979-ONC-1625)

1. Smith EJ, et al. *Sci Rep*. 2015;5:17943;
2. Choi BD, et al. *Expert Opin Biol Ther*. 2011;11:843–53;
3. Bannerji R, et al. *Blood*. 2019;134(Supplement_1):762;
4. Bannerji R, et al. ASH Annual Meeting 2020. Abstract #400.

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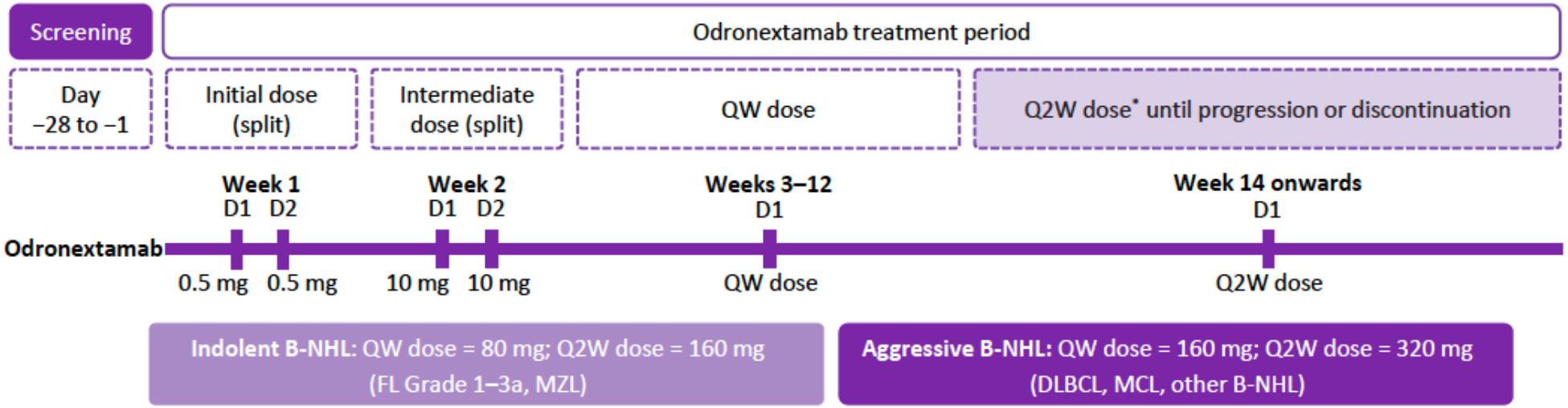
Odronextamab dose schedule



- Odronextamab is administered IV in the outpatient setting†
- Dexamethasone premedication‡ and split, step-up doses are used to mitigate the risk for CRS
- Response is assessed according to Lugano criteria: Q8W in first year, Q12W in second year, and Q24W thereafter

*If a patient has demonstrated a CR that is durable for at least 9 months, then study treatment will be administered Q4W at the same dose.
†Patients are hospitalized for observation during step-up dosing and for the first full QW dose.
‡Dexamethasone is administered IV prior to each odronextamab infusion during weeks 1–4, before being tapered or discontinued, or substituted with a different corticosteroid, from week 5.
B-NHL, B-cell non-Hodgkin lymphoma; CR, complete response; CRS, cytokine release syndrome; D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IV, intravenous; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QW, once weekly; QXW, once every X weeks.

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Adverse Events

TEAE (any Gr)*	Total (N=110) n (%)
Pyrexia	88 (80.0)
CRS	65 (59.1)
Chills	56 (50.9)
Infections and infestations†	55 (50.0)
Fatigue	40 (36.4)
Anemia	39 (35.5)
Increased C-reactive protein	34 (30.9)
Hypotension	33 (30.0)
Hypophosphatemia‡	33 (30.0)
Thrombocytopenia‡	31 (28.2)
Nausea	30 (27.3)
Cough	28 (25.5)
IRR	27 (24.5)
Tachycardia	27 (24.5)
Headache	27 (24.5)
Peripheral edema	25 (22.7)
Neutropenia‡	25 (22.7)
Dyspnea	24 (21.8)
Lymphopenia‡	23 (20.9)
Vomiting	23 (20.9)
Decreased appetite	23 (20.9)

