Loncastuximab Tesirine: Role in Crowded Real World Space?

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Disclosures

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Speakers Bureau:

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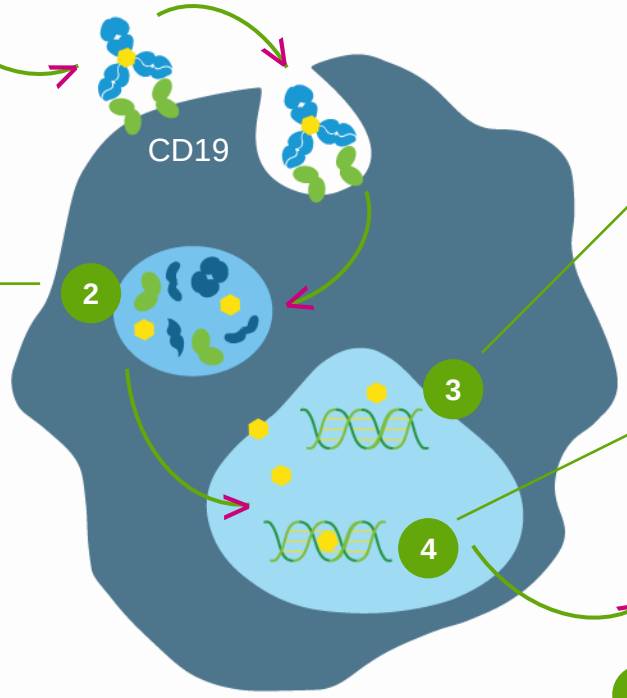
Loncastuximab Tesirine: CD19 ADC

Loncastuximab tesirine

1 Loncastuximab tesirine binds to the CD19 antigen on the tumor cell surface

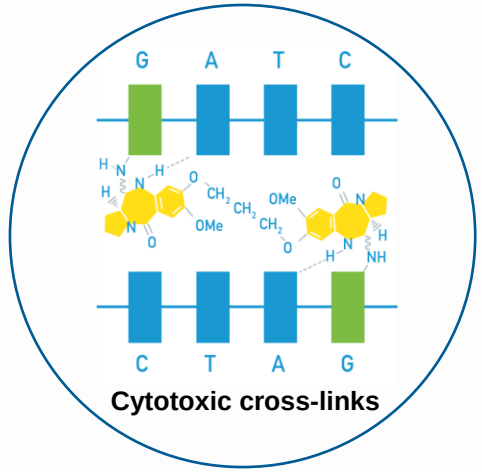


Following internalization of loncastuximab tesirine, the linker is cleaved and cytotoxic PBD dimers are released inside the cell

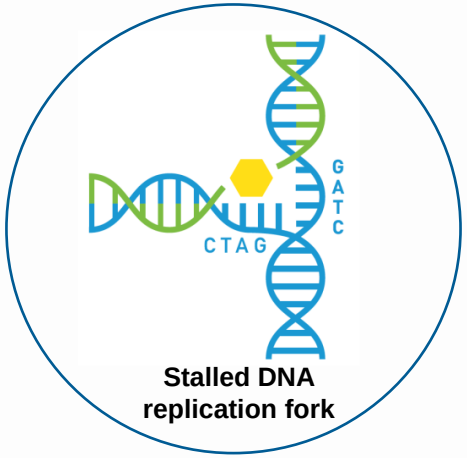
In the nucleus, the PBD dimer forms cross-links in the minor groove of the DNA, making it less visible to DNA repair mechanisms

The cross-links interrupt cell replication

5 The cancer cell goes into apoptosis



Cytotoxic cross-links



Stalled DNA replication fork

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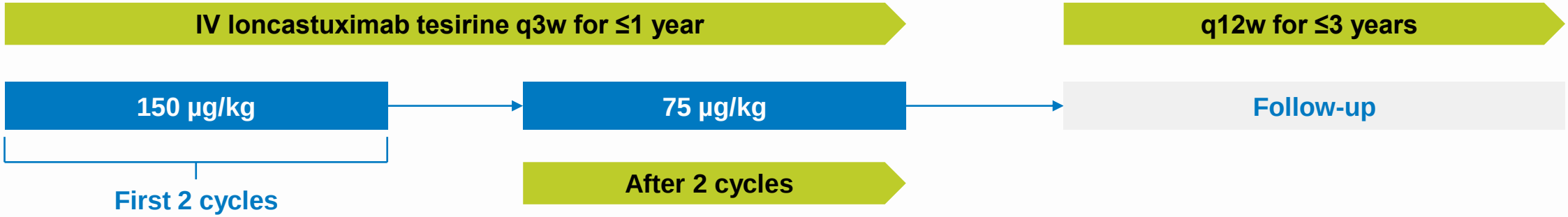
Hamadani & Kahl. Blood. 2021;137(19):2634-45.

LOTIS-2: Study Design

- Patients with R/R DLBCL for whom salvage chemotherapy/SCT is unsuccessful and who have a poor prognosis and limited treatment options[1,2]
- Loncastuximab tesirine comprises a humanized anti-CD19 antibody conjugated to a potent PBD dimer toxin[3]
- LOTIS-2 is a multicenter, open-label, single-arm, phase II study in patients aged ≥18 years with pathologically defined R/R DLBCL and ≥2 prior systemic treatments[4-6]
  - Included patients with high-risk characteristics such as double-hit, triple-hit, transformed, or primary refractory DLBCL[4]



- Primary efficacy and safety data have been published (**≥6 months** since first dose)[4]
- Presented are updated results (**≥17 months** since first dose)

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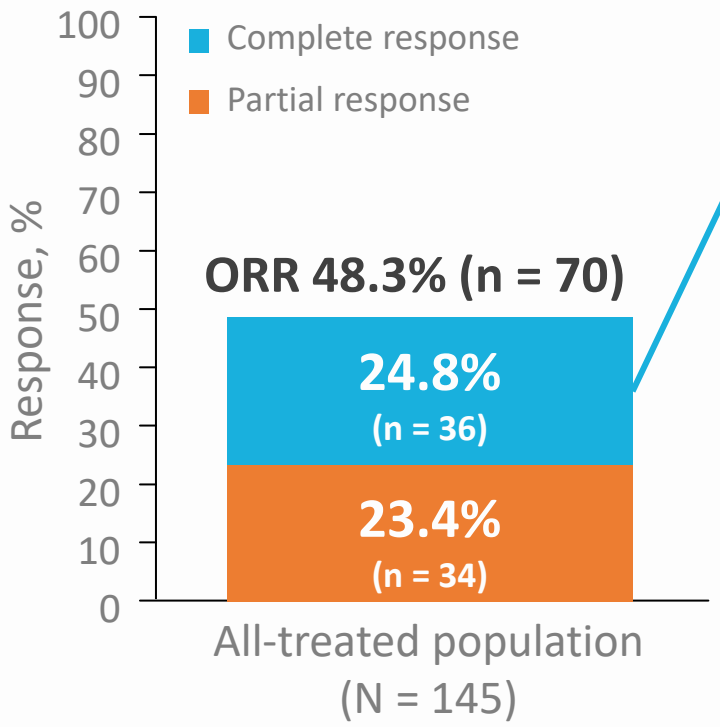
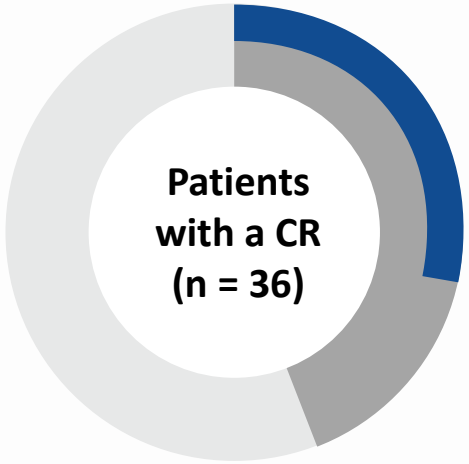
Study findings were previously presented as a poster at the International Conference on Malignant Lymphoma (ICML) Virtual Congress, June 18–22, 2021.

