New Advances in Aggressive Lymphomas beyond CAR-T cell therapy

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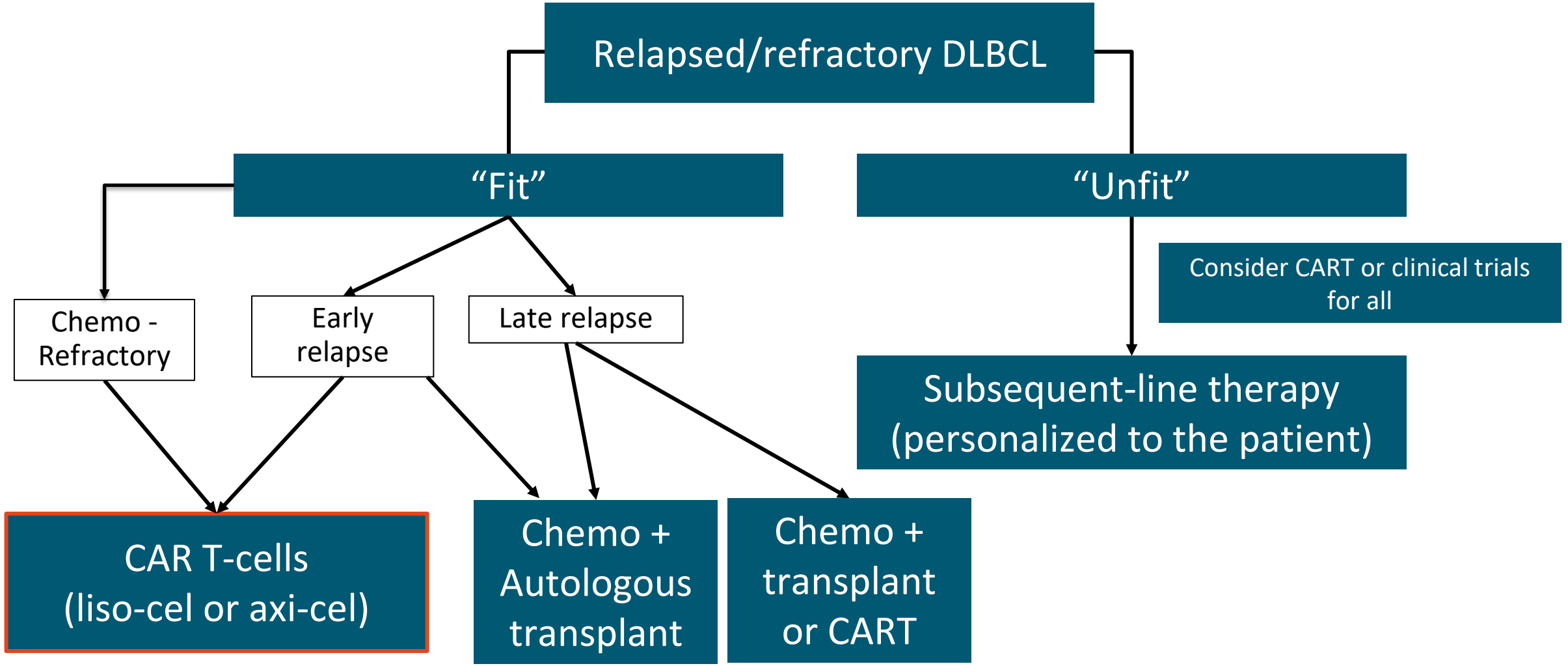
DISCLOSURES

Consultancy: Genentech, Astrazeneca, Abbvie, Janssen, Pharmacyclics, Gilead sciences, Kite pharma, Celgene, Karyopharm, MEI Pharma, Verastem, Incyte, Beigene, Johnson and Johnson, Dava Oncology, BMS, Merck, Epizyme, Cardinal Health, ADCT therapeutics, Epizyme

Principles

- Improved outcomes
  - Survival vs Progression
- Limited Toxicity

Current Paradigm



Recent Advances

- Chemotherapy Add On
- Targeted therapies
- BITEs

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Polatuzumab Vedotin + BR vs BR for R/R DLBCL

- Polatuzumab vedotin: antibody-drug conjugate targeting CD79b with a toxic payload (MMAE)

Phase II trial

Stratified by DoR to last Tx (≤12 vs >12 mo)

≤6 21-day cycles

Pts with histologically confirmed R/R DLBCL, received ≥ 1 prior tx, ECOG PS 0-2, ineligible for SCT, no grade IIIb FL, no transformed DLBCL, no CNS lymphoma, no prior allo HSCT, no auto HSCT within 100 days
(N = 80)

Polatuzumab vedotin 1.8 mg/kg, D1 of each cycle +
Bendamustine 90 mg/m^2 on D1,3 (C1), then D1,2 (each cycle) +
Rituximab 375 mg/m^2, D1 (each cycle)
(n = 40)

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Rituximab 375 mg/m^2, D1 (each cycle)
(n = 40)

- Primary endpoints: CR rate (PET-CT)
- Key secondary endpoints: ORR at EOT, DoR, PFS

Sehn. JCO. 2020;38:155.

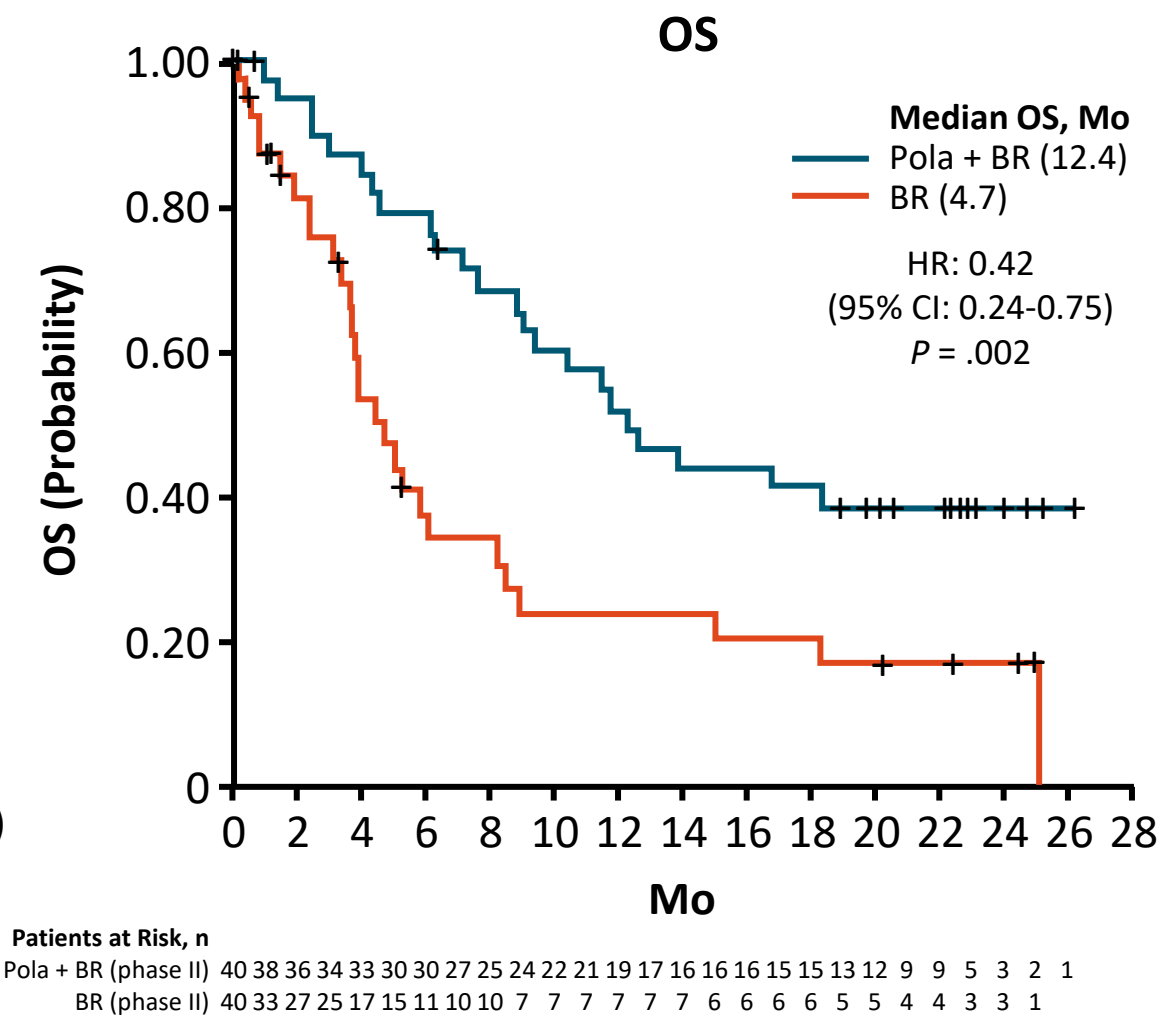
Polatuzumab Vedotin + BR vs BR in R/R DLBCL: Efficacy