TEAE (Gr 3–4)§	Total (N=110) n (%)
Anemia	24 (21.8)
Hypophosphatemia‡	21 (19.1)
Neutropenia‡	21 (19.1)
Lymphopenia‡	21 (19.1)
Thrombocytopenia‡	15 (13.6)
Leukopenia‡	11 (10.0)
Increased aspartate aminotransferase	9 (8.2)
Hypotension	9 (8.2)
Increased alanine aminotransferase	7 (6.4)
CRS	7 (6.4)
Fatigue	6 (5.5)
Dyspnea	6 (5.5)
Hyperglycemia	6 (5.5)

TEAE (Gr 5)	Total (N=110) n (%)
Cardiac arrest (unrelated)	1 (0.9)
Gastric perforation	1 (0.9)
Lung infection	1 (0.9)
Multi-organ failure (unrelated)	1 (0.9)
Acute renal failure (unrelated)	1 (0.9)
Pneumonia	1 (0.9)

*Occurred in ≥20% of patients; †Comprises SOC terms infections and infestations; ‡Composite terms; thrombocytopenia, lymphopenia, neutropenia, leukopenia, and hypophosphataemia include decrease in platelet count, lymphocytes, neutrophils, white blood cells, and blood phosphorus, respectively; §Occurred in >5 patients. CRS, cytokine release syndrome; Gr, grade; IRR, infusion-related reaction; SOC, system organ class; TEAE, treatment-emergent adverse event.

Data cut-off date: September 03, 2019

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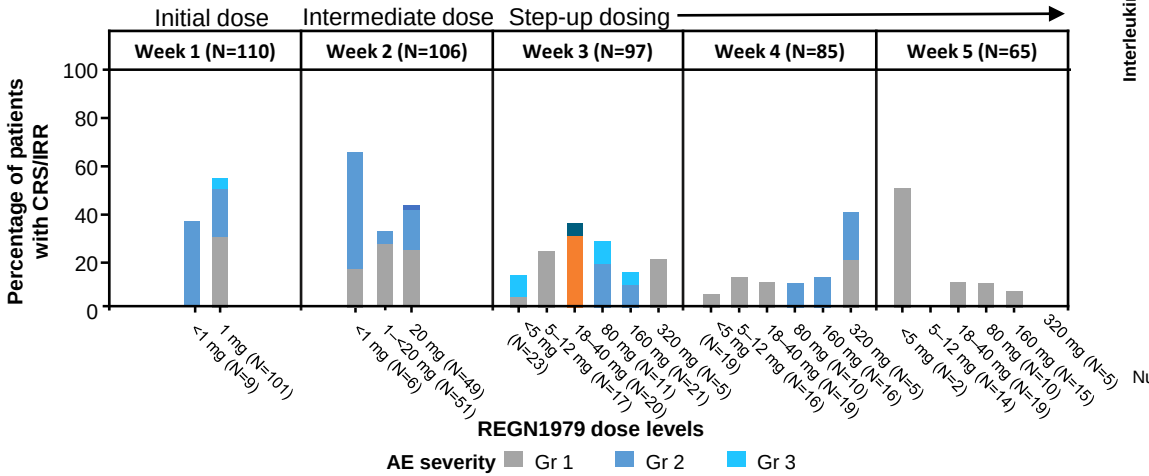
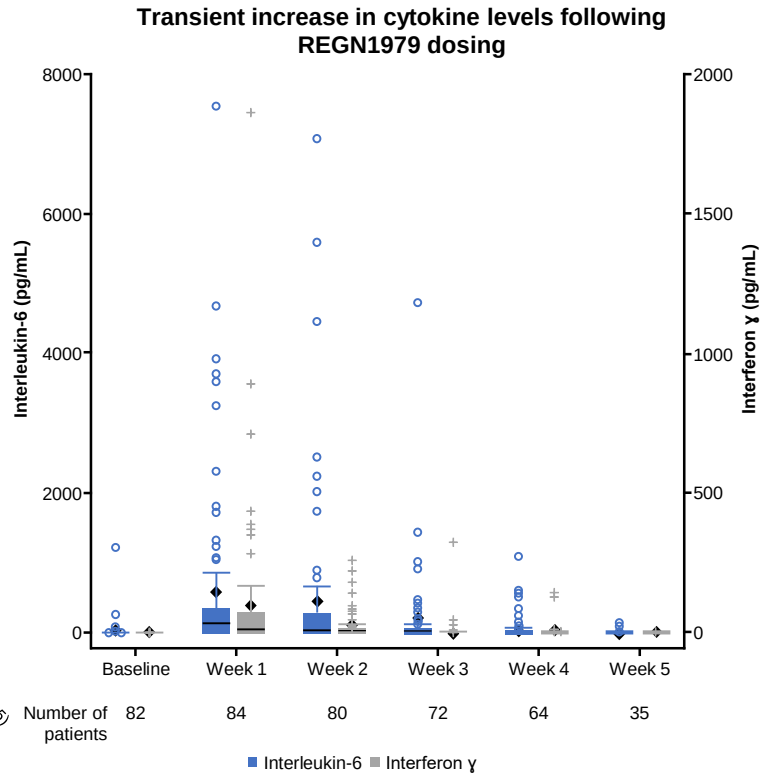
AEs with step up dosing

