NOVEL ANTIBODIES IN AGGRESSIVE LYMPHOMAS

Unmet challenges in high risk hematological malignancies:
From benchside to clinical practice
Turin, September 13-14, 2021

Martin Hutchings, Rigshospitalet

DISCLOSURES

- **Scientific advisory boards:**
  - AbbVie, Celgene, Genmab, Janssen, Roche, Takeda
- **Research support (institution):**
  - Celgene, Genentech, Genmab, Incyte, Janssen, Novartis, Roche, Takeda

OVERVIEW OF THIS PRESENTATION

- Monoclonal antibodies
- Antibody-drug conjugates
- Checkpoint inhibitors and immune agonists
- Bispecific antibodies

MONOCLONAL ANTIBODIES

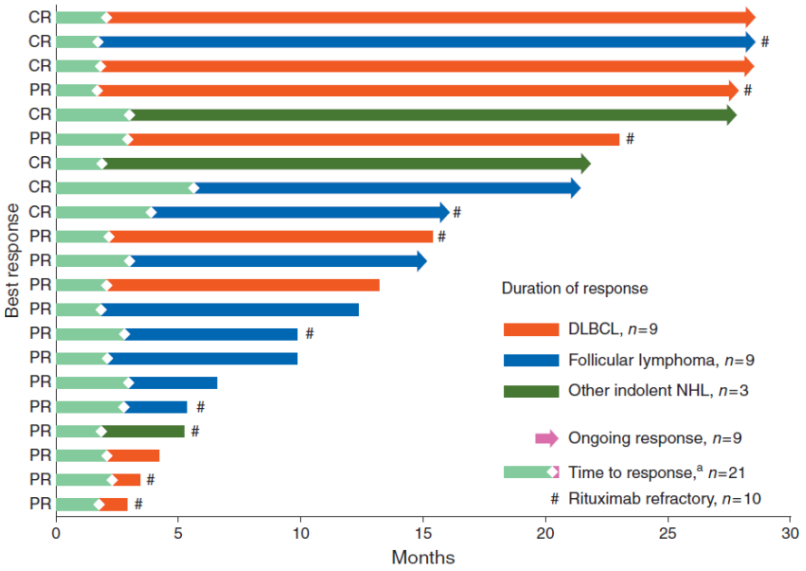
- Tafasitamab
- (Mogamulizumab)

TAFASITAMAB

Fc-engineered, humanized, anti-CD19 monoclonal antibody

Phase 2 trial of tafasitamab monotherapy in 92 patients with r/r B-NHL[1]:

- ORR 26% and CRR 6% in 35 patients with r/r DLBCL
- ORR 29% and CRR 9% in 34 patients with r/r FL
- Median DOR (median FU 21 months):
  - 20 months in DLBCL
  - not reached in FL
- Median PFS:
  - 2.7 months in DLBCL
  - 8.8 months in FL
- Most common AEs: IRR and neutropenia, both 11%



[1]Jurczak W, et al. Ann Oncol 2018; 29: 1266–1272.

TAFASITAMAB

L-MIND study: Combination of tafasitamab and lenalidomide in r/r DLBCL

Phase 2 study of tafasitamab + lenalidomide in 81 ASCT-ineligible patients with r/r DLBCL[1]:

- ORR 60%
- CRR 43%
- Median FU 17.3 months
- Median DOR 21.7 months
- Median PFS 12.1 months

EHA 2020 update[2]:

- Median DOR 34.6 months

The FDA granted accelerated approval in July 2019 for this combination in r/r DLBCL

Ongoing studies:

- **Randomized phase 2/3 study of R-bendamustine +/- tafasitamab in r/r DLBCL (NCT02763319)**
- **Phase 1 study of tafasitamab with R-CHOP and R-CHOP + lenalidomide in newly diagnosed DLBCL (NCT04134936)**

Most frequent toxicities: hematologic toxicity, diarrhea, and fatigue

[1]Salles G, et al. Lancet Oncol. 2020;21(7): 978-988.
[2]Salles G, et al. 25th EHA Congress 2020. Abstract EP1201.

ANTIBODY-DRUG CONJUGATES

- (Brentuximab vedotin)
- Polatuzumab vedotin
- Loncastuximab tesirine

POLATUZUMAB VEDOTIN

ADC targeting CD79b with MMAE payload

CD79b is a component of the B-cell receptor expressed on > 90% of B-NHL

Randomized phase 2 trial of R-Bendamustine +/- polatuzumab vedotin:

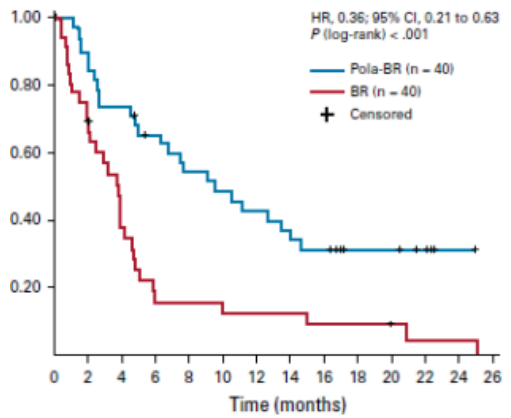
- 80 patients with r/r DLBCL
- End-of-treatment CR: 40.0% v 17.5%
- Median PFS: 9.5 v 3.7 months (P < 0.001)
- Median OS: 12.4 v 4.7 months (P = 0.002)
- AEs: More neutropenia and more peripheral neuropathy

Activity independent of COO and of response to prior treatments

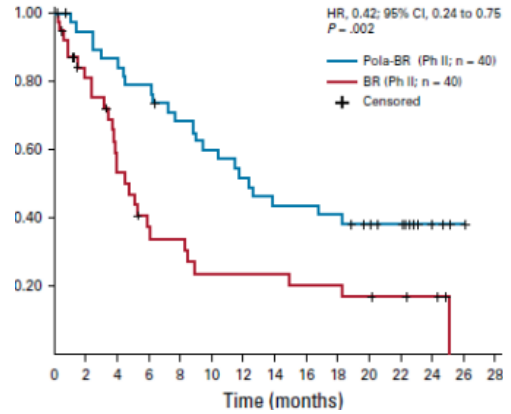
Phase 3 trial of 875 de-novo DLBCL patients evaluating R-CHOP versus R-CHOP + polatuzumab (NCT03274492) recently completed accrual

Approved for ASCT-ineligible r/r DLBCL by FDA in 2019 and EMA in 2020

PFS per IRF



Overall survival



[1]Sehn L, et al. J Clin Oncol 2020; 38:155-165.