1. Crump M, et al. *Blood.* 2017;130:1800-1808; 2. Gisselbrecht C, et al. *Br J Haematol.* 2018;182:633-643; 3. Zammarchi F, et al. *Blood.* 2018;131:1094-1105; 4. Caimi PF, et al. *Lancet Oncol.* 2021;22:790-800; 5. Caimi PF, et al. ASH 2020. Abstract 1183; 6. Caimi PF, et al. ASCO 2021. Abstract 7546.

Overall Response Rate and Long-term Responses Observed in the All-Treated Population





Of the patients with a CR, **44% (16 of 36)** were event-free for ≥1 year.

Of the patients with a CR, **31% (11 of 36)** were event-free for ≥2 years.

Median (range) number of treatment cycles	
All-treated population	3.0 (1-26)
Pts with a CR	8.0 (1-26)
Pts with a CR, event-free ≥1 year[a]	12.5 (1-26)
Pts with a CR, event-free ≥2 years[a]	13.0 (1-22)

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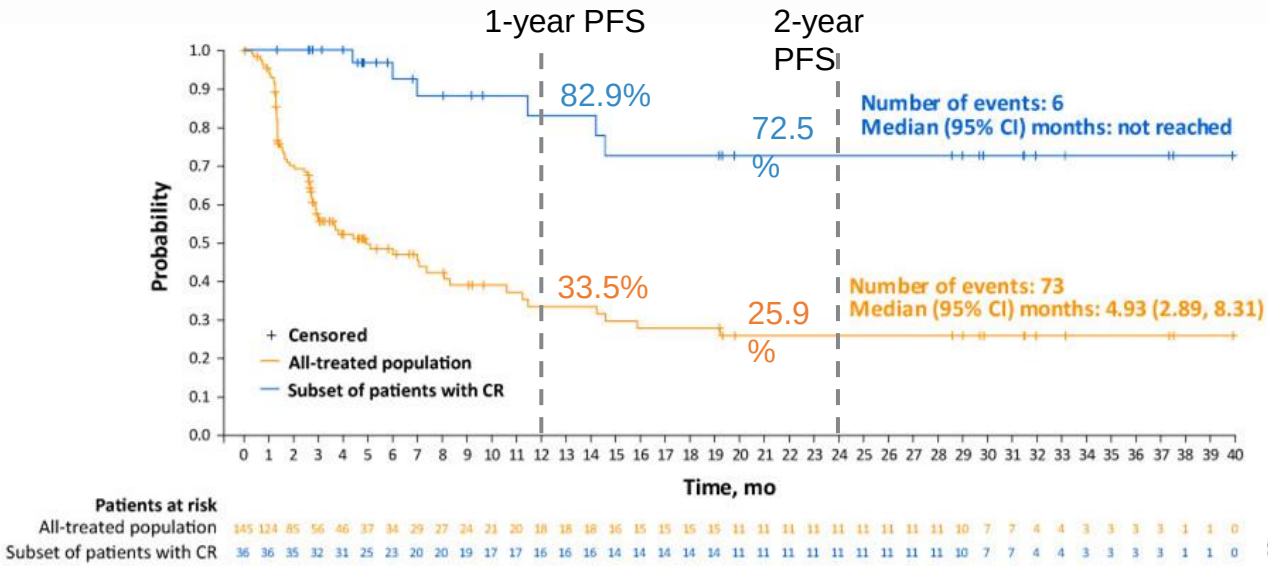
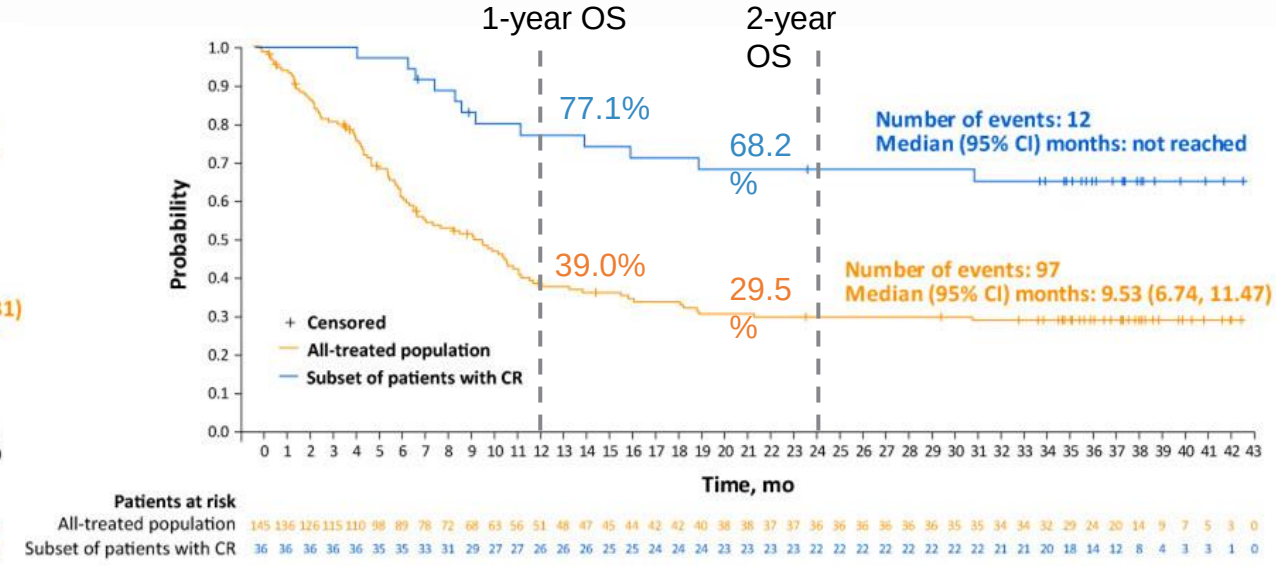
Data cutoff: September 15, 2022.
The median duration of follow-up was 7.8 months (range, 0.3-42.6 months) in the all-treated population and 35.0 months (range, 4.4-42.6 months) in patients with a CR.
[a]Event-free is defined as no progressive disease or death starting from day 1, cycle 1 of Lonca treatment.
CR, complete response; Lonca, loncastuximab tesirine-lpyl; ORR, overall response rate; pts, patients.

PFS and OS: All-Treated Population and Patients With a CR

Progression-free survival



Overall survival



DOR for CR pts not reached; for all responders 13.4 months.

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Data cutoff: September 15, 2022.
CR, complete response; OS, overall survival; PFS, progression-free survival.

All-Grade and Grade ≥3 Adverse Events

TEAEs, any grade in ≥30% of patients	All-treated population, N = 145	Patients with a CR, n = 36
Patients with any TEAE	98.6%	100%
Increased GGT	42%	50%
Neutropenia	40%	42%
Thrombocytopenia	33%	36%
Anemia	26%	36%
Peripheral edema	20%	33%
Nausea	23%	31%

TEAEs, grade ≥3 in ≥10% of patients	All-treated population, N = 145	Patients with a CR, n = 36
Patients with any TEAE	73.8%	75%
Neutropenia	26%	28%
Thrombocytopenia	18%	19%
Increased GGT	17%	19%
Anemia	10%	8.3%
Leukopenia	9%	14%
Hypophosphatemia	6%	11%

No new safety signals were identified during the long-term follow-up.

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Data cutoff: September 15, 2022.
CR, complete response; GGT, gamma-glutamyltransferase; TEAE, treatment emergent adverse events.