- IRR/CRS events occurred predominantly during Weeks 1–3 and declined thereafter, without dose-dependent increase in incidence or severity
- At data cut-off, eight patients experienced Gr 3 IRR/CRS*, without reported Gr 4 or 5 IRR/CRS events†
  - After data cut-off, one patient with aggressive MCL blastoid variant, with bone marrow involvement and bulky disease, experienced Gr 4 CRS (and TLS)
- No patient discontinued due to IRR/CRS





*IRR, infusion-related reaction according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03; CRS, cytokine release syndrome according to adapted Lee DW et al. *Blood* 2014;124:188–195.; †For patients who experienced both IRR and CRS during the same week, the maximum Gr of either was used. AE, adverse event; Gr, grade; MCL, mantle cell lymphoma; TLS, tumor lysis syndrome.

Data cut-off date: September 03, 2019

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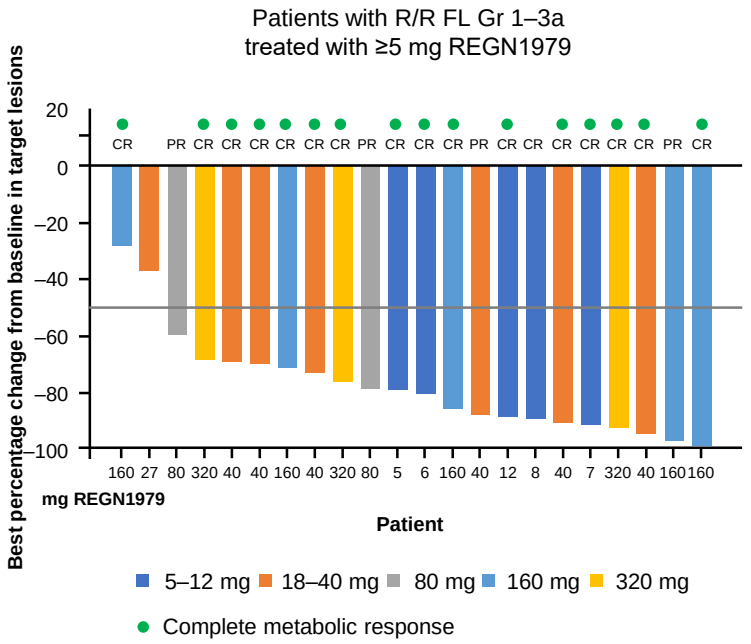
Efficacy Follicular

ORR/CR rate in patients treated with REGN1979 ≥5 mg was 95%/77%

	REGN1979 dose groups						
BOR by Lugano Criteria[1]	<5 mg (N=7)	5–12 mg (N=5)	18–40 mg (N=7)	80 mg (N=2)	160 mg (N=5)	320 mg (N=3)	Total for ≥5 mg (N=22)
ORR (CR/PR), **n** (%)	**1** (14.3)	**5** (100)	**6**(85.7)	**2** (100)	**5** (100)	**3** (100)	**21** (95.5)
Complete response	**1** (14.3)	**5** (100)	**5**(71.4)	0	**4** (80.0)	**3** (100)	**17** (77.3)
Partial response	0	0	**1** (14.3)	**2** (100)	**1** (20.0)	0	**4** (18.2)
Stable disease	**4** (57.1)	0	**1** (14.3)	0	0	0	**1** (4.5)
Progressive disease	**2** (28.6)	0	0	0	0	0	0



*First dose at least 12 weeks before data cut-off. BOR, best overall response; CR, complete response; FL, follicular lymphoma; Gr, grade; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory. 1. Cheson BD et al. *J Clin Oncol.* 2014;32:3059–3067.