LONCASTUXIMAB TESIRINE

Humanized anti-CD19 antibody conjugated to a pyrrolobenzodiazepine dimer

Most common toxicities: hematologic toxicity, fatigue, edema, liver test abnormalities, nausea, rash, and dyspnea

Phase 1 study of 61 patients with r/r DLBCL[1]:

49% ORR, 32% CR

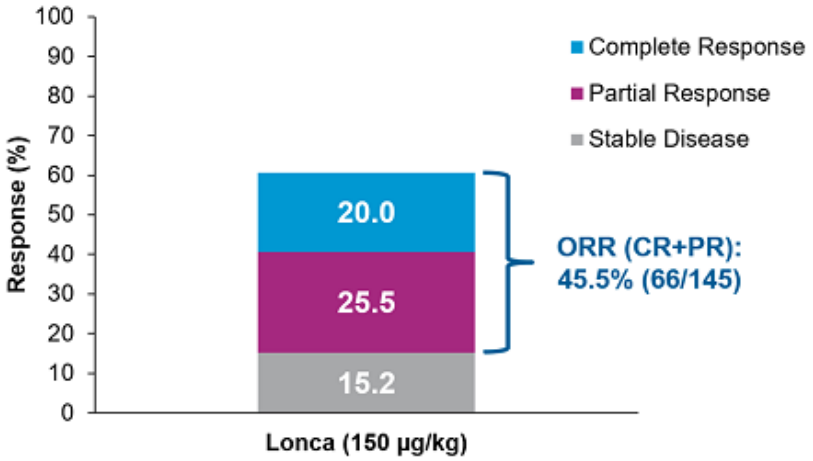
median DOR 4.8m

Median PFS 2.9m

MTD not reached

Phase 2 study of 145 ptts with r/r DLBCL[2]:

45.5% ORR and 20% CR



[1]Kahl BS, et al. Clin Cancer Res. 2019;25(23):6986-6994.
[2]Carlo-Stella C, et al. 25th EHA Congress 2020. Abstract S233.

CHECKPOINT INHIBITORS AND IMMUNE AGONISTS

- (Anti PD1 and anti PDL1)
- (Anti 4-1BB/CD137)
- Anti CD47

MAGROLIMAB

Humanized, anti-CD47 monoclonal antibody

Induces macrophage phagocytosis by blocking the “do not eat me” signal

An ongoing phase 1b/2 study of magrolimab and rituximab (NCT02953509)[1,2]:

- 100 patients included for EHA 2019 abstract (63 DLBCL, 35 FL, 2 MZL)
- Pooled efficacy results from Ph1b+2 efficacy evaluable patients (n=75):
  - ORR and CR rate of 49% and 21%, respectively
- In indolent lymphoma (n=28 FL, 1 MZL), ORR/CR rate 66/24%
- In DLBCL (n=46), the ORR/CR rate 39/20%
- Median DOR not reached at median FU of 12 months

Treatment-related AEs occurring in >10% of patients (mostly grades 1-2):

Infusion reactions (38%)
Headache (34%)
Chills (30%)
Fatigue (30%)
Anemia (27%)
Nausea (24%)
Pyrexia (23%)
Vomiting (13%)
Back pain (11%)

[1]Advani R, et al. N Engl J Med 2018; 379:1711-1721.
[2]Advani R, et al. 24th EHA Congress 2019. Abstract S867.

BISPECIFIC ANTIBODIES

- Glofitamab
- Epcoritamab
- (Mosunetuzumab, Odronextamab, Plamotamab)

rapid communications

Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial

Martin Hutchings, PhD[1]; Franck Morschhauser, MD, PhD[2]; Gloria Iacoboni, MD[3,4]; Carmelo Carlo-Stella, MD[5]; Fritz C. Offner, MD, PhD[6]; Anna Sureda, MD, PhD[7]; Gilles Salles, MD[8]; Joaquín Martínez-Lopez, MD, PhD, MBA[9]; Michael Crump, MD[10]; Denise N. Thomas, MSc[11]; Peter N. Morcos, PharmD[11]; Cristiano Ferlini, MD[11]; Ann-Marie E. Bröske, PhD[12]; Anton Belousov, PhD[13]; Marina Bacac, PhD[13]; Natalie Dimier, PhD[14]; David J. Carlile, PhD[14]; Linda Lundberg, PhD[15]; David Perez-Callejo, MD, PhD[15]; Pablo Umaña, PhD[13]; Tom Moore, MD[12]; Martin Weisser, MD[12]; and Michael J. Dickinson, MBBS, DMedSci[16]