Phase II Trial

Baseline Characteristic	BR (n = 40)	Pola + BR (n = 40)
Median age, yr (range)	71 (30-84)	67 (33-86)
IPI ≥3, n (%)	29 (73)	22 (55)
Median prior tx, no (range)	2 (1-5)	2 (1-7)
Prior BMT, n (%)	6 (15)	10 (25)

Response, %	BR (n = 40)	Pola + BR (n = 40)
CR	17.5	40.0
Median PFS, mo	3.7	9.5

- Consider in:
  - Nontransplant/non–CAR-T patient
  - Bridging therapy prior to CAR-T (caution with bendamustine)
  - Post CAR-T failure (caution with bendamustine)



Sehn. JCO. 2020;38:155.

Recent Advances

- Chemotherapy Add On

- Targeted therapies

- BITEs

L-MIND: Phase II Study of Tafasitamab + Len in R/R DLBCL

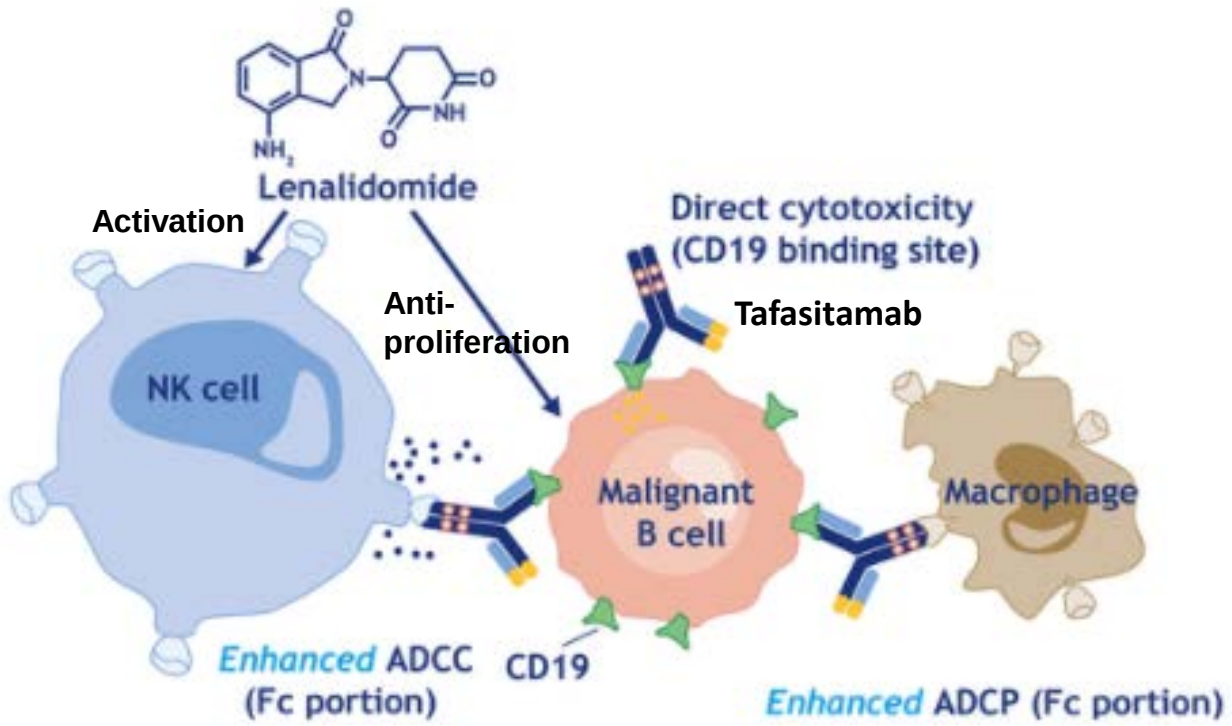
Patients with R/R DLBCL;
1-3 prior regimens
(≥1 anti-CD20); ECOG PS 0-2;
ineligible for HDT/ASCT;
primary refractory excluded
(N = 81)

→ **Lenalidomide** 25 mg/d PO, D1-21 x ≤12 28-d cycles
Tafasitamab 12 mg/kg/wk IV, cycles 1-3 (Q4W; D1,8,15,22)
(+ additional loading dose C1, D4) and C4-12 (Q4W, D1,15)

If no PD after 12 cycles →

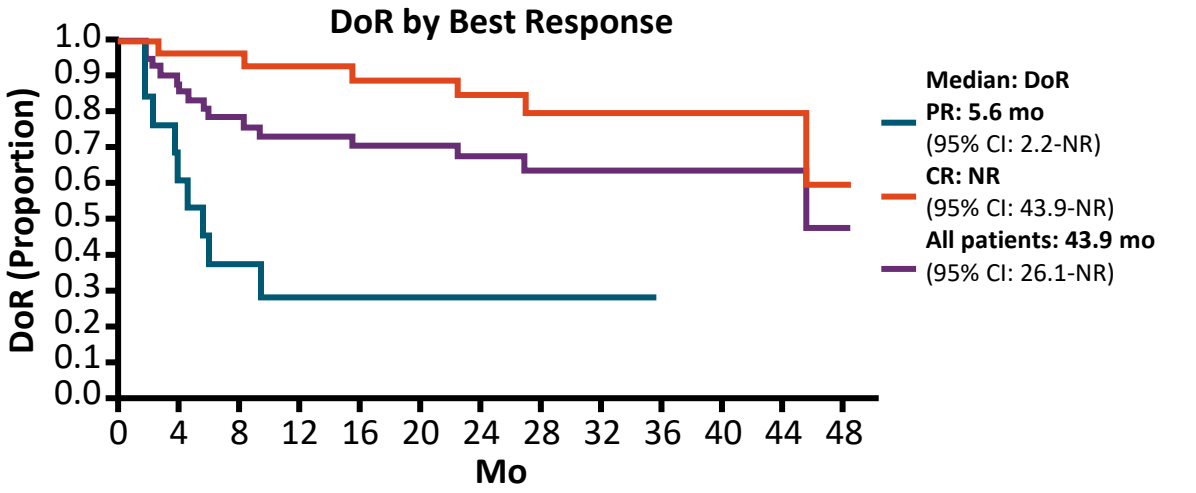
Tafasitamab
12 mg/kg/wk
D1,15 until PD

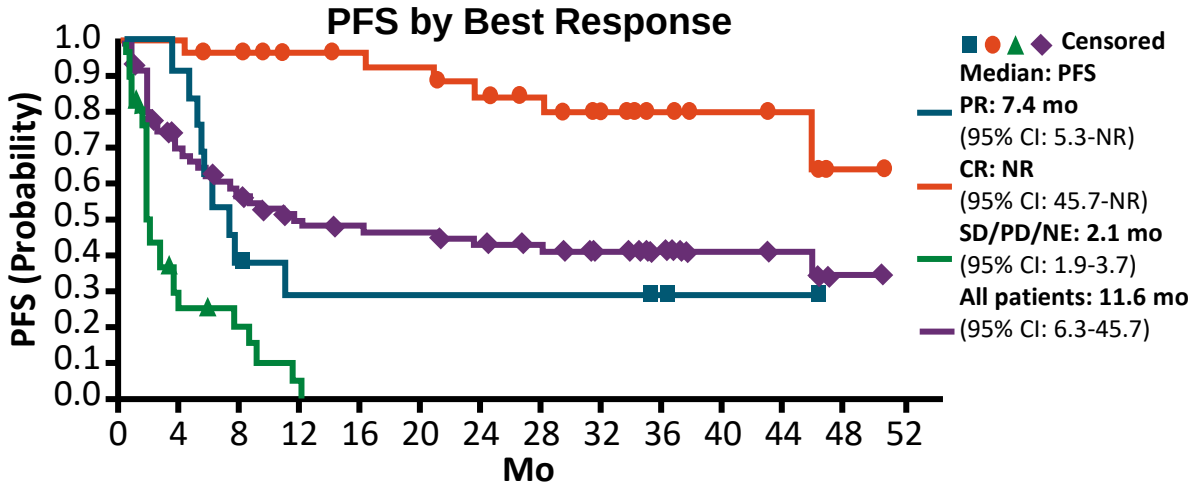
Baseline Characteristics	N = 81
Median age, yr (range)	72 (41-87)
IPI 3-5, n (%)	42 (52)
Median prior tx, n (range)	2 (1-4)
Refractory to previous line, n (%)	34 (42)