Data cut-off date: September 03, 2019

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Efficacy DLBCL

ORR/CR rate in patients treated with REGN1979 ≥80 mg: 58%/42%

Without prior CAR T-cell therapy† with REGN1979 ≥80 mg: 71%/71%

With prior CAR T-cell therapy† with REGN1979 ≥80 mg: 50%/25%

	REGN1979 dose groups						
BOR by Lugano Criteria[1]	<5 mg (N=15)	5 mg–12 mg (N=11)	18 mg–40 mg (N=11)	80 mg (N=6)	160 mg (N=11)	320 mg (N=2)	Total ≥80mg (N=19)
ORR (CR/PR), **n** (%)	**2** (13.3)	**2** (18.2)	**6** (54.5)	**5** (83.3)	**5** (45.5)	**1** (50.0)	**11** (57.9)
Complete response	0	**1** (9.1)	**2** (18.2)	**4** (66.7)	**3** (27.3)	**1** (50.0)	**8** (42.1)
Partial response	**2** (13.3)	**1** (9.1)	**4** (36.4)	**1** (16.7)	**2** (18.2)	0	**3** (15.8)
Stable disease	**4** (26.7)	**4** (36.4)	**3** (27.3)	0	**1** (9.1)	**1** (50.0)	**2** (10.5)
Progressive disease	**8** (53.3)	**4** (36.4)	**1** (9.1)	**1** (16.7)	**2** (18.2)	0	**3** (15.8)
Not available	**1** (6.7)	**1** (9.1)	**1** (9.1)	0	**3** (27.3)	0	**3** (15.8)

	Without prior CAR T at doses ≥80 mg	With prior CAR T at doses ≥80 mg
BOR by Lugano Criteria[1]	Total (N=7)	Total (N=12)
ORR (CR/PR), n (%)	**5** (71.4)	**6** (50.0)
Complete response	**5** (71.4)	**3** (25.0)
Partial response	0	**3** (25.0)
Stable disease	**1** (14.3)	**1** (8.3)
Progressive disease	**1** (14.3)	**2** (16.7)
Not available	0	**3** (25.0)

*First dose at least 12 weeks before data cut-off. †CD19-directed CAR T-cell therapy.
BOR, best overall response; CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory.

1. Cheson BD et al. *J Clin Oncol.* 2014;32:3059–3067.

Data cut-off date: September 03, 2019

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Plamotamab

- XmAb13676 (plamotamab) is a humanized bispecific antibody that binds to CD20-expressing target cells and to CD3, to recruit and activate T cells..

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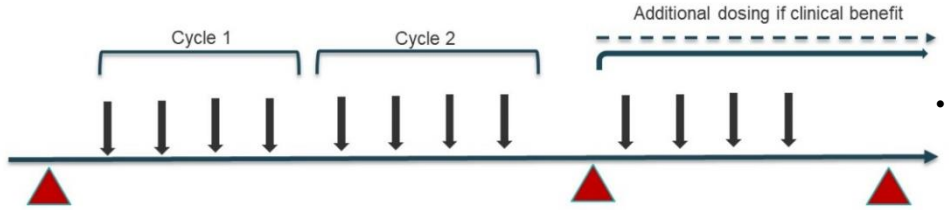
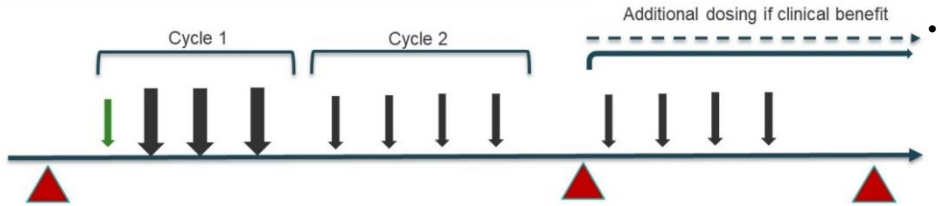
Study Schema