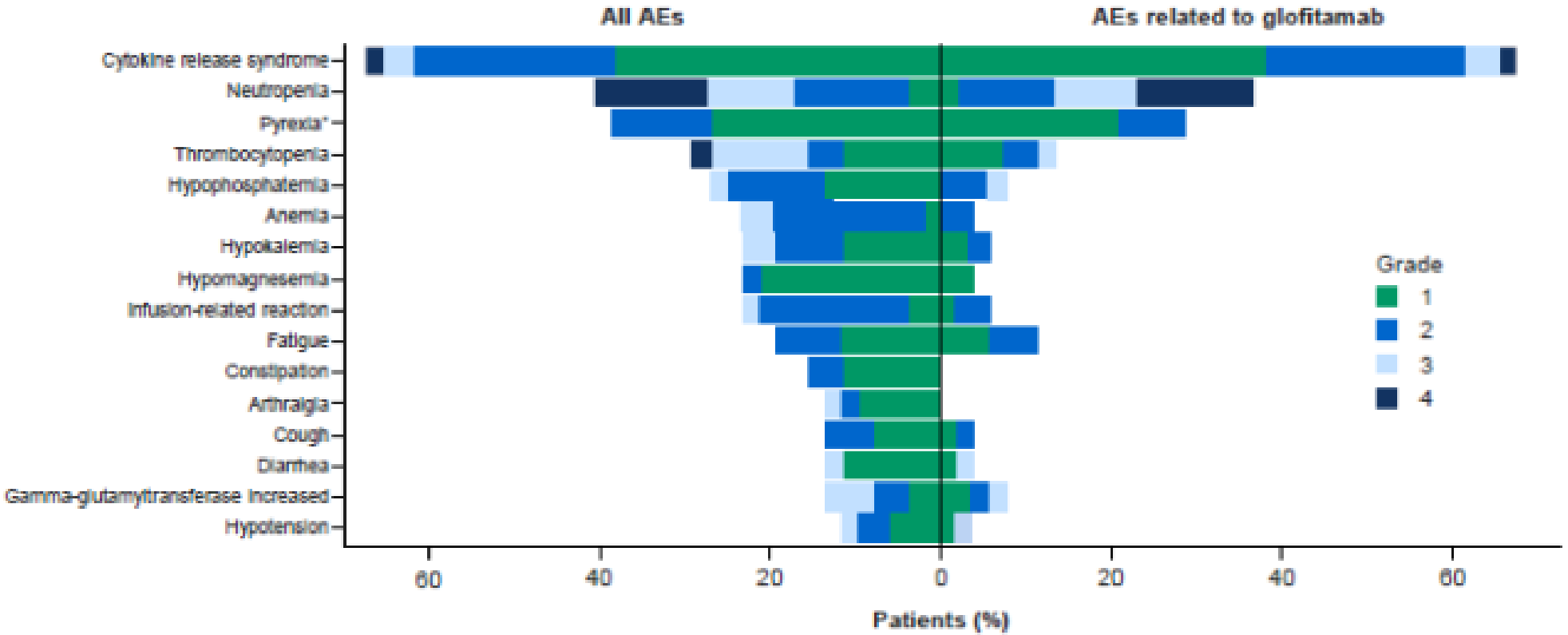
J Clin Oncol 00.

Most recent data about glofitamab at the RP2D: Most patients had heavily pretreated B-NHL

Baseline characteristics	2.5/10/16 and 2.5/10/30mg cohorts (N=52)
Median age (range), years	68 (44–85)
Male gender, n (%)	28 (53.8)
Prior lines of therapy, median (range)	3 (1–12)
Prior therapy, n (%)	
Chemotherapy and anti-CD20 monoclonal antibody	52 (100)
Autologous stem-cell transplant	11 (21.2)
PI3Ki	5 (9.6)
CAR-T	3 (5.8)
Cancer immunotherapy	1 (1.9)
Refractory status, n (%)	
Refractory to any prior therapy	44 (84.6)
Refractory to most recent therapy line	40 (76.9)
Refractory to any prior anti-CD20	38 (73.1)
Aggressive NHL, n (%)	**28 (53.8)**
DLBCL	10 (19.2)
Transformed FL	6 (11.5)
Richter's transformation	5 (9.6)
MCL	5 (9.6)
High-grade B-cell lymphoma	1 (1.9)
FL Grade 3B	1 (1.9)
Indolent NHL, n (%)	**24 (46.2)**
FL Grade 1–3A	24 (46.2)

Hutchings M, et al. J Clin Oncol 2021;39(18):1959-1970.