Crowded Therapy Landscape in R/R DLBCL

Approved Therapy Options in U.S.A:

- Polatuzumab ± BR
- Tafasitamab / Lenalidomide
- Loncastuximab tesirine
- Selinexor
- Bispecifics (epcoritamab, glofitamab)

Cellular Immunotherapy:

- CAR T-cell therapy (CD19 directed) & investigational platforms
- Bispecifics (***knocking on the door***)

Hematopoietic Cell Transplant (HCT):

- Autologous and allogeneic transplant

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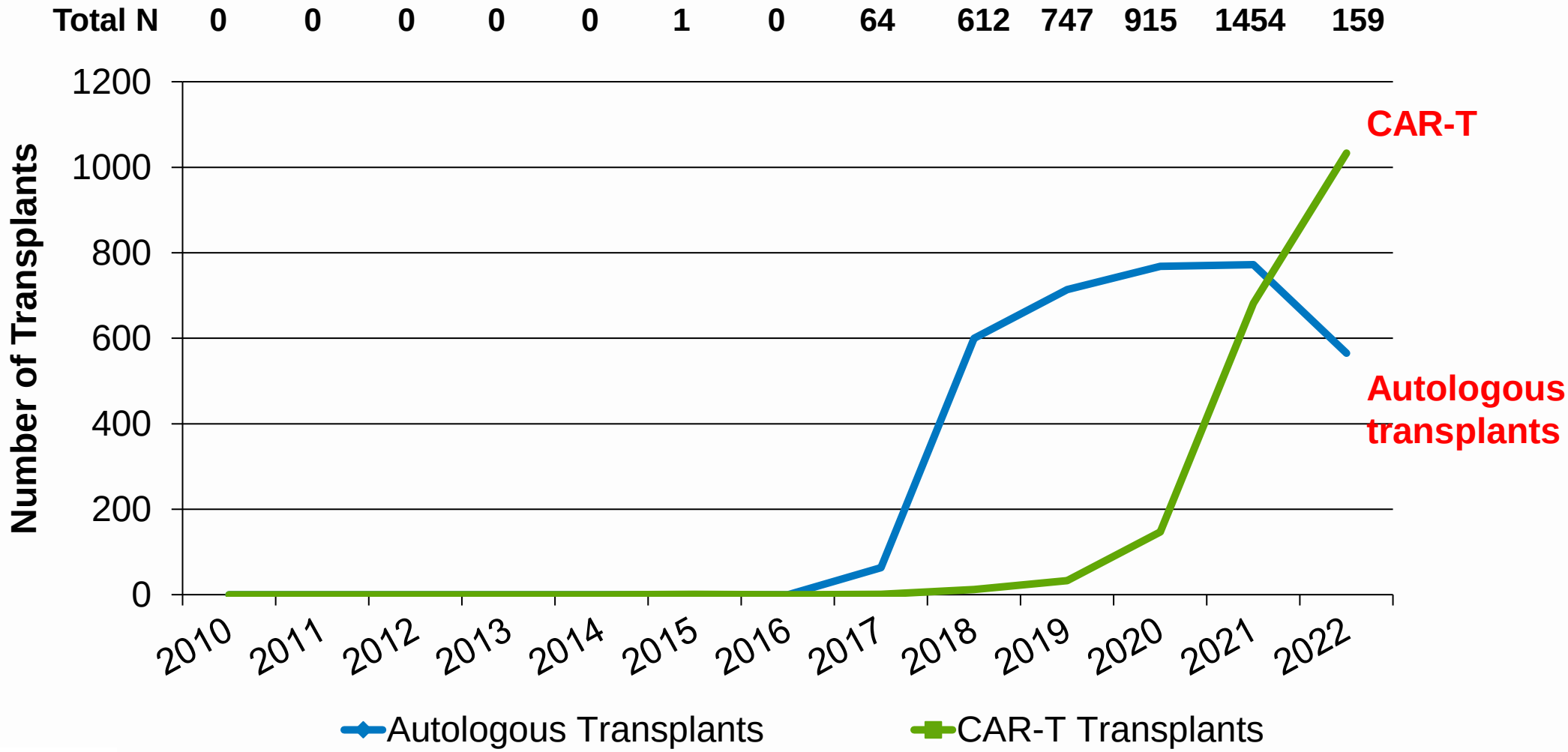
U.S. Trends for autologous transplant vs. CAR-T for Diffuse Large B-Cell Lymphoma (2010-22)



CIBMTR
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CIBMTR unpublished data

Clinical Application of Lonca in Off-trial setting

- Pre or post-CD19 directed CAR Lonca application?
- When CAR is not feasible (age or comorbidities)
- How much CD19 expression do we need?
- Real world uptake and experience?

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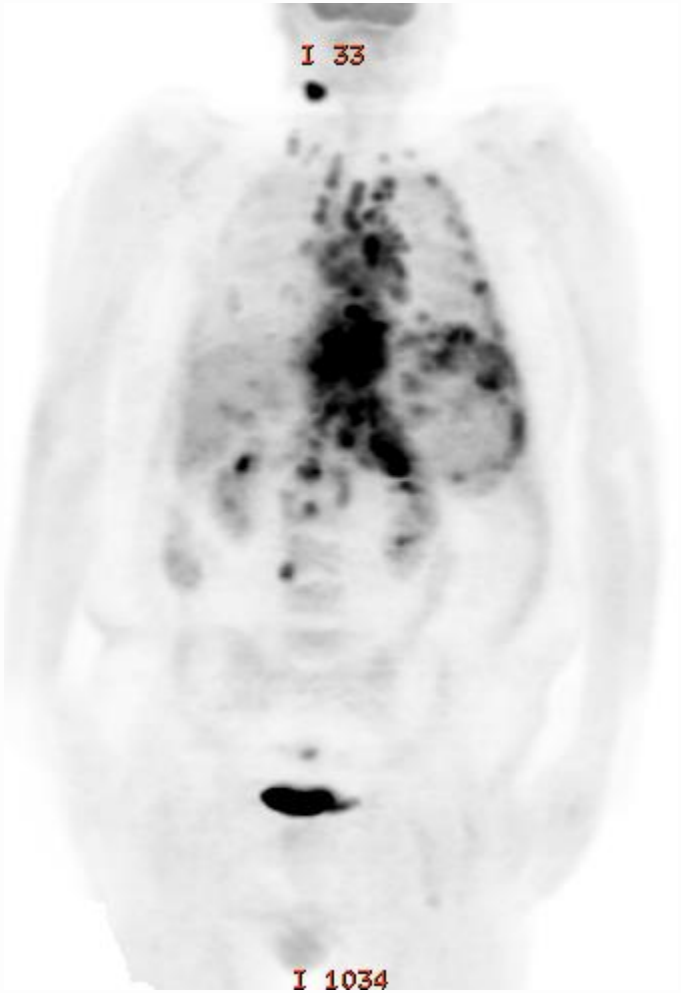
Clinical Case #1:

- Male subject at age 43 diagnosed with non-GCB DLBCL, Stage IV-E, IPI =4; CNS IPI = 4
- **First line treatment** R-CHOP with primary refractory disease
- **Second line treatment** moved to CAR-T cell therapy, using polatuzumab as a bridge (with no response to pola bridge)