Part A — Dose cohorts to establish priming dose in a 28-day cycle



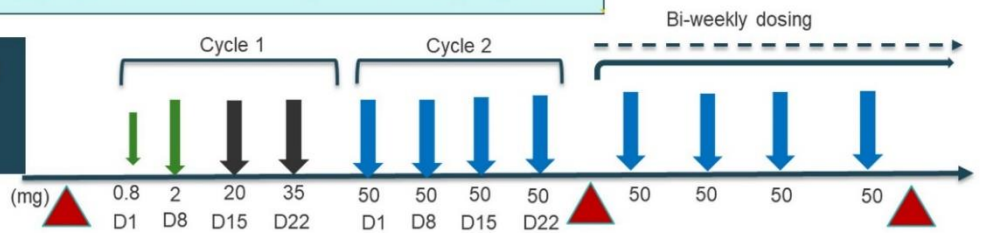
Part A dosing schedule: 0.7 – 170 µg/kg QW

Part B — Establish an MTD using the priming dose on C1D1 and fixed or step-up dosing



Part B dosing schedule:
Priming Dose C1D1: 10 – 80 µg/kg QW
Peak Dose (within 2 cycles): 125 – 450 µg/kg Q2W; currently at 360 µg/kg QW

Part C — Flat dosing using the priming dose on C1D1 and then step-up dosing



Part C dosing schedule:
Cycle 1: 0.8 / 2 / 20 / 35 QW
Cycle 2: 50 mg QW; Cycle 3 onwards: 50 mg Q2W

- This study has 3 Parts. Parts A and B are weight based, and Part C is a flat, step-up dose regimen with biweekly dosing from Cycle 3 Day 1, enabling a more convenient dosing schedule.
- Part C uses a priming dose level of 0.8 mg which was informed by Parts A and B to mitigate cytokine release syndrome (CRS).
- RP2D from Part C→ DLBCL and FL expansion; n=20 each

Footnote: QW = weekly dosing, Q2W = biweekly dosing

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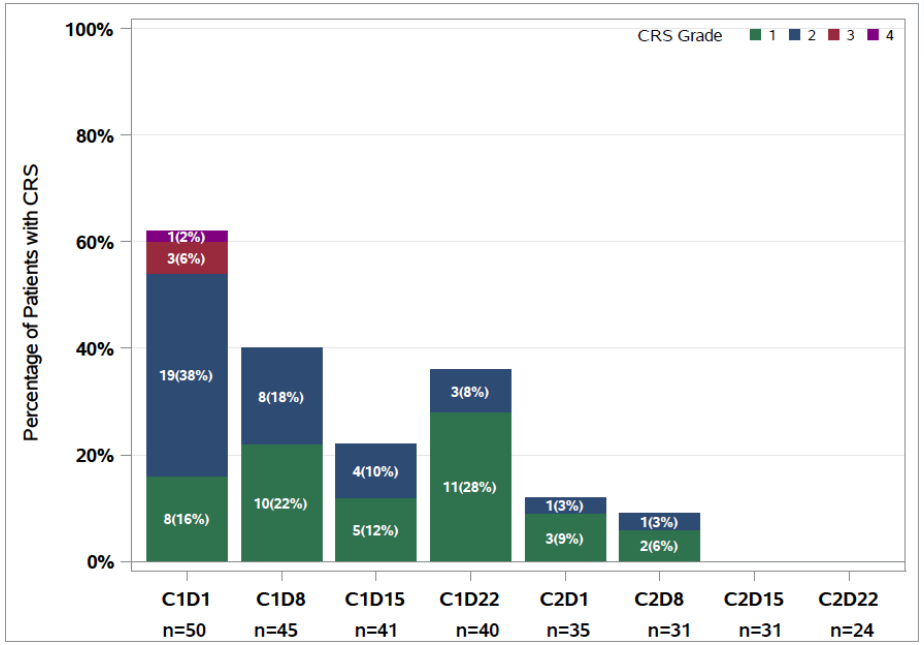
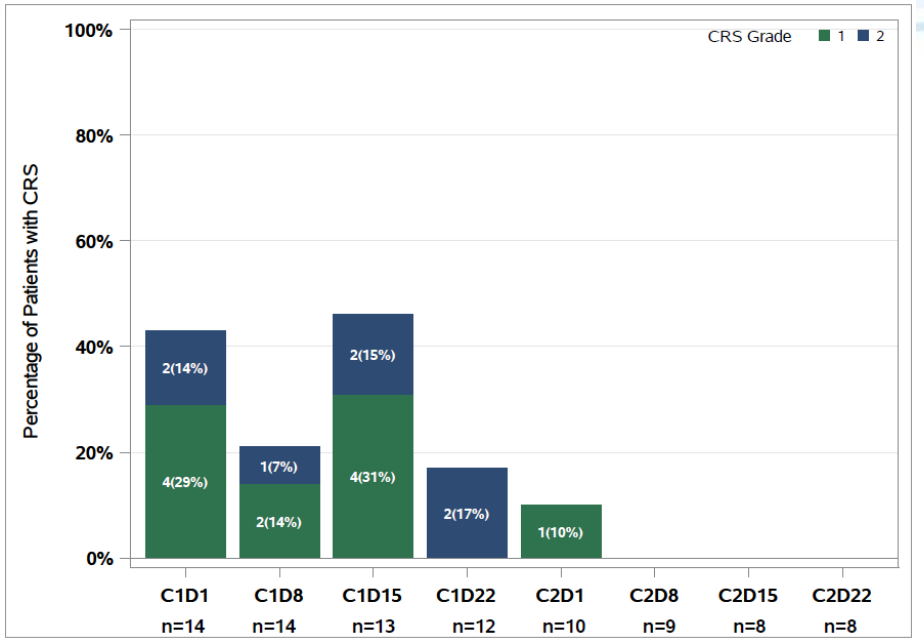
Cytokine Release Syndrome