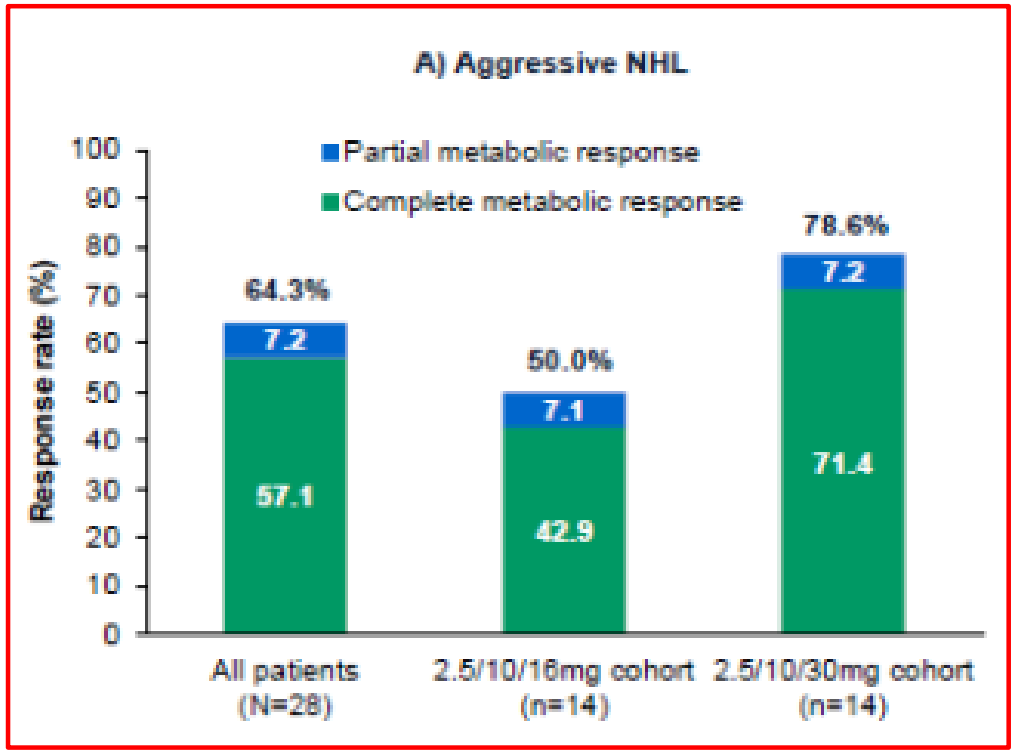
AEs with an incidence of ≥10%

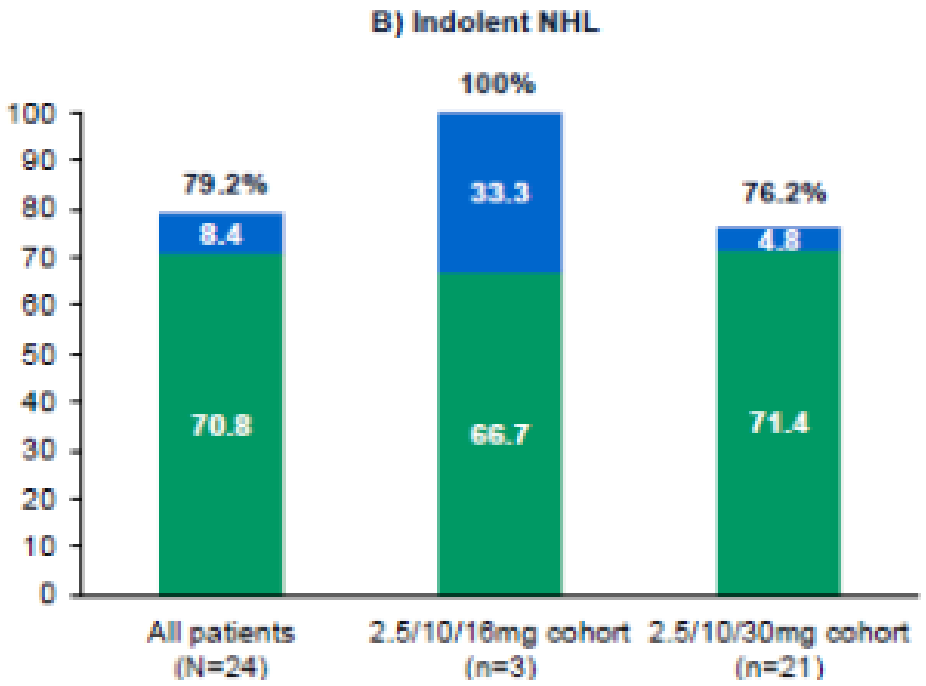


Hutchings M, et al. J Clin Oncol 2021;39(18):1959-1970.

High response to glofitamab was maintained with step-up dosing

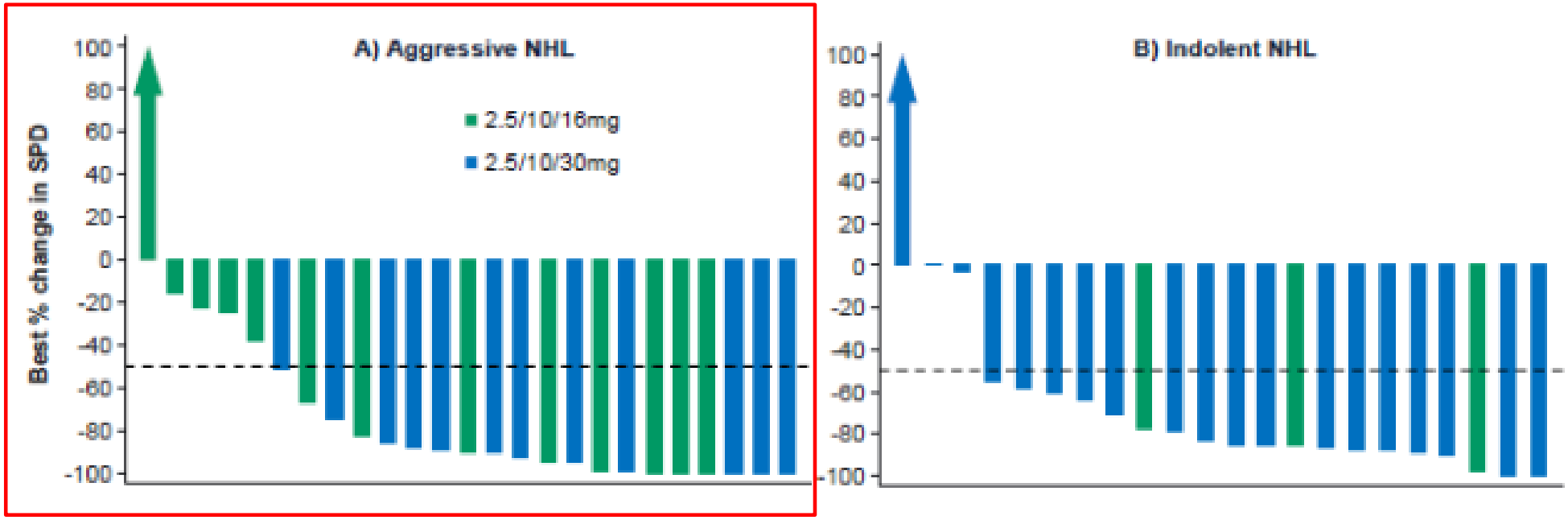
- For aggressive NHL, a trend of improved response was observed at the RP2D (2.5/10/30mg; N=14), with CMR rate of 71.4%
- 4/5 pts (80%) with mantle cell lymphoma achieved a CMR.





Hutchings M, et al. J Clin Oncol 2021;39(18):1959-1970.