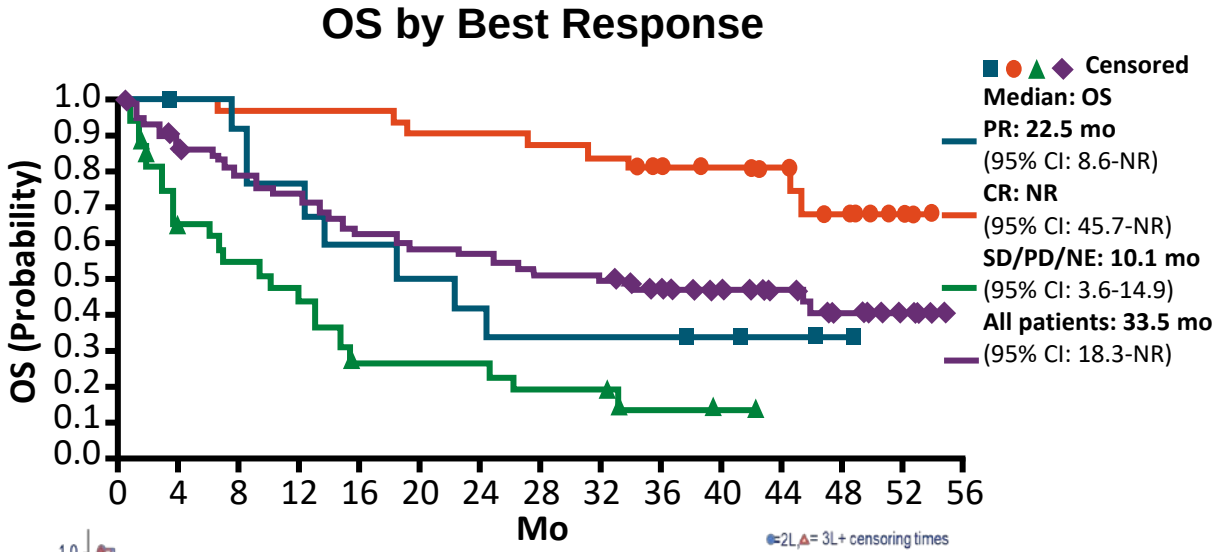


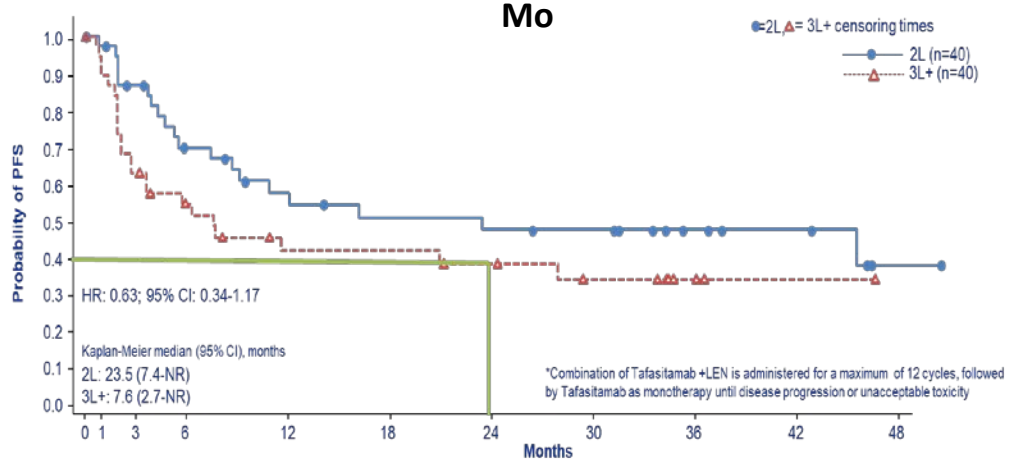
Salles. Lancet Oncol. 2020;21:978.

L-MIND 3-Yr Update: Tafasitamab + Lenalidomide in R/R DLBCL







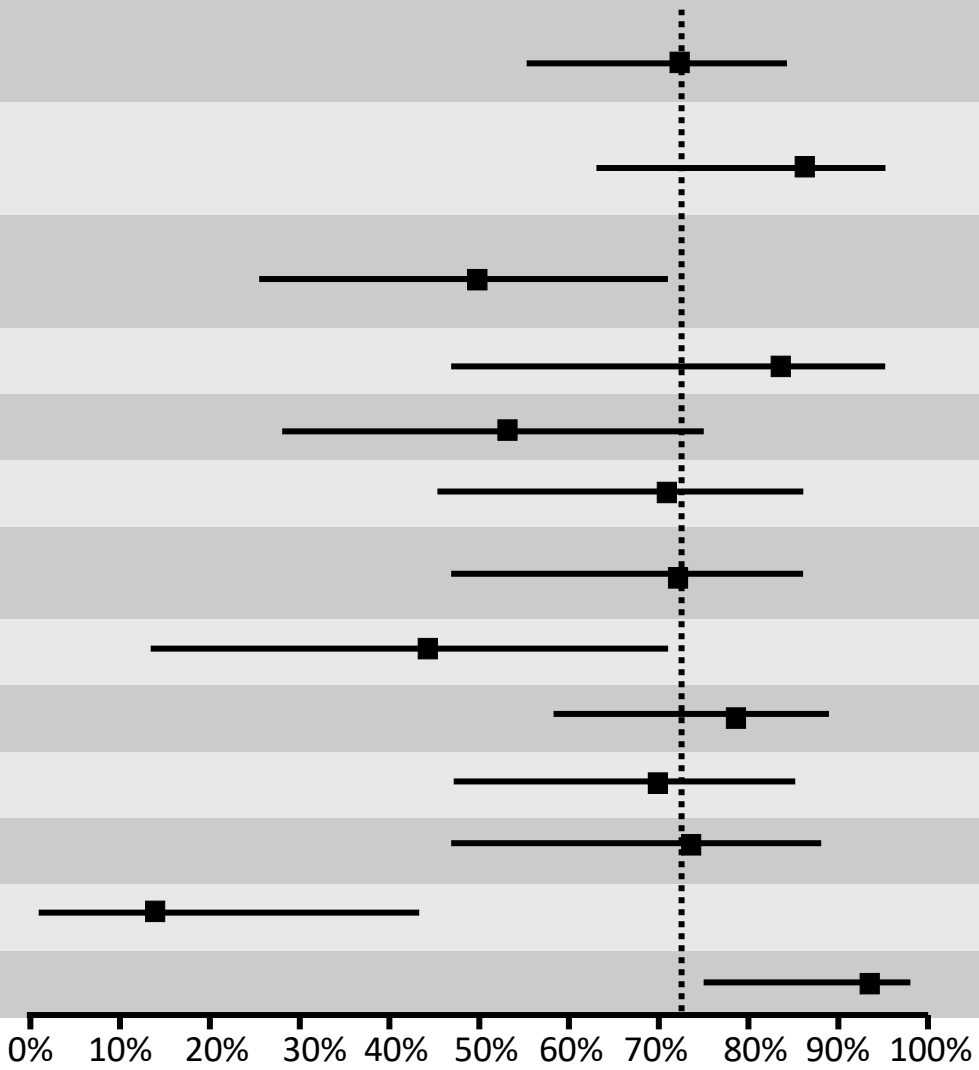


- ORR: 58% (40% CRs)
  - Median DoR: 43.9 mo

Dull. ASCO 2021. Abstract 7513.