Weight-Based Dose Cohorts



Flat-Dose Cohort (Part C)



- Lower frequency and less severe CRS in flat-dose Part C cohort (57.1%) compared to weight-based 80 to 360 µg/kg cohorts (74.0%)
- No Grade 3 CRS at priming dose in Part C supports 0.8mg priming dose
- CRS generally resolved by Cycle 2

Footnote: Data cut = 27 October 2021. Weight-based cohorts includes all Part B cohorts with highest planned weekly weight-based dosing of 80 to 360 µg/kg. Adverse events with preferred term Cytokine Release Syndrome (CRS) are used in the analysis. CRS was graded as per the ASTCT Consensus

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Best Objective Response Rate - DLBCL and FL

Weight-Based Cohorts	Response Rate: n/N(%)
25 µg/kg	
ORR	1/1 (100.0)
CR	0/1
80 µg/kg	
ORR	1/4 (25.0)
CR	0/4
125 µg/kg	
ORR	6/12 (50.0)
CR	5/12 (41.7)
170 µg/kg	
ORR	4/7 (57.1)
CR	2/7 (28.6)
250 µg/kg	
ORR	4/10 (40.0)
CR	1/10 (10.0)
360 µg/kg	
ORR	2/4 (50.0)
CR	1/4 (25.0)
Flat Dose Cohort, Part C	**Response Rate: n/N(%)**
50 mg	
ORR	6/9 (66.7)
CR	3/9 (33.3)
Overall	
ORR	24/47 (51.1)
CR	12/47 (25.5)

- ORR in all evaluable patients was 51.1% with CR 25.5%
- ORR in Flat-dose Part C cohort was 66.7% with CR 33.3%
  - ORR in FL was 100% (4/4), with CR 50% (2/4) w/ median 4 prior lines
  - ORR in DLBCL was 40% (2/5); all had prior CAR-T, median 5 prior lines
  - 2 were refractory to first-line therapy