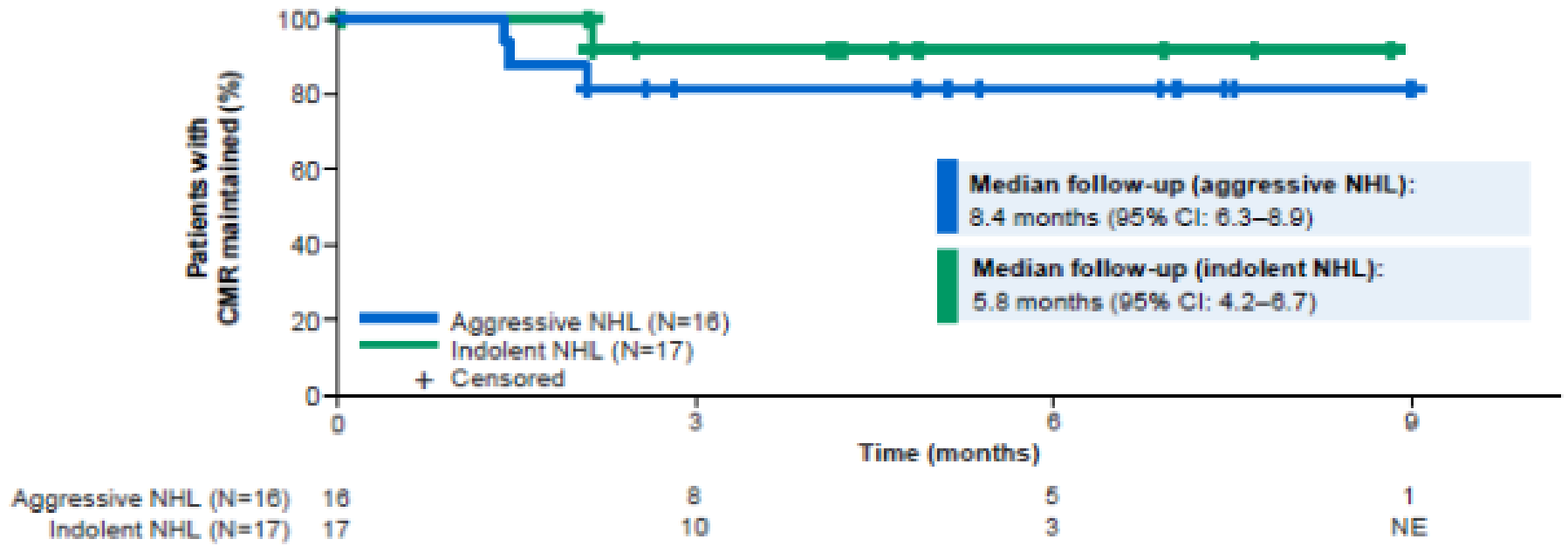
With glofitamab step-up dosing, antitumor activity was seen across NHL subtypes



Hutchings M, et al. J Clin Oncol 2021;39(18):1959-1970.

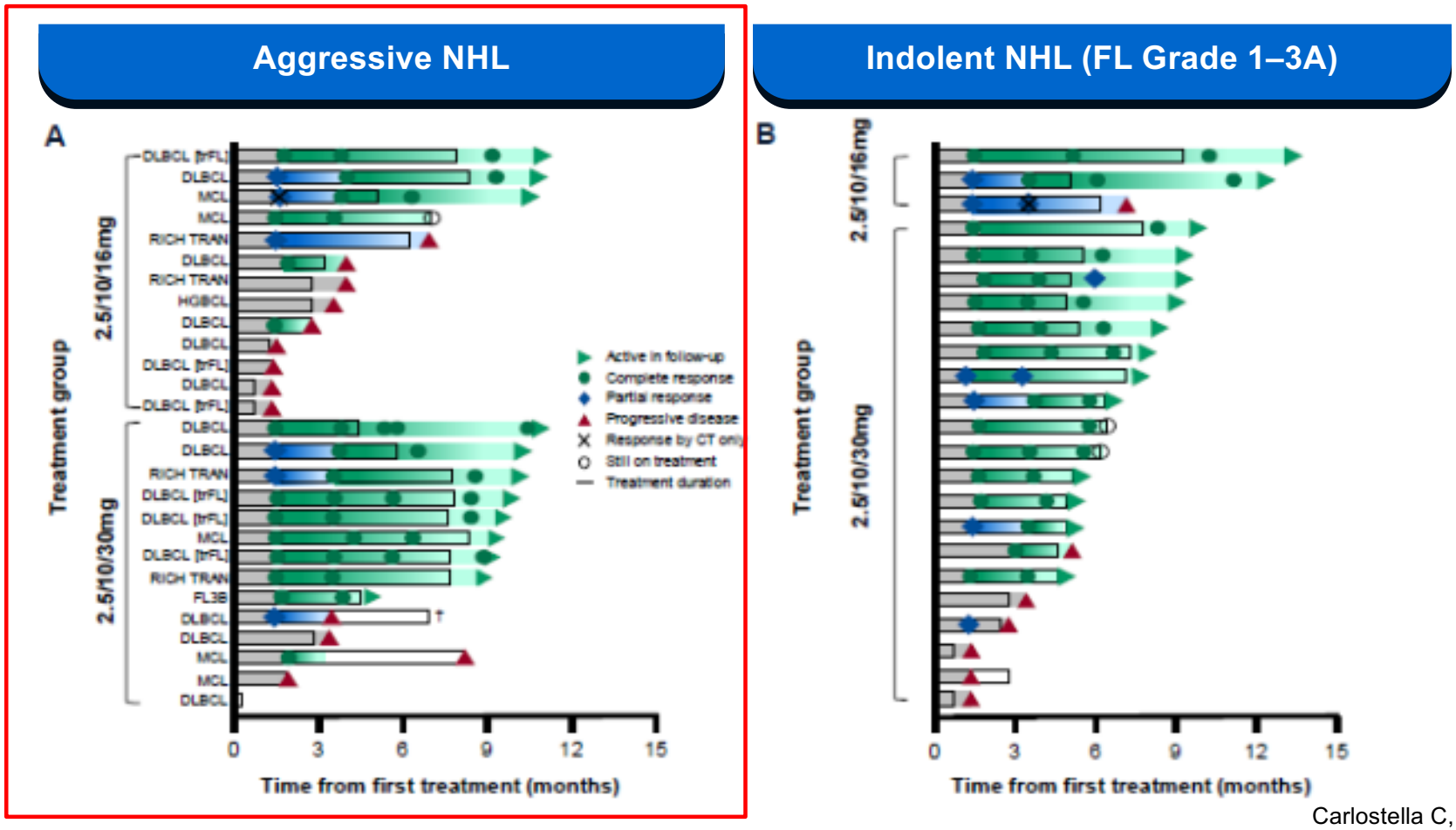
Most patients have ongoing responses

- Aggressive NHL: 13/16 CMRs are ongoing, 8 CMRs lasting >3 months; 5 CMRs lasting >6 months.
- Indolent NHL:16/17 CMRs are ongoing, 10 CMRs lasting >3 months; 3 CMRs lasting >6 months.