L-MIND: 12-Month DoR by Subgroup

Subgroup		n	12-month duration of response (%) (95% CI)	12-month rate (%)	95% CI
Responders in the FAS		48		72	55-83
IPI score	Low risk and low-intermediate risk	28		87	63-96
	Intermediate-high risk and high risk	20		50	26-71
Cell or origin phenotype	Non-GCB	15		83	47-96
	GCB	18		53	28-74
Refractoriness to last prior therapy	Yes	21		71	46-86
	No	27		72	47-86
Primary refractory	Yes	9		44	14-72
	No	39		78	59-89
No. of prior lines	1	28		70	47-85
	> 2	20		73	46-88
BOR (CR or PR only)	PR	14		14	1-44
	CR	34		93	75-98



Salles. Lancet Oncol. 2020;21:978.

LOTIS-2 Phase II Study of Loncastuximab Tesirine (Anti-CD19 ADC) in R/R Aggressive DLBCL

Patients with relapsed/refractory DLBCL (N = 145)

Treat for ≤1 yr

Loncastuximab tesirine 150 µg/kg Q3W (C1-2) then 75 µg/kg (C3+); 30-min infusion

Responders

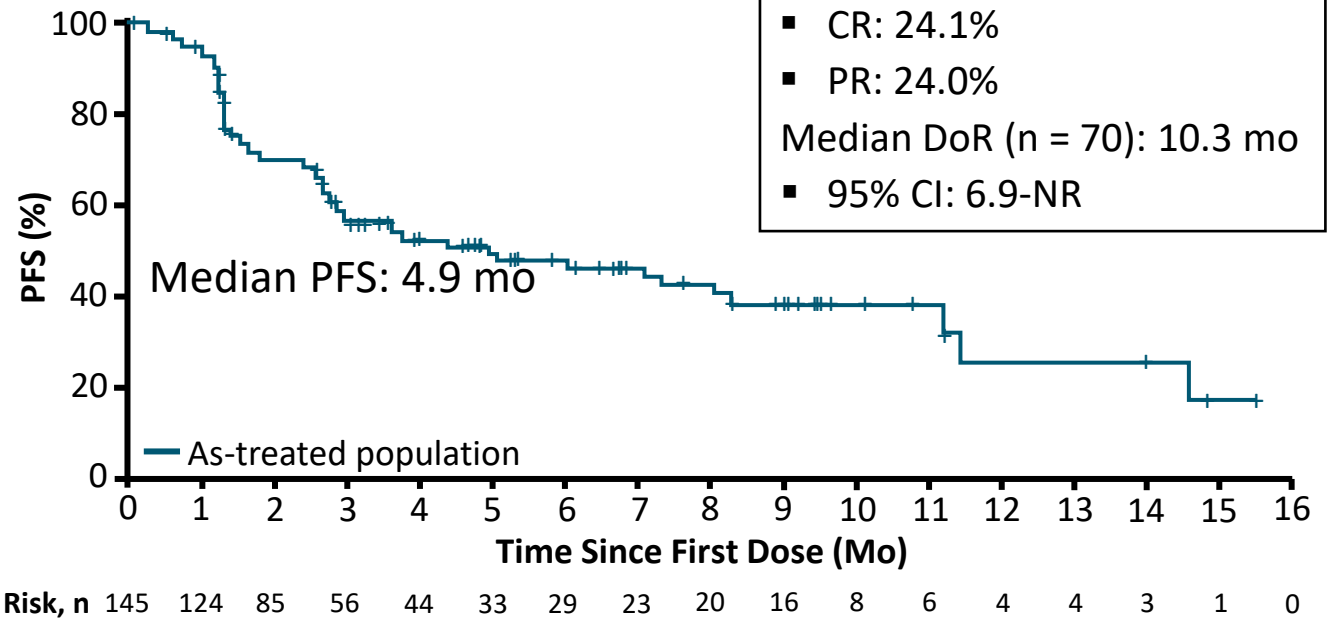
Treat for ≤3 yr

Loncastuximab tesirine Q3W

Baseline Characteristic	N = 145
Median age, yr (range)	66 (23-94)
Histology, n (%) ▪ DLBCL NOS ▪ HGBCL ▪ PMBCL	 127 (88) 11 (8) 7 (5)
Median prior tx (IQR)	3 (2-4)
Relapsed to prior tx, n (%)	43 (30)
Refractory to prior tx, n (%)	84 (58)
Prior CAR T-cells, n (%)	13 (9)

ORR: 48.3%
- CR: 24.1%
- PR: 24.0%

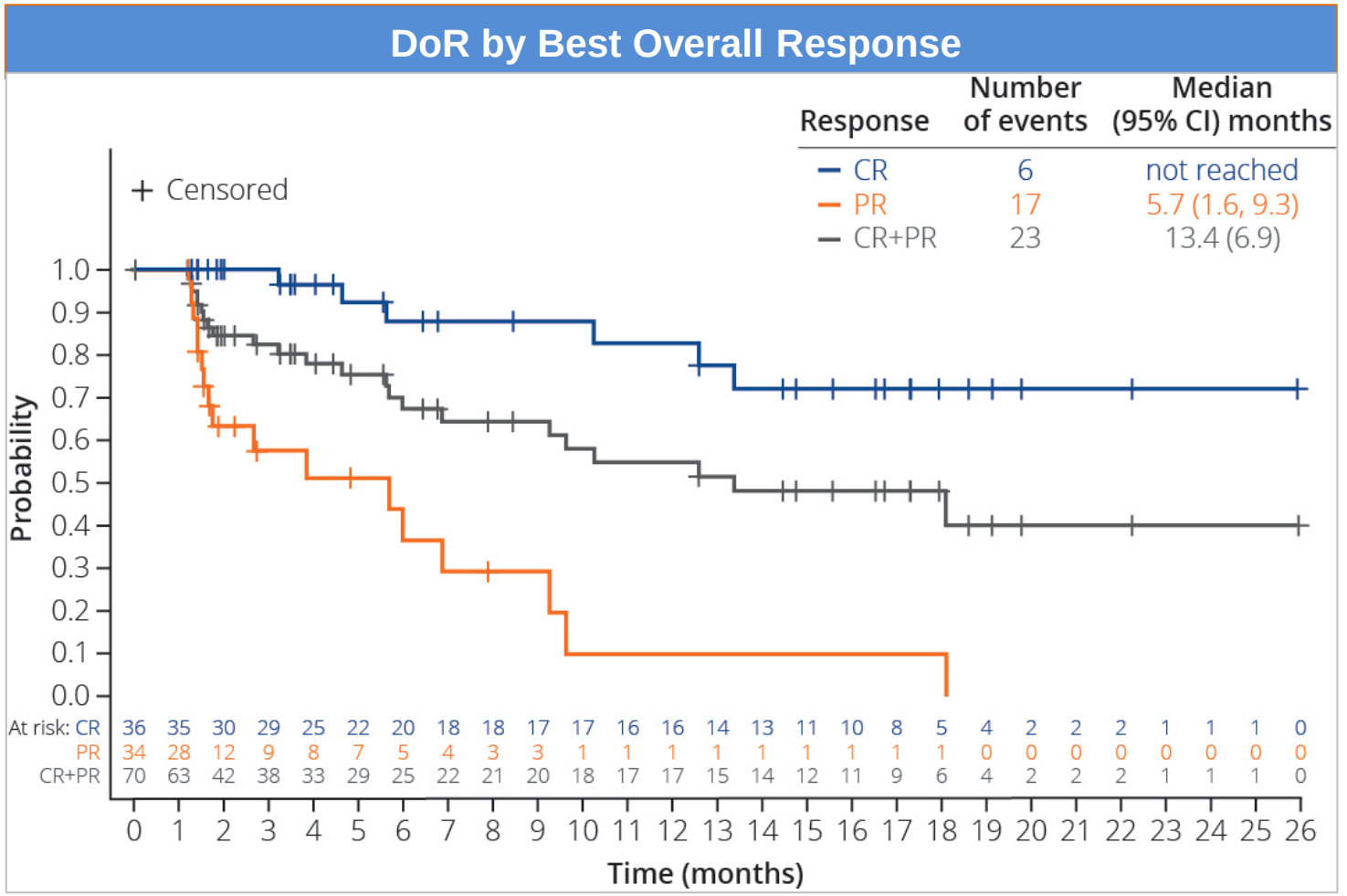
Median DoR (n = 70): 10.3 mo
- 95% CI: 6.9-NR



- Key toxicities: GGT increase, cytopenias, fatigue, nausea/vomiting, edema (requires dex x 3 days, starting day prior)