At diagnosis

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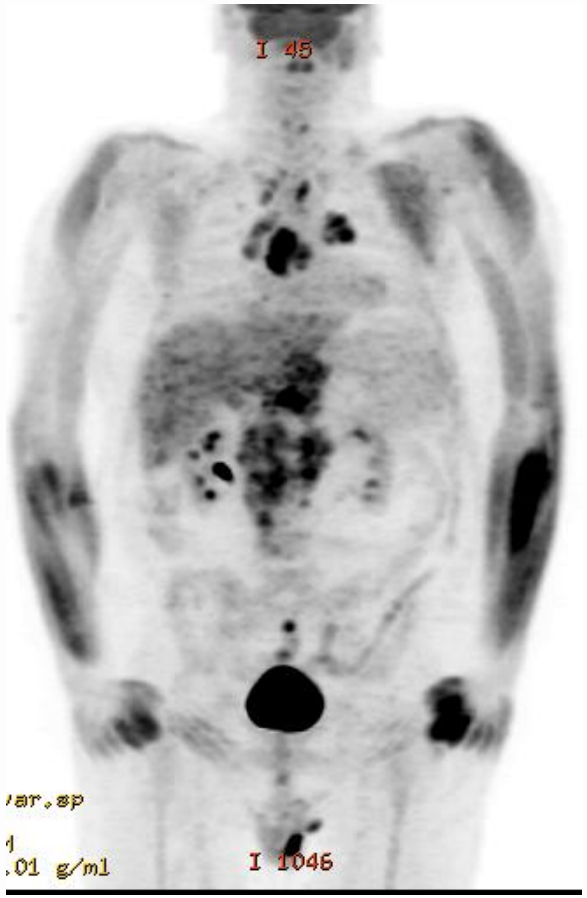
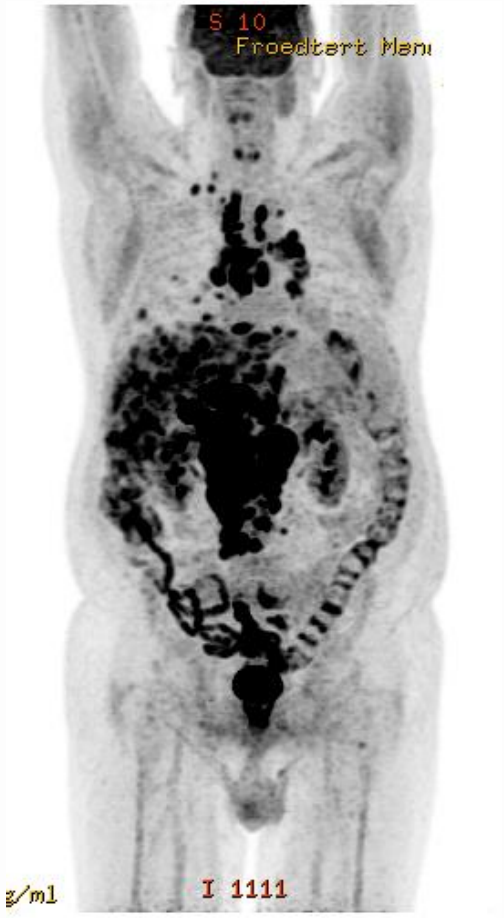
Patient Response to CAR-T cell Treatment



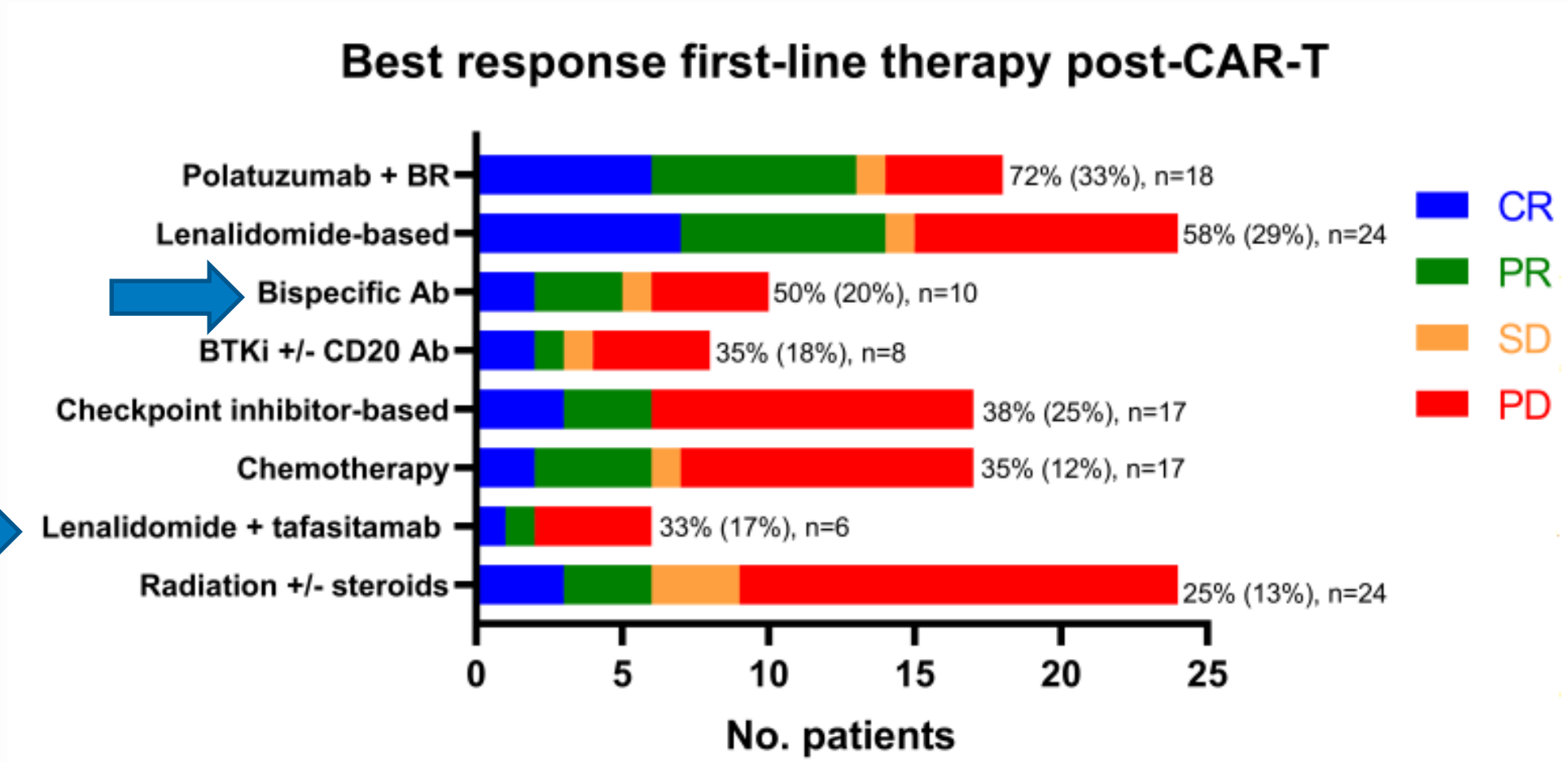
Prior to CAR-T



After CAR-T (~ day90)