Carlostella C, et al. ASCO 2021

Time on initial treatment and response



Carlostella C, et al. ASCO 2021

Dose-escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study

Martin Hutchings, Rogier Mous, Michael Roost Clausen, Peter Johnson, Kim M Linton, Martine E D Chamuleau, David John Lewis, Anna Sureda Balari, David Cunningham, Roberto S Oliveri, Brian Elliott, Dena DeMarco, Ada Azaryan, Christopher Chiu, Tommy Li, Kuo-mei Chen, Tahamtan Ahmadi, Pieternella J Lugtenburg

The Lancet, published online 08 September 2021

Majority of Patients were heavily pre-treated and were refractory to their most recent line of therapy

	R/R DLBCL (n=46)	R/R FL (n=12)	All Histologies* (N=68)
Median age, years (range)	68 (21–82)	73 (35–84)	68 (21–84)
Median time since most recent relapse or progression, months (range)	1.5 (0–88)	1.6 (1–17)	1.6 (0–88)
Prior lines of therapy, median (range)	3 (1–6)	5 (1–18)	3 (1–18)
Prior therapies, n (%)			
Anti-CD20 mAb	46 (100)	12 (100)	68 (100)
Anthracyclines	46 (100)	9 (75)	62 (91)
Alkylating agents	46 (100)	12 (100)	67 (99)
Autologous stem cell transplant	5 (11)	1 (8)	7 (10)
CAR-T cell therapy	5 (11)	0	6 (9)
Refractory to, n (%)			
Most recent systemic therapy	42 (91)	10 (83)	59 (87)
Alkylating agents	40 (87)	9 (75)	56 (82)
CD20 mAbs	42 (91)	10 (83)	60 (88)

*Includes 10 patients with MCL, marginal zone lymphoma, or small lymphocytic lymphoma. Data cutoff: January 31, 2021.

1. Hutchings M, et al. Lancet, online ahead of print 08 September 2021. Data presented at ICML 2021.

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			

1. Hutchings M, et al. Lancet, online ahead of print 08 September 2021. Data presented at ICML 2021.

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

1. Hutchings M, et al. Lancet, online ahead of print 08 September 2021. Data presented at ICML 2021.

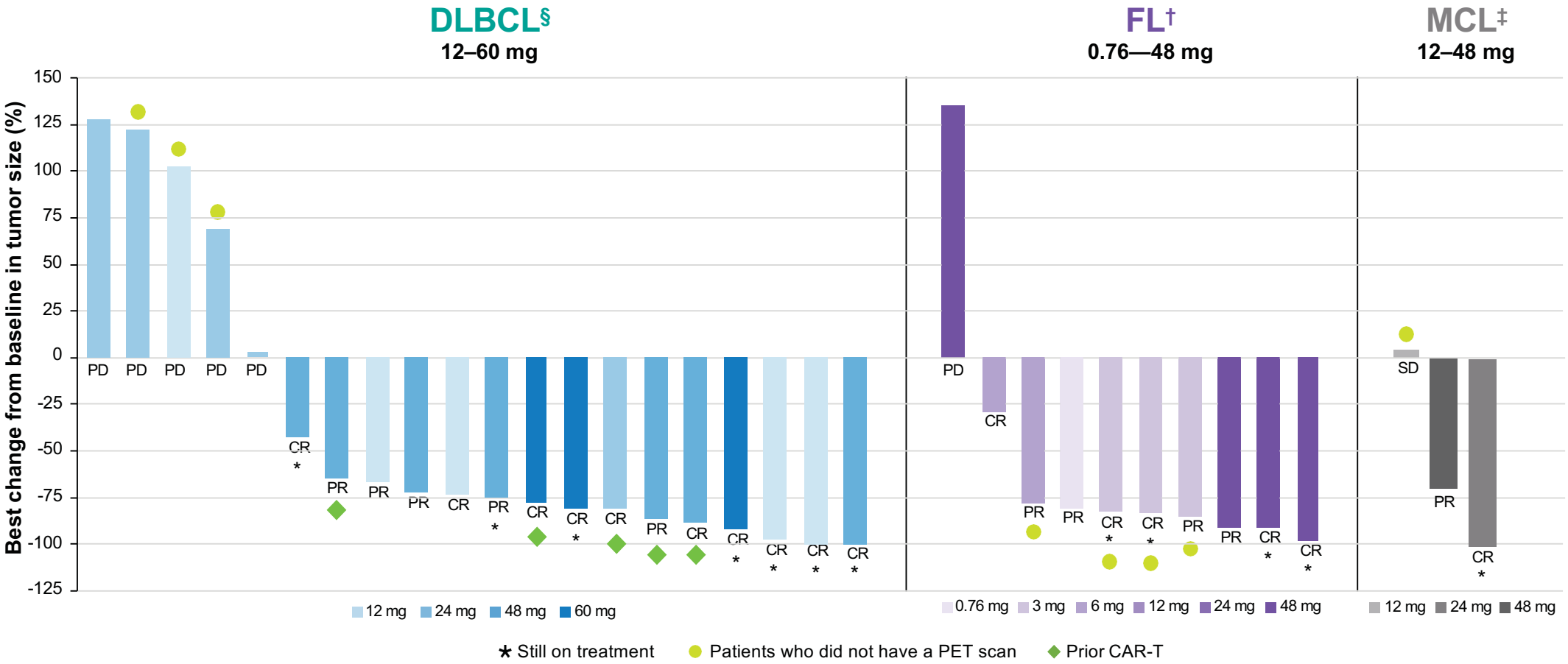
Responses to epcoritamab was seen across B-NHL histologies

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).