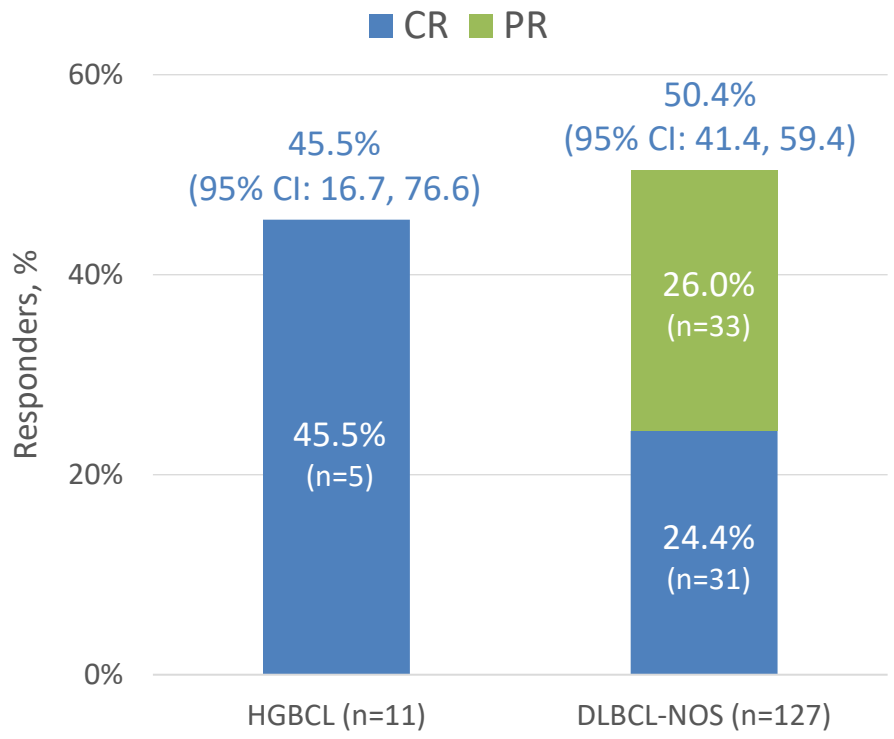
Caimi. Lancet Oncol. 2021;22:790.

LOTIS-2 Phase II Study of Loncastuximab Tesirine (Anti-CD19 ADC) in R/R Aggressive DLBCL



LOTIS-2: High-Grade BCL and Sequencing Around CAR T-Cell Therapy

HGBCL/DLBCL NOS Response Rates[1]



Lonca After CAR T-Cell Therapy Relapse[2]

		n=13
Best response to CAR T-cell therapy, n (%)	CR	7 (54)
	PR	2 (15)
	No response	4 (31)
Best response to Lonca post CAR T-cell therapy[a], n (%)	CR	2 (15)
	PR	4 (31)
	SD	1 (8)
	PD	2 (15)

CAR T-Cell Therapy After Lonca Failure[3]

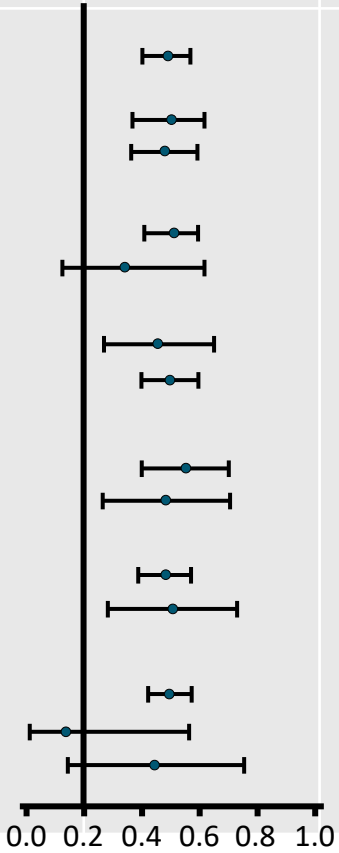
		n=14
Best response to Lonca, n (%)	CR	1 (7)
	PR	5 (36)
	Refractory	8 (57)
Best response to CAR T-cell therapy post Lonca, n (%)	CR	6 (43)
	PR	1 (7)
	Refractory	7 (50)

[a] 4 patients were not evaluable (30.8%).

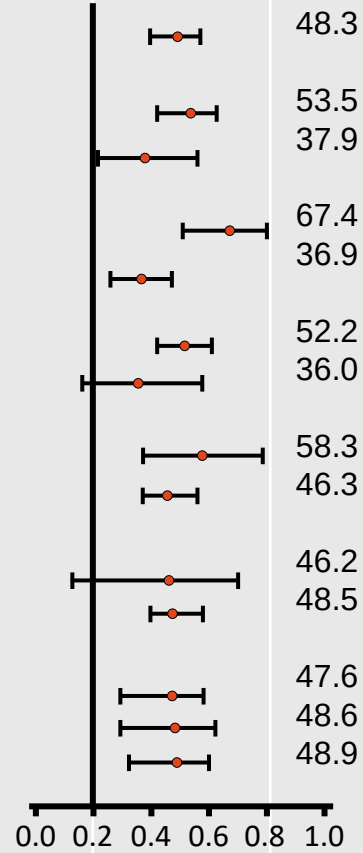
1. Alderuccio J, et al. ASH 2021. Abstract 3575. 2. Caimi PF, et al. *Clin Lymphoma Myeloma Leuk*. 2021 Nov 12:S2152-2650(21)02437-X. Online ahead of print. 3. Thapa et al. *Blood Adv*. 2020;4(16):3850-3852.

LOTIS-2 Loncastuximab Tesirine in R/R Aggressive DLBCL: ORR by High-Risk Subgroup

Subgroup	Patients (n/N)	ORR	ORR (95% CI)
All	70/145		48.3 (39.9, 56.7)
Age			
▪ <65 yr	32/65		49.2 (36.6, 61.9)
▪ ≥65 yr	38/80		47.5 (36.2, 59.0)
Double/triple hit			
▪ No	65/130		50.0 (41.1, 58.9)
▪ Yes	5/15		33.3 (11.8, 61.6)
Transformed disease			
▪ Transformed	13/29		44.8 (26.4, 64.3)
▪ De novo	57/116		49.1 (39.7, 58.6)
Cell of origin			
▪ GCB	26/48		54.2 (39.2,68.6)
▪ ABC	11/23		47.8 (26.8, 69.4)
Double/triple expressor			48.0 (39.0, 57.1)
▪ No	60/125		50.0 (27.2, 72.8)
▪ Yes	10/20		
WHO classification			50.4 (41.4, 59.4)
▪ DLBCL NOS	64/127		14.3 (0.4, 57.9)
▪ PMBCL	1/7		45.5 (16.7, 76.6)
▪ HGBCL	5/11		