Repeat biopsy CD19+, CD20+

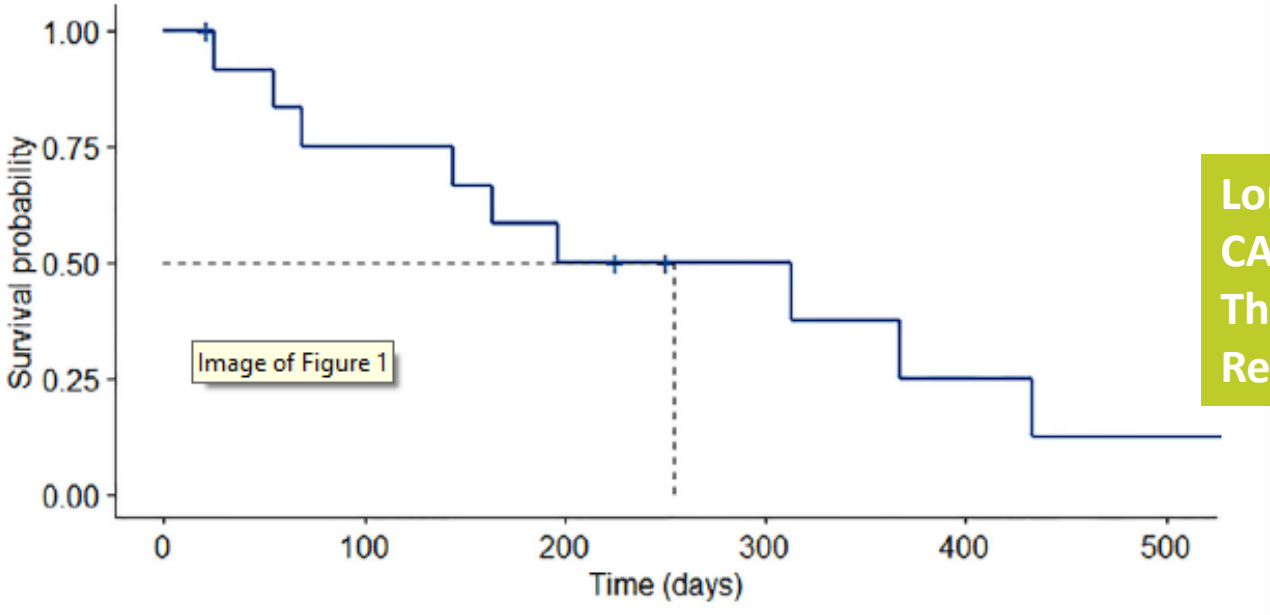
CD19 Sequencing after CAR-19 Failure?



Zurko J. & Karmali R. Blood Adv. 2023;7(12):2657-2669.

Rationale for Considering Lonca?

OS (median)	8.2 months
DOR (median)	8 months



Lonca After CAR T-Cell Therapy Relapse[2]

		n=13
Best response to CAR T-cell therapy, n (%)	CR	7 (54)
	PR	2 (15)
	NR	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)

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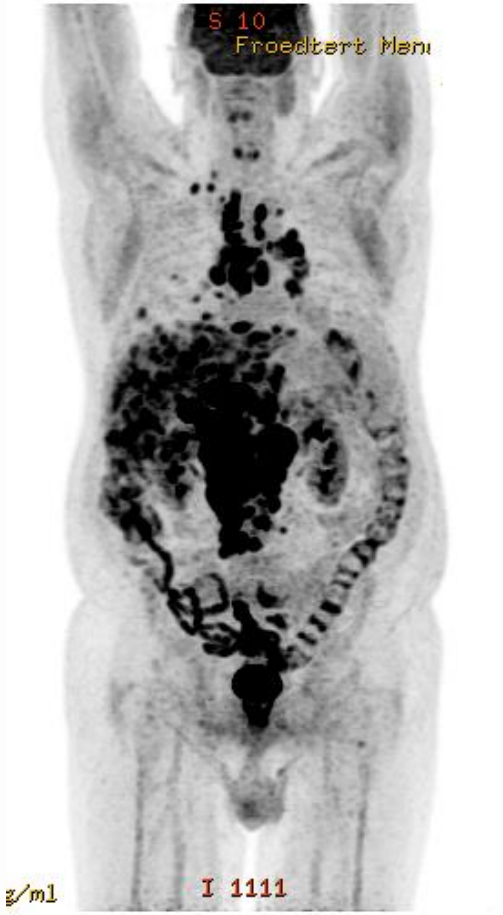
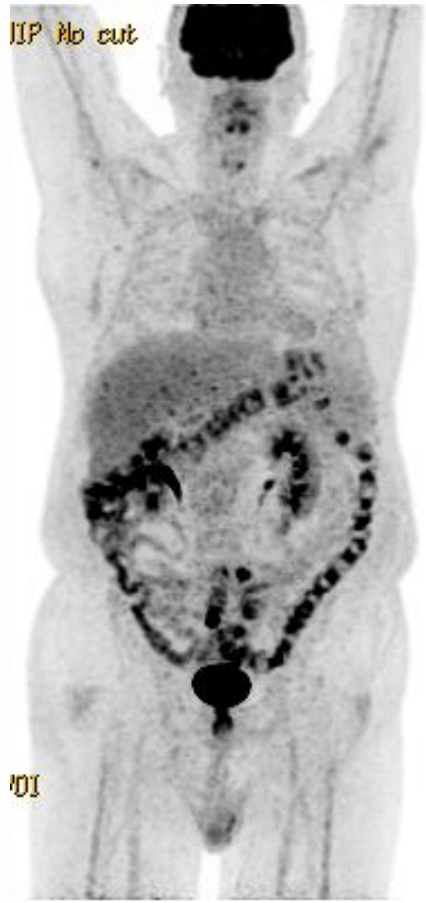
Caimi & Hamadani. CLML. 2022 May;22(5):e335-e339

Response after 2 Cycles of Lonca-R



Baseline Line LOTIS 5



After Cycle #2

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CD19 Directed CAR-T after Loncastuximab

- Patients progressing after lonca on LOTIS-1 and undergoing CAR-T (N=14) identified from 6 centers
- Median age = 58 (range: 27-86)
- High risk IPI = 36%
- MYC rearranged = 21%
- No **CD19 loss** was seen in the 10 subjects where a repeat assessment was performed

CD19 CAR-T Outcomes	N = 14
Median follow-up (months)[1]	6 (3, 22)
Clinical Outcomes	
Complete response (%)	6 (43%)
Overall response rate (%)	7 (50%)
Median DOR (months)	2 (2., 11)
Survival information	6 Alive @LFU

[1]Reverse Kaplan-Meier estimator[3]

Prior lonca does not appear to preclude CAR-T cell therapy and its role as bride to CAR-T warrants further exploration

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Thapa & Hamadani. Blood Adv. 2020;4(16):3850-2.

Can Loncastuximab be Used as a Bridge to CD19 CAR-T?

- CD19 loss following Loncastuximab exposure is exceeding rare (0/40+ lonca treated patients at MCW)
- ADC internalized post binding to CD19 receptor potentially means epitope masking less likely
- Bridging strategy will be evaluated in an Italian IIT
- CIBMTR Analysis will be presented at Tandem Meetings

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Clinical Application of Lonca in Off-trial setting

- Pre or post-CD19 directed CAR Lonca application?
- When CAR is not feasible (age or comorbidities)
- How much CD19 expression do we need?
- Real world uptake and experience?

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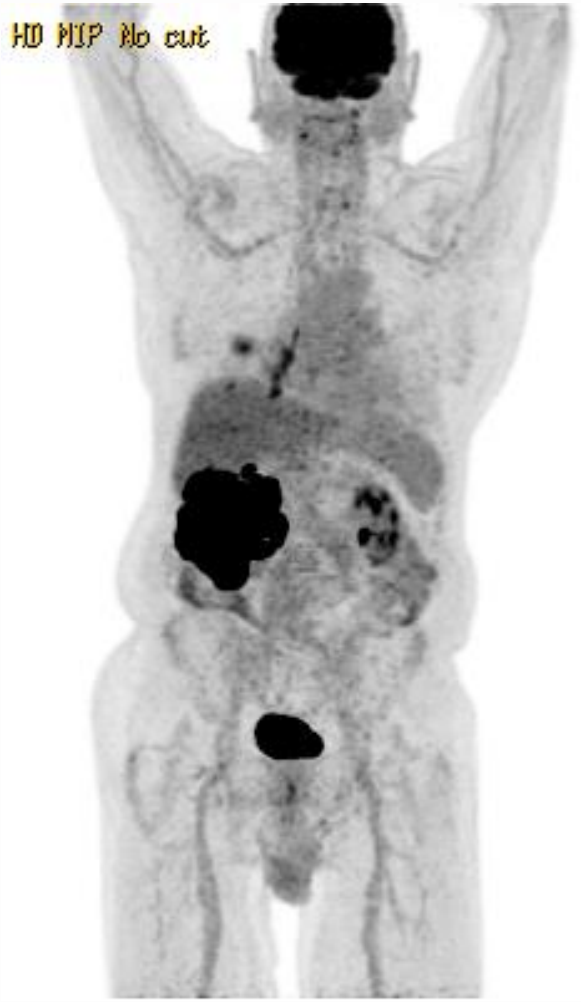
Clinical Case #2:

- 88-year-old male with multiple medical issues was diagnosed with stage IV **DH** **HGBCL**, IPI = 4
- Treatment:
  - Split-dose R-CHOP with primary refractory disease
  - R-Pola x 2 with no response



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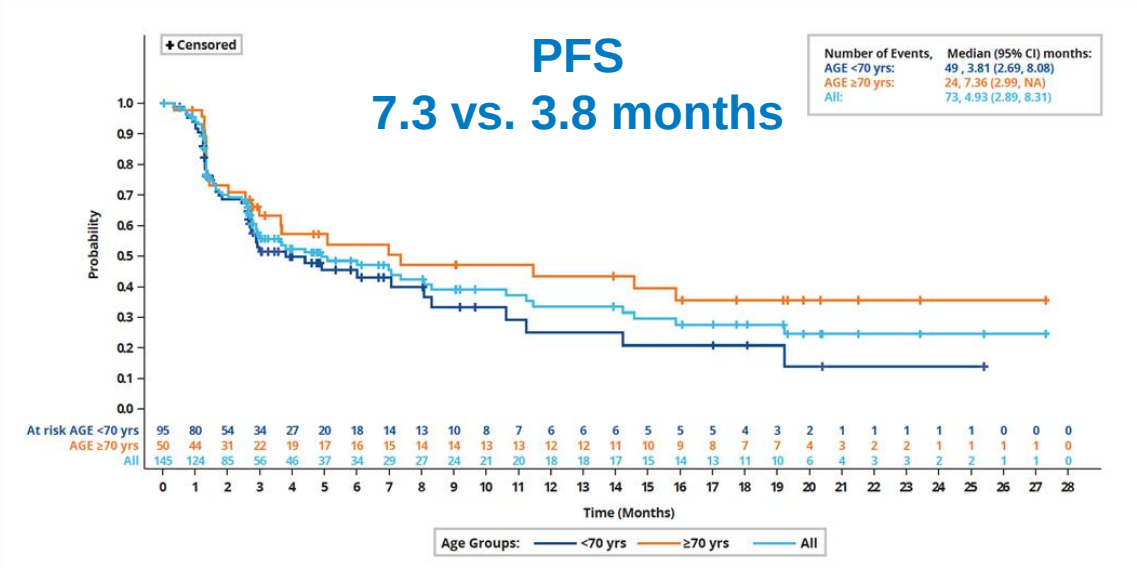
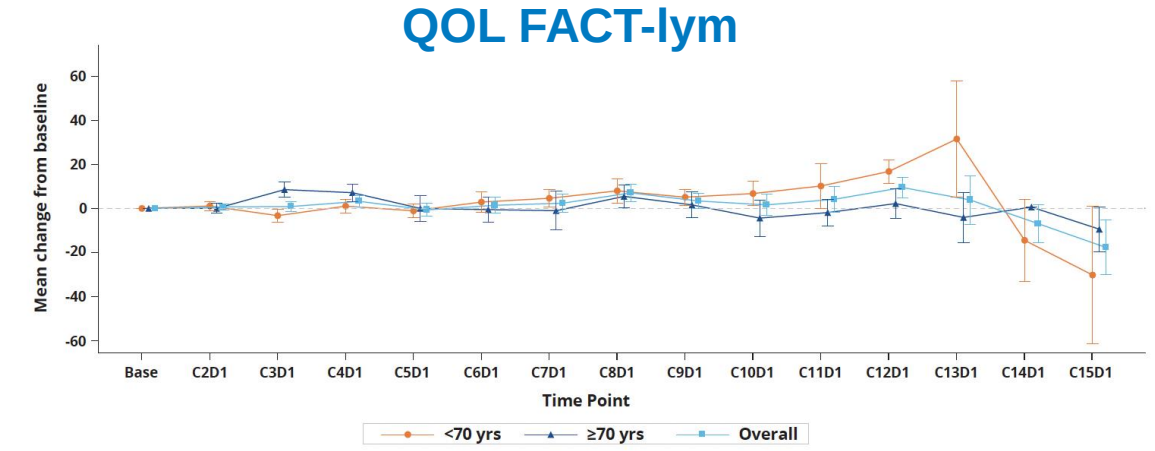
Data Supporting Lonca Use in Elderly Patients?

LOTIS-2 Post hoc analysis

	<70 years (n = 95)	≥70 years (n = 50)
BOR, n (%) CR PR	 21 (22.1) 25 (26.3)	 15 (30.0) 9 (18.0)
ORR	**46 (48.4%)**	**24 (48.0%)**
	<70 years (n = 46)	≥70 years (N = 24)
Time to CR/PR, days, median	41.5 (35, 247)	41.0 (36, 142)
	<70 years (n = 21)	≥70 years (N = 15)
Time to CR, days, median	42.0 (37, 247)	41.0 (36, 59)