1. Hutchings M, et al. Lancet, online ahead of print 08 Sept 2021. Data presented at ICML 2021.

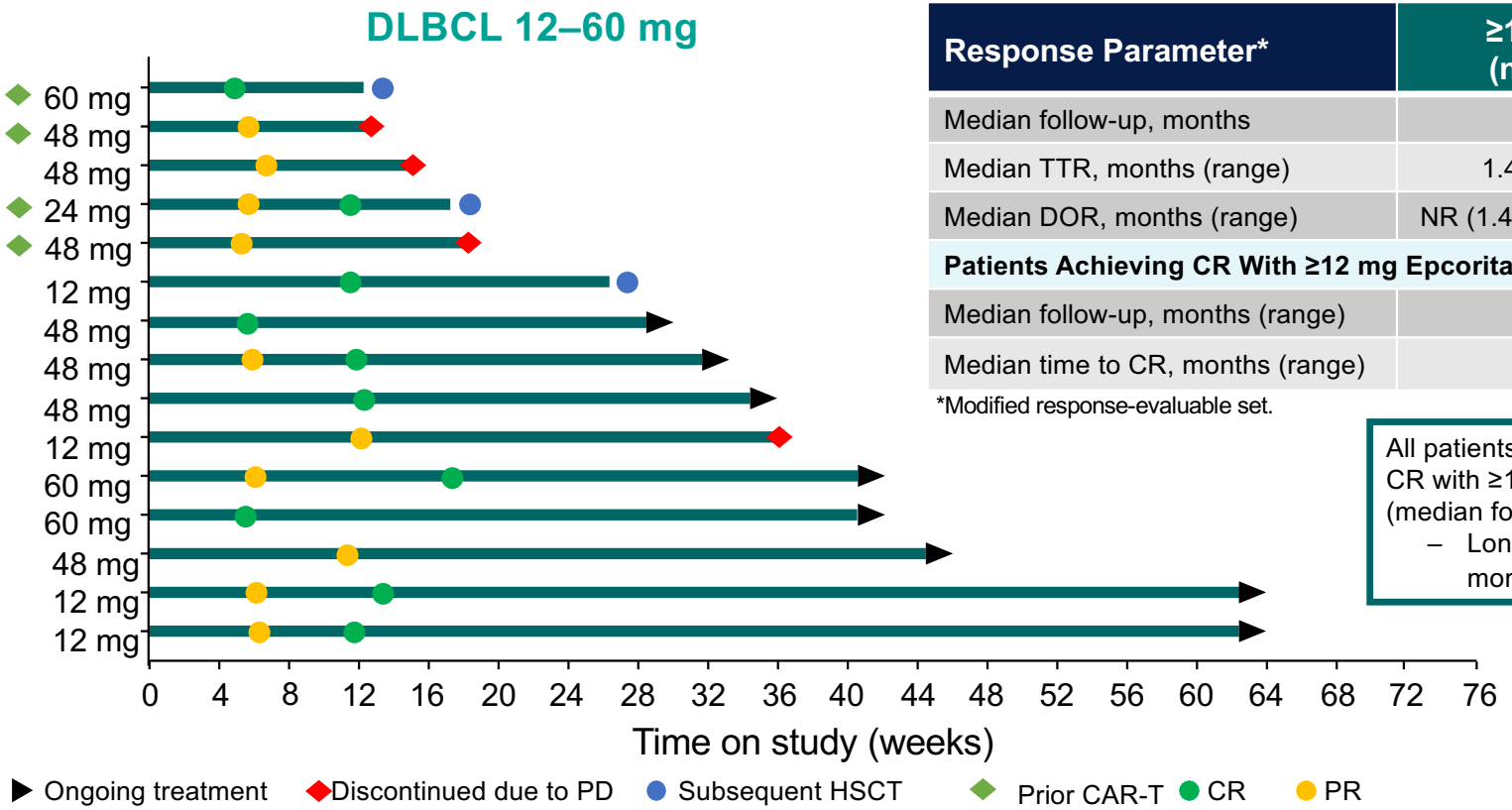
Anti-tumor activity of epcoritamab across major subtypes



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.

1. Hutchings M, et al. Lancet, online ahead of print 04 Sept 2021. Data presented at ICML 2021.

Response Profile in Patients With R/R DLBCL



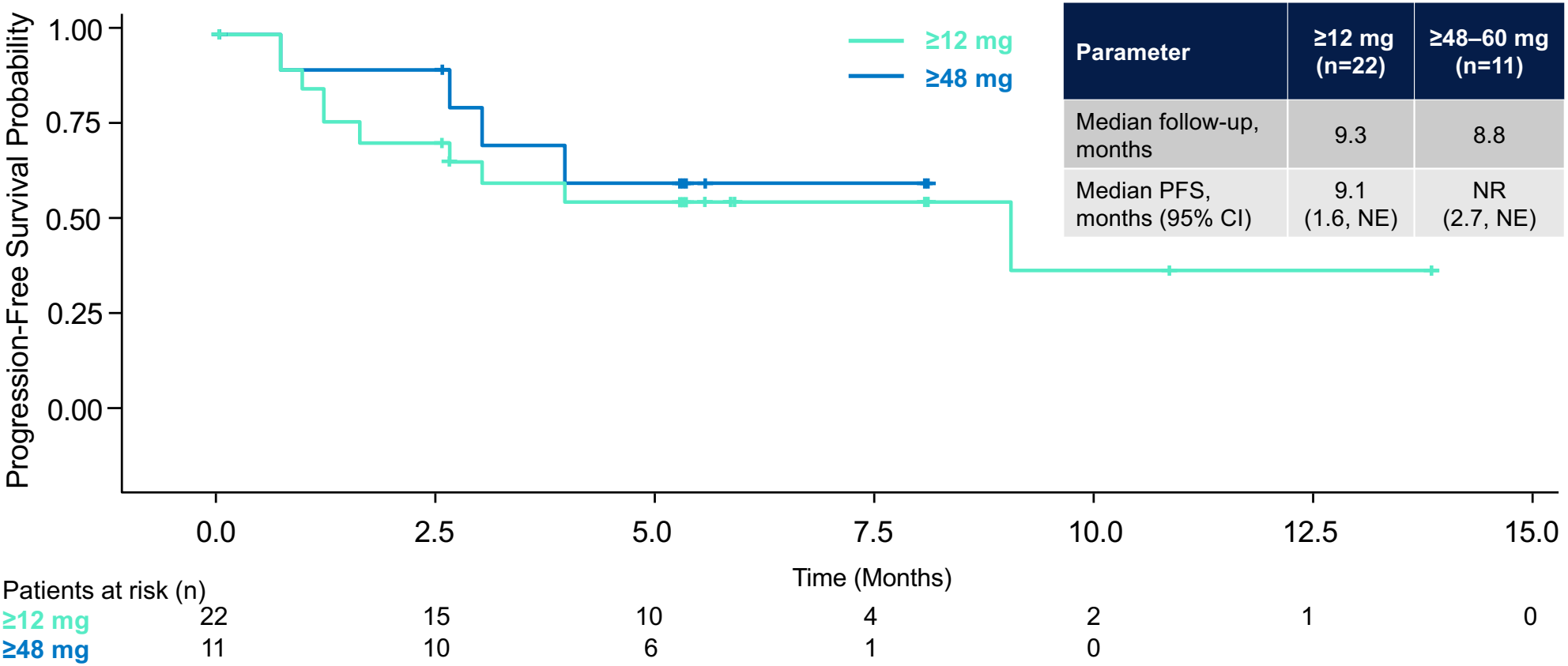
Response Parameter*	≥12 mg (n=22)	48-60 mg (n=11)
Median follow-up, months	9.3	8.8
Median TTR, months (range)	1.4 (1–4)	1.3 (1–3)
Median DOR, months (range)	NR (1.41+, 12.45+)	NR (1.41+, 12.45+)
Patients Achieving CR With ≥12 mg Epcoritamab		
Median follow-up, months (range)	9.23 (5.49+–14.78)	
Median time to CR, months (range)	2.7 (1.12–3.94)	