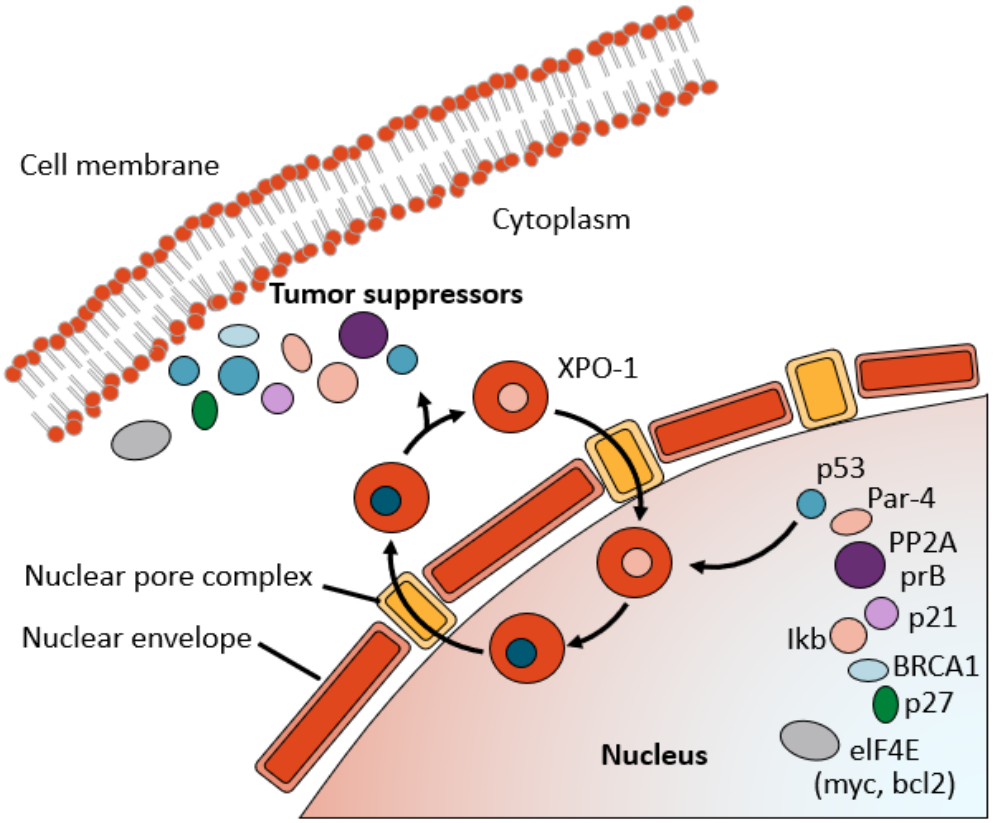


Subgroup	Patients (n/N)	ORR	ORR (95% CI)
All	70/145		48.3 (39.9, 56.7)
Age-line response*			
▪ Relapse	53/99		53.5 (43.2, 63.6)
▪ Refractory†	11/29		37.9 (20.7, 57.7)
Last-line response*			
▪ Relapse	29/43		67.4 (51.5, 80.9)
▪ Refractory†	31/84		36.9 (26.6, 48.1)
Response to any prior line			52.2 (42.7. 61.6)
▪ Relapse	60/115		36.0 (18.0, 57.5)
▪ Refractory†	9/25		
Prior stem cell transplant			58.3 (36.6, 77.9)
▪ Yes	14/24		46.3 (37.2, 55.6)
▪ No	56/121		46.2 (19.2, 74.9)
Prior CAR-T Therapy			48.5 (39.7, 57.3)
▪ Yes	6/13		
▪ No	64/132		47.6 (34.9, 60.6)
Prior systemic therapies			48.6 (31.4, 66.0)
▪ 2 prior lines	30/63		48.9 (34.1, 63.9)
▪ 3 prior lines	17/35		
▪ >3 prior lines	23/47		



Caimi. ASH 2020. Abstract 1183.

Selinexor—Third-line Relapsed DLBCL: Mechanism of Action



- XPO1 is the major nuclear export protein for:
  - TSPs (eg, p53, IkB, and FOXO)
  - eIF4E-bound oncoprotein mRNAs (eg, c-Myc, Bcl-xL, cyclins)
- Selinexor is an oral selective XPO1 inhibitor; preclinical data support that XPO1 inhibition:
  - Reactivates multiple TSPs relevant to NHL, including p53, p21, IkB, and FOXO
  - Promotes nuclear localization of eIF4e, which is overexpressed in most B-cell lymphomas
  - Reduces c-Myc, Bcl-2, and Bcl-6 levels
  - Toxicities: GI toxicities may be prohibitive

Theodoropoulos. Target Oncol. 2020;15:697.

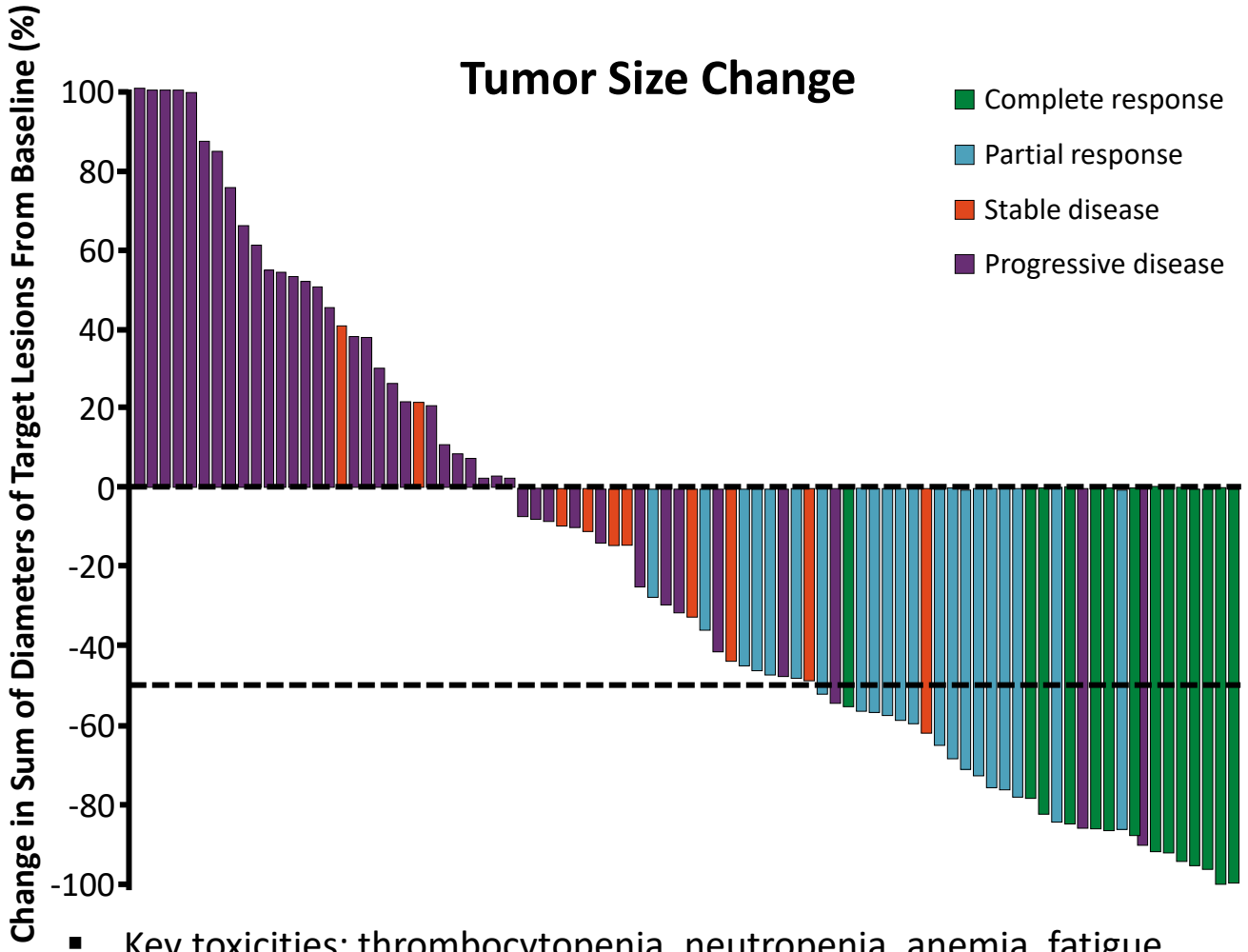
SADAL Phase II Study of Selinexor (XPO1 Inhibitor) in R/R DLBCL

Patients with R/R DLBCL; 2-5 prior lines; ≥60 days from last tx if PR or CR, otherwise ≥98 days (N = 127)

→ **Selinexor** 60 mg PO twice weekly until PD or unacceptable toxicity

Baseline Characteristic	N = 127
Median prior tx (range)	2 (2-5)

Responses	N = 145
ORR, %	28
CR, %	12
PR, %	17
Median DoR, mo	9.3
Median PFS, mo	2.6



- Key toxicities: thrombocytopenia, neutropenia, anemia, fatigue, hyponatremia, nausea