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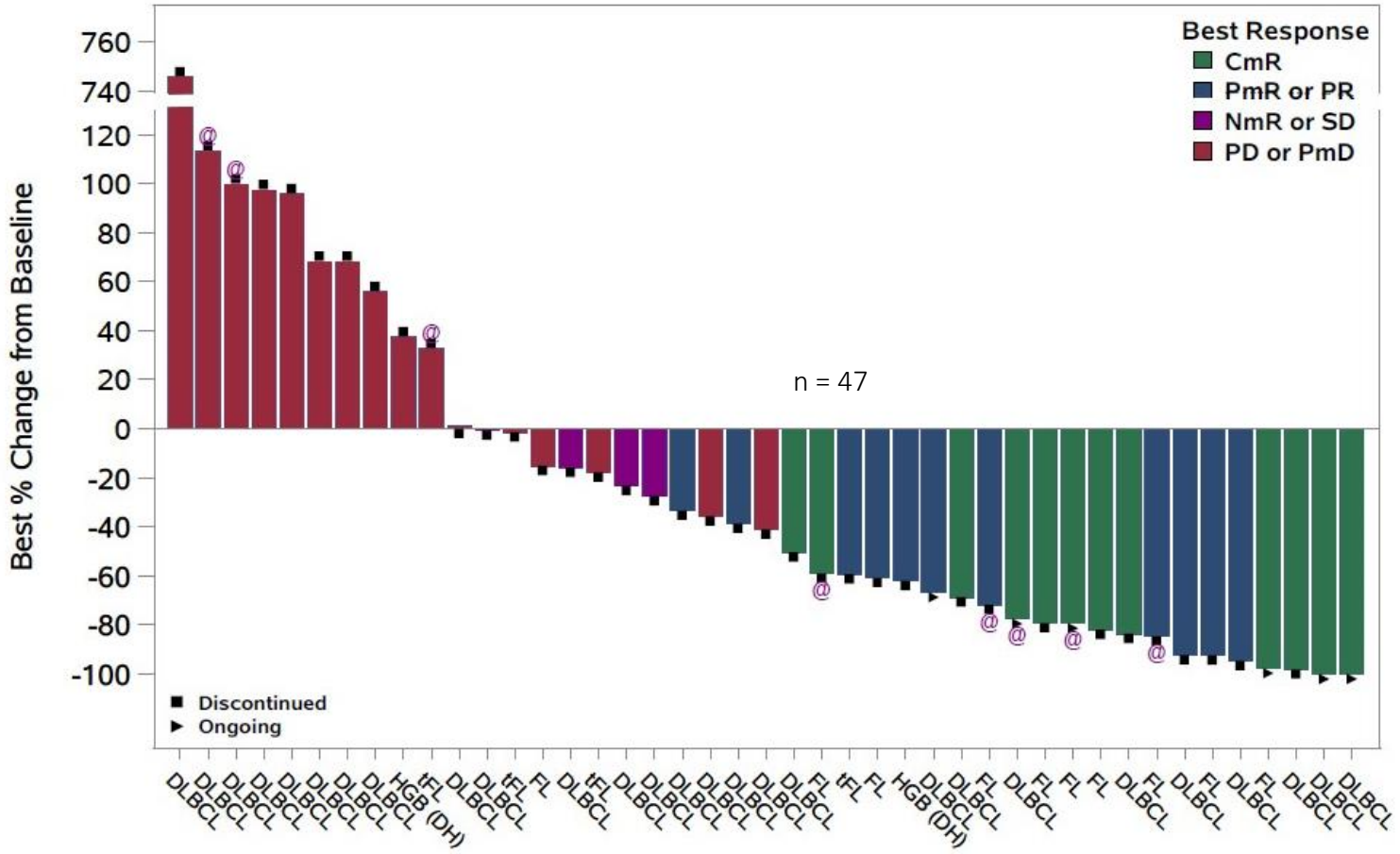
Tumor Response - DLBCL and FL



Footnote: Data cut = 27 October 2021. Included here is the efficacy evaluable population, as defined in Table 3.
@ = Cohort Part C.
All other subjects are from weight-based cohorts (highest planned weekly dose of 80 to 360 µg/kg).
One subject has a Percent Change in SPD = 0 and is represented as 1% in the graph. One subject from Part C did not have all post baseline target measurements but was a responder as per Lugano PET-CT 5-PS. DLBCL = Diffuse large B cell lymphoma; FL = Follicular lymphoma; CmR = Complete metabolic response; PmR = Partial metabolic response; PR = Partial response; NmR = No metabolic response; SD = Stable disease; PD = Progressive disease. Response is assessed based on Lugano Classification(4).

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Next Steps

- Studies indicate efficacy of CD20/CD3 bispecific antibodies in R/R NHL
  - Several studies open or planned to evaluate as single agent or in combination vs. SOC in R/R DLBCL, FL and MCL.
  - Frontline study completed with mosunetuzumab-CHOP, ongoing study with epcoritamab-CHOP and planned study of glofitamab-CHOP
- Several other bispecifics in development
  - CD20/CD3 IgM antibody
  - CD37/CD3 IgG
  - CD20/CD47 IgG

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Questions

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