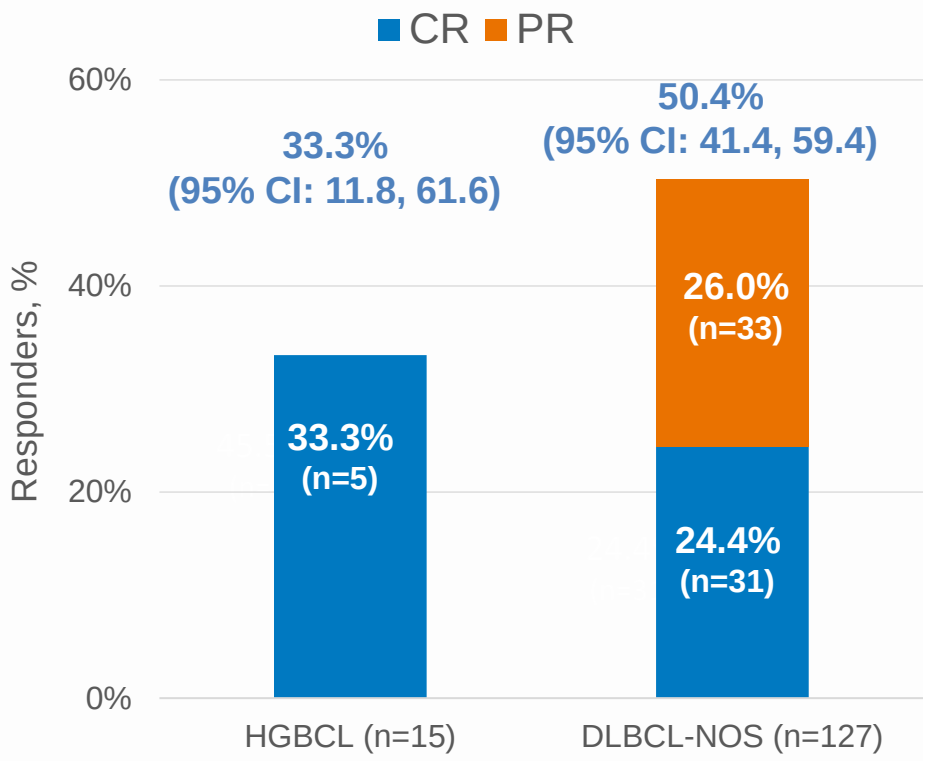


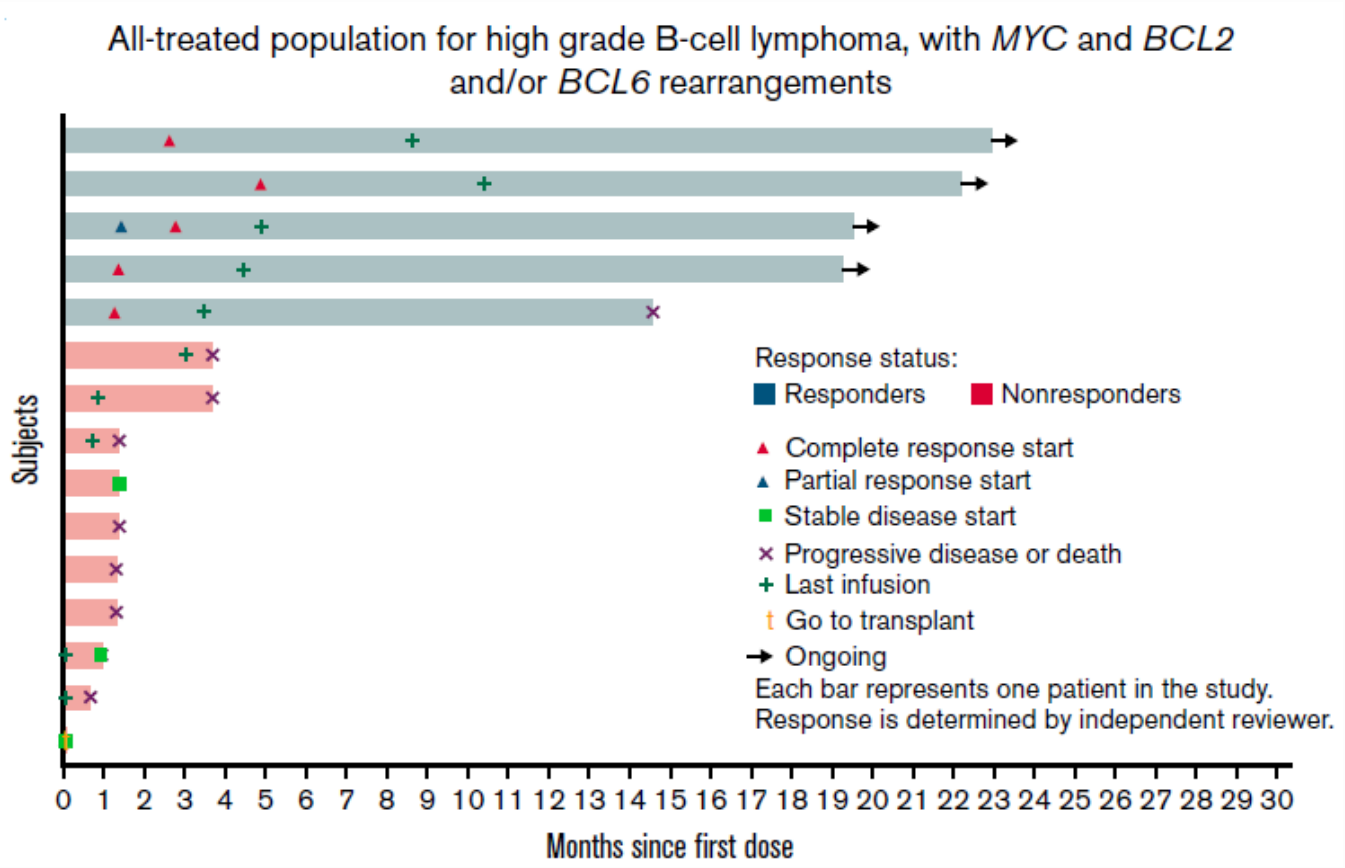


Hamadani & Zinzani. Blood Adv. 2024;8(1):93-98.

Loncastuximab's Activity in Double Hit Lymphoma

HGBCL/DLBCL NOS Response Rates





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Alderuccio & Caimi. Blood Adv. 2022;6(16):4736-9

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- How much CD19 expression do we need?
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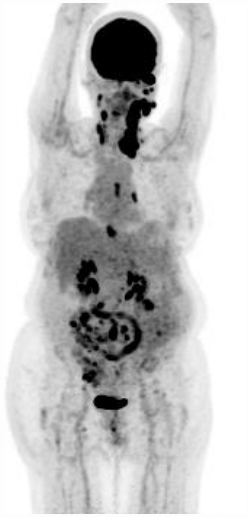
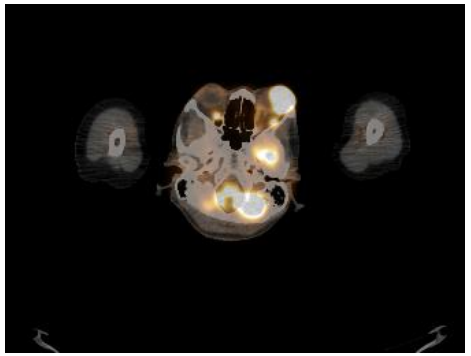
Clinical Case #3:

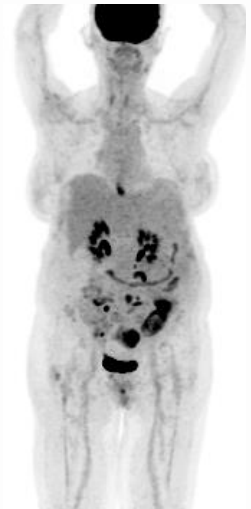
- 55-year-old AA female with 5 prior therapy lines, including an invCD19.20 CAR
- Experienced symptomatic progression including an ocular mass causing proptosis. Undergoes biopsy and started Loncastuximab
- After first dose the biopsy returned without CD19 expression