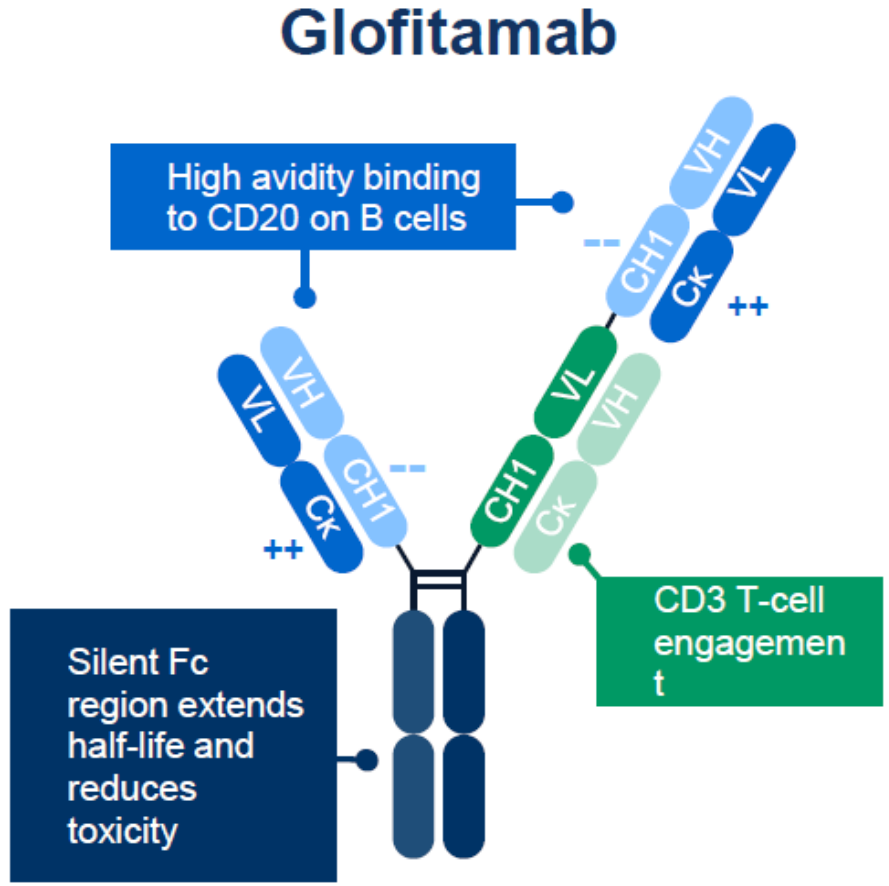
Kalakonda. Lancet Haematol. 2020;7:e511.

Recent Advances

- Chemotherapy Add On
- Targeted therapies
- BITEs

Glofitamab: A Bispecific Antibody Targeting CD3 and CD20 in 2:1 Ratio

- **CD3/CD20 bispecific antibody for DLBCL**
- Unique 2:1 molecular configuration allows "double binding" to CD20 (highlighted in the blue zones)
- Advantages of the 2:1 design
  - Associated with superior potency under experimental conditions compared with 1:1 binding bispecifics
  - Allows concomitant treatment with anti-CD20 antibodies—predosing

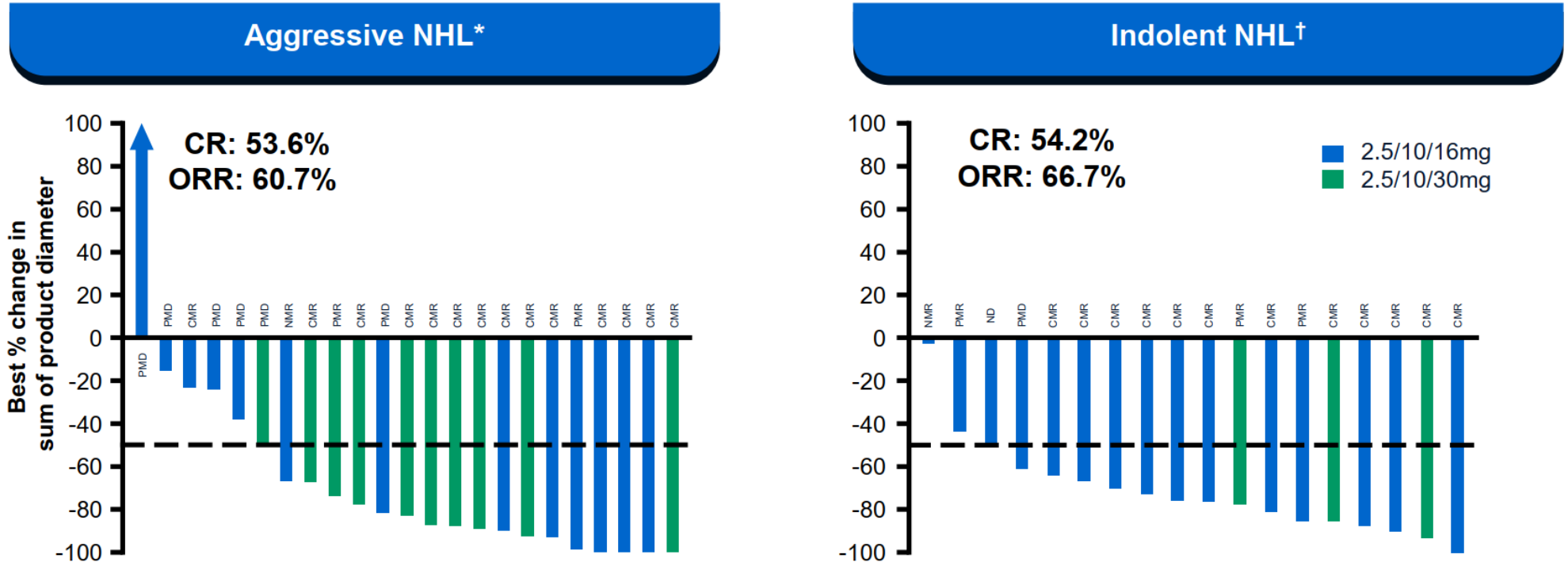


Dickinson. EHA 2020. Abstr S241.

Phase I Dose Escalation Study: Glofitamab Step-up Dosing Shows Promising Activity Across NHL Subtypes

Although 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 ≥10 mg fixed-dosing vs 30.7% in the step-up dosing cohort)

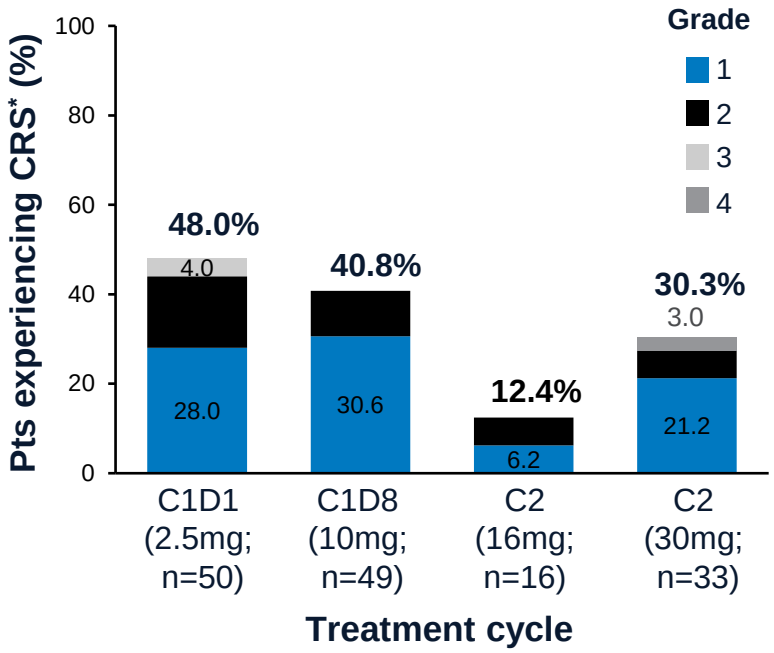
Glofitamab Step-up Dosing 2.5/10/16 mg or 2.5/10/30 mg



Hutchings. ASH 2020. Abstr 403. Dickinson. EHA 2020. Abstr S241.