*Modified response-evaluable set.

All patients with R/R DLBCL who achieved CR with ≥12 mg doses remained in remission (median follow-up, 9.3 months)
- Longest duration of ongoing CR: 11.2+ months

1. Hutchings M, et al. Lancet, online ahead of print 08 September August 2021. Data presented at ICML 2021.

Progression-Free Survival in Patients With R/R DLBCL (≥ 12 mg)

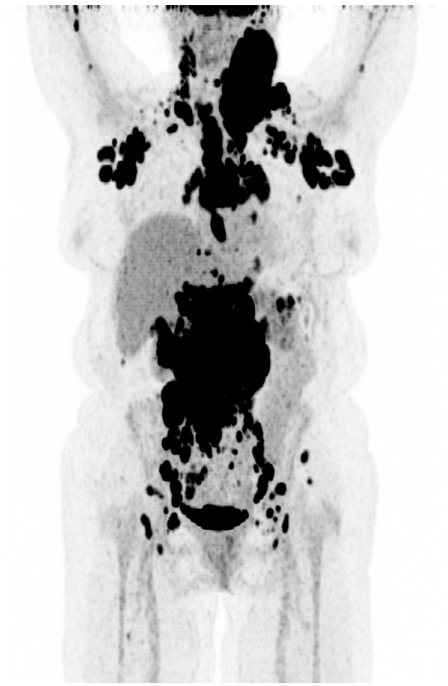


Parameter	≥12 mg (n=22)	≥48–60 mg (n=11)
Median follow-up, months	9.3	8.8
Median PFS, months (95% CI)	9.1 (1.6, NE)	NR (2.7, NE)

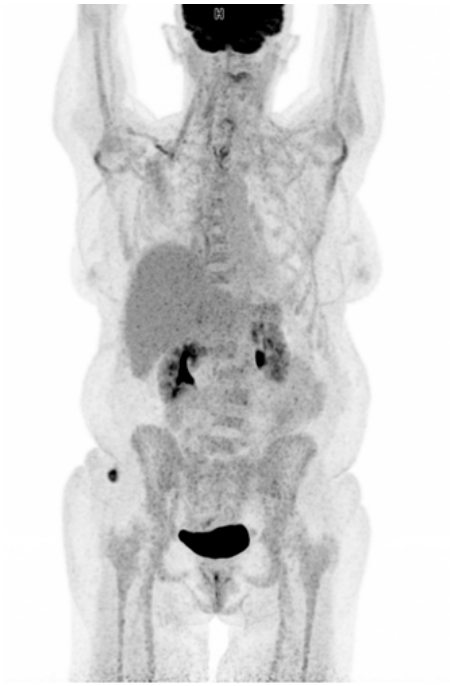
1. Hutchings M, et al. Lancet, online ahead of print 08 September 2021. Data presented at ICML 2021.

- 76-year old lady with Richter transformation
- 8 prior lines of treatment
- Refractory to the 3 most recent lines

Before treatment

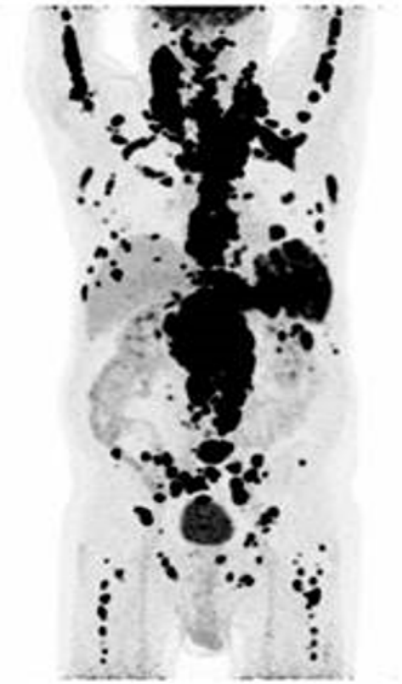


After 2 cycles = CR



- 69-year old man with non-GCB DLBCL
- 3 prior lines of treatment
- Refractory to the 2 most recent lines

Before treatment



After 2 cycles = PR

SUMMARY

- 20 years after the introduction of rituximab, the anti-CD19 antibody tafasitamab demonstrates high anti-lymphoma activity, particularly in combination with lenalidomide for treatment of r/r DLBCL
- The anti-CD79b ADC polatuzumab vedotin and the anti-CD19 ADC loncastuximab tesirine are promising agents for the treatment of r/r DLBCL
- Anti-PD1 and anti-PDL1 are mainly active in HL and PMBCL, but the 4-1BB agonist utomilumab and the anti-CD47 antibody magrolimab both enhance the activity of rituximab in r/r B-NHL and could be useful companions in other combinations
- The CD3/CD20 bispecific antibodies are probably the most active drugs ever seen in r/r B-NHL and their toxicity profile make them eligible for combinations with most other classes of drugs, including combination chemotherapy
    - Most AEs occur during the first two cycles of treatment
    - Very little CRS > grade 2
    - Very little treatment-related CNS toxicity > grade 2


THANK YOU