Summary of AEs

CRS[1] by dose, cycle and grade



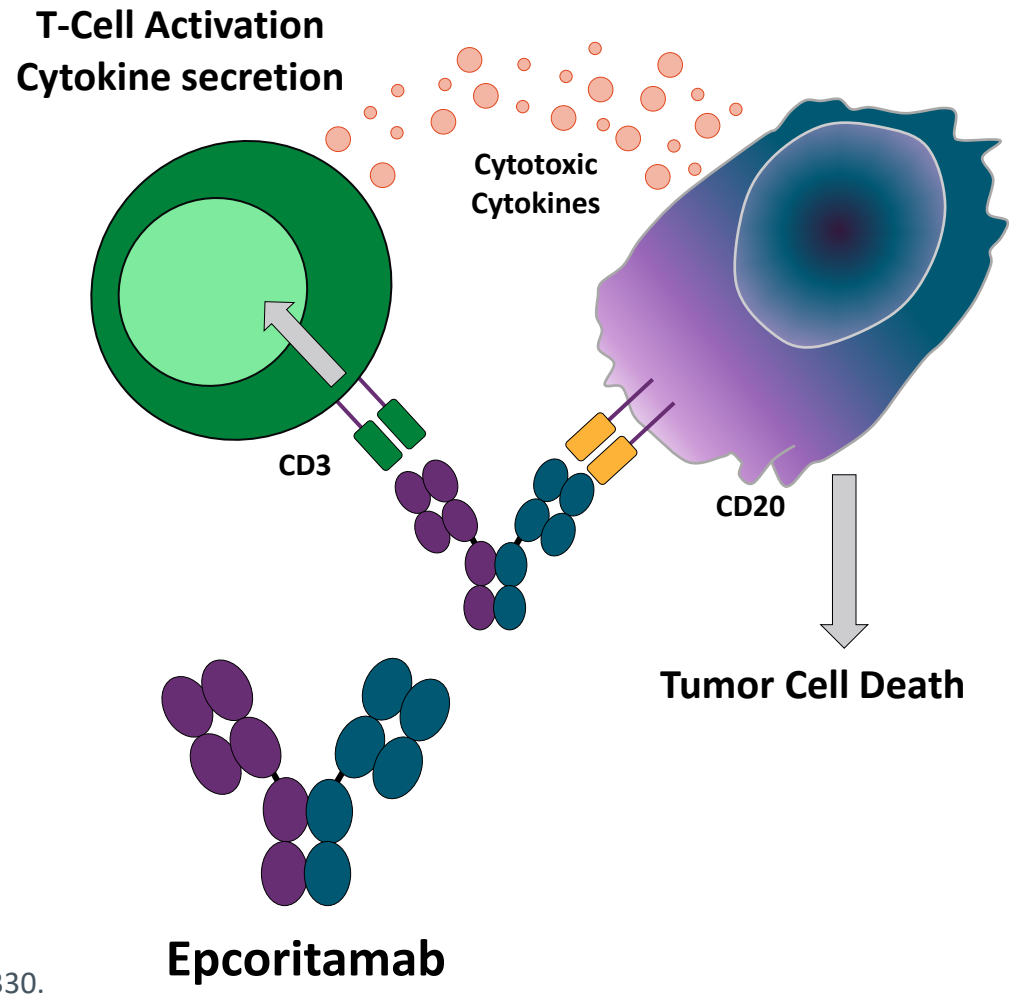
n (%)	All pts (N=52)
CRS	35 (67.3)
Grade 1	20 (38.5)
Grade 2	12 (23.1)
Grade 3	2 (3.8)
Grade 4	1 (1.9)
Grade 5	0

n (%)	All pts (N=52)
Any AE	51 (98.1)
Treatment related	47 (90.4)
Serious AE	32 (61.5)
Treatment related	29 (55.8)
Grade 3–4 AE	31 (59.6)
Treatment related	21 (40.4)
Grade 5 (fatal) AE	0
AE leading to treatment discontinuation	2 (3.8)
Treatment related†	2 (3.8)

Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

Epcoritamab: Subcutaneously Administered CD3 x CD20 Bispecific Antibody

- Epcoritamab: novel subcutaneously administered CD3 x CD20 bispecific antibody
  - Induces T-cell activation by binding to CD3 on T-cells and CD20 on malignant B-cells
  - Promotes immunologic synapse between bound cells, resulting in apoptosis of B-cells
  - Binds to a distinct epitope on CD20 differently from epitopes of rituximab or obinutuzumab
  - Retains activity in the presence of CD20 mAbs



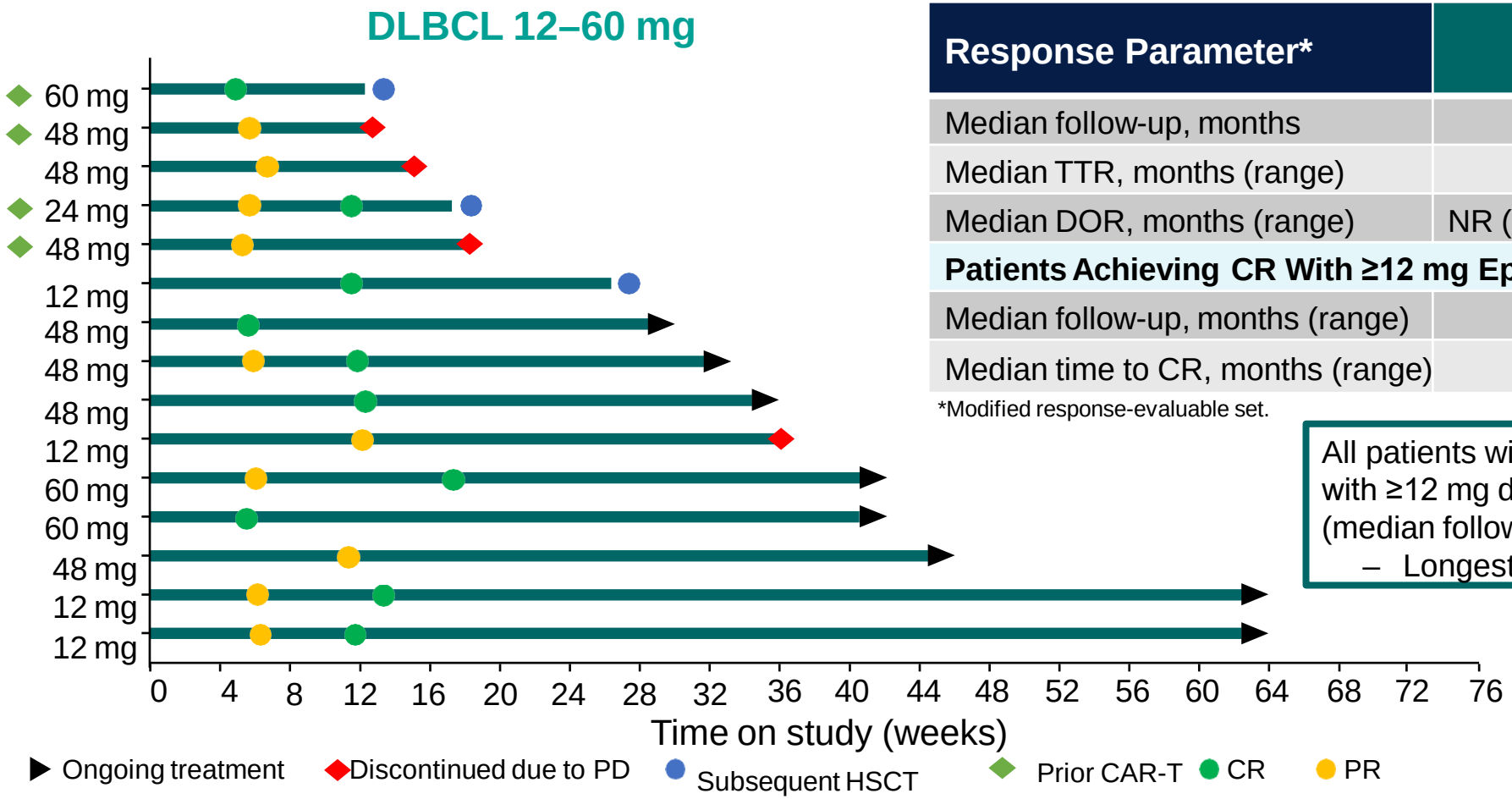
Huchings. ASH 2020. Abstr 402. Engelberts. EBioMedicine. 2020;52:102625. Chiu. EHA 2020. Abstr EP1330.

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).

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+ mo

Toxicity: CAR-T vs. Novel Agents

	Grade ≥ 3 CRS	Grade ≥ 3 Neurotoxicity	Other AEs
CAR T Associated Rates	2-22%	10-28%	- HLH - Cytopenias
BiTE Platforms	0-7%	0-3.5%	- Infections - Cytopenias
Tafasitamab-based	N/A	N/A	- Infections - Cytopenias - Cardiac / PE
Polatuzumab or Loncastuximab	Fluid 3rd spacing with Lonca	9% (PN)	- Cytopenias - Hepatotoxicity - Infections

Conclusion

- DLBCL is a heterogeneous disease
- Treated with curative intent in most patients
- Pola + R-CHOP expected to get approval in the front line setting
- CAR T-cells approved in second line
- BiTEs are promising alternatives
- Consider early referral

Thank you for your attention

Questions?

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