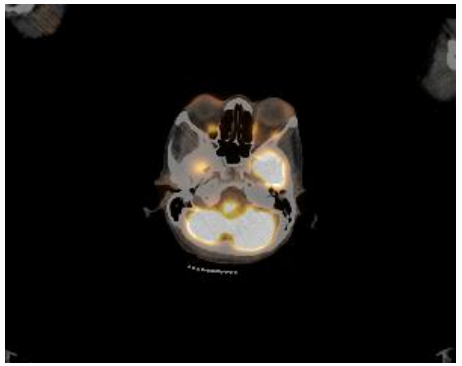
Baseline





Post 2 cycles of Loncastuximab





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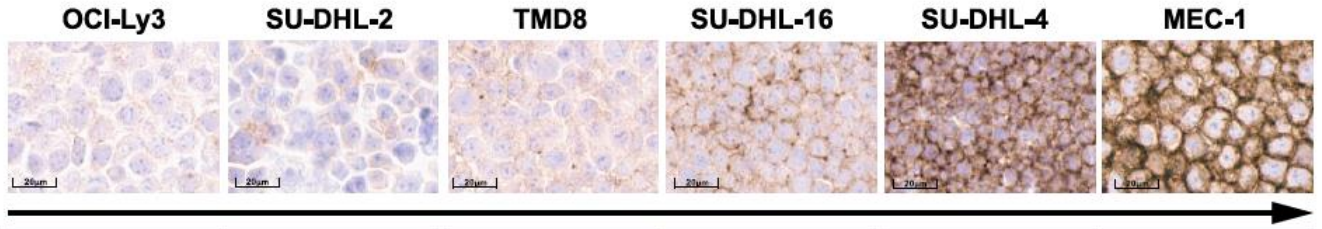
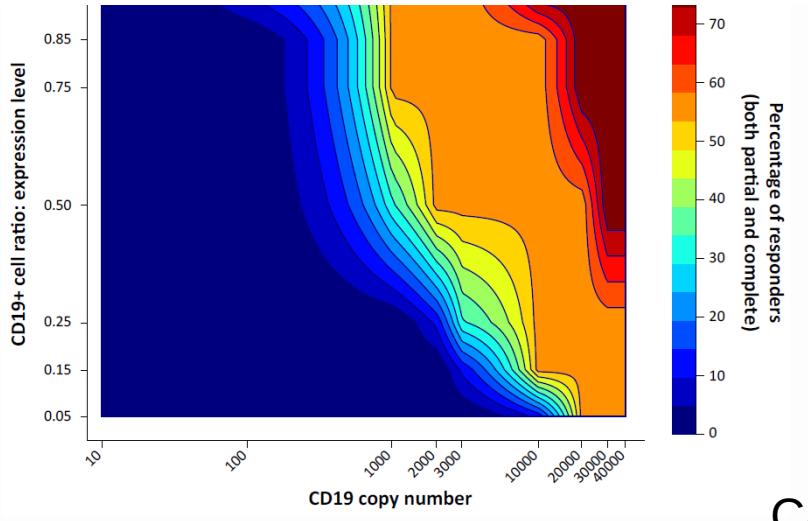
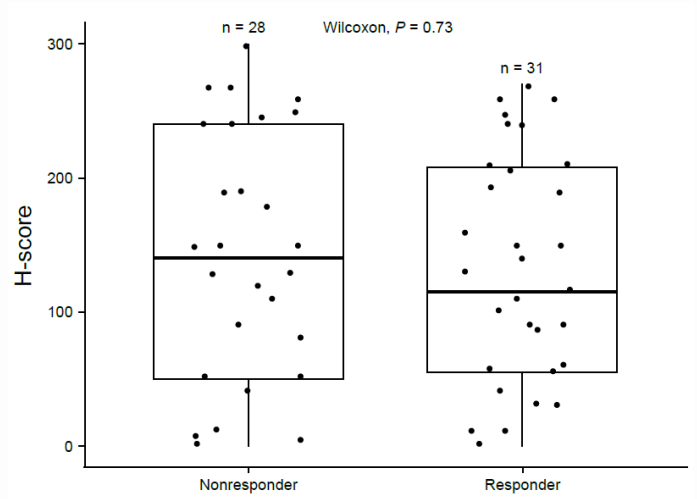
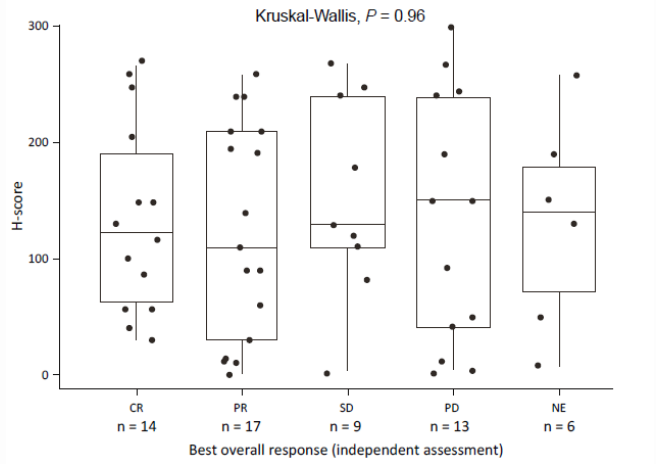
CD19 Expression and Loncastuximab Responses



CD19 H-score (IHC)	2	30	55	142	150	265
Percent of CD19-positive cells (IHC)	2%	30%	40%	80%	65%	90%
CD19 copy number (±SEM) (Flow cytometry)	24,420 (±24)	63,921 (±240)	61,357 (±555)	116,553 (±681)	340,761 (±2301)	288,531 (±2227)
Lonca in vitro cytotoxicity IC50 pM (±SEM)	216 (±15.7)	12.5 (±1.1)	47.3 (±10.7)	3.3 (±1.1)	9.6 (±3.2)	17.2 (±1.3)







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Caimi & Boni. eJHaem. Epublished

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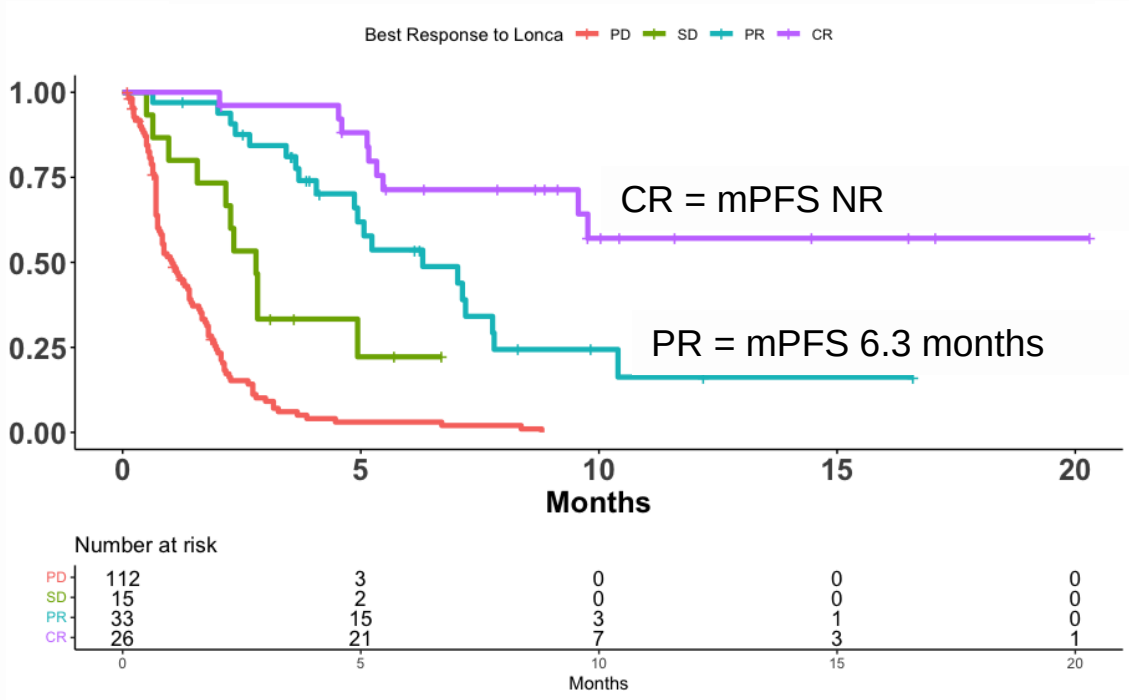
Real World Data for Loncastuximab

N = 187	ORR (%)	CR (%)
Overall Study Population	**32**	**14**
CD19 Status		
Positive	32	14
Negative	26	21
Bulky disease (N=32)	16	0
Prior CAR-T		
Yes (N=112)	30	15
No	35	12
# Prior Therapies		
<4	33	14
4+	30	13
Age >75		
Yes	32	14
No	26	21

PFS by Response to Lonca



Ayers E. & Epperla N. ASH Annual Meetings 2023.

Conclusion

- Lonca is approved in the U.S. in third line setting as a single agent
- LOTIS 5 trial is evaluating the lonca plus R in second line setting or beyond
- Lonca has demonstrated activity in the peri-CAR setting
- RWD in more heavily treated patients show activity (except in bulky or HGBCL patients)

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Thank you for your kind attention!

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Potential to add Loncastuximab to Anthracyclines?

UT Southwestern
Harold C. Simmons
Comprehensive Cancer Center

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

The Ohio State University

Northwestern Medicine
Robert H. Lurie Comprehensive Cancer Center
of Northwestern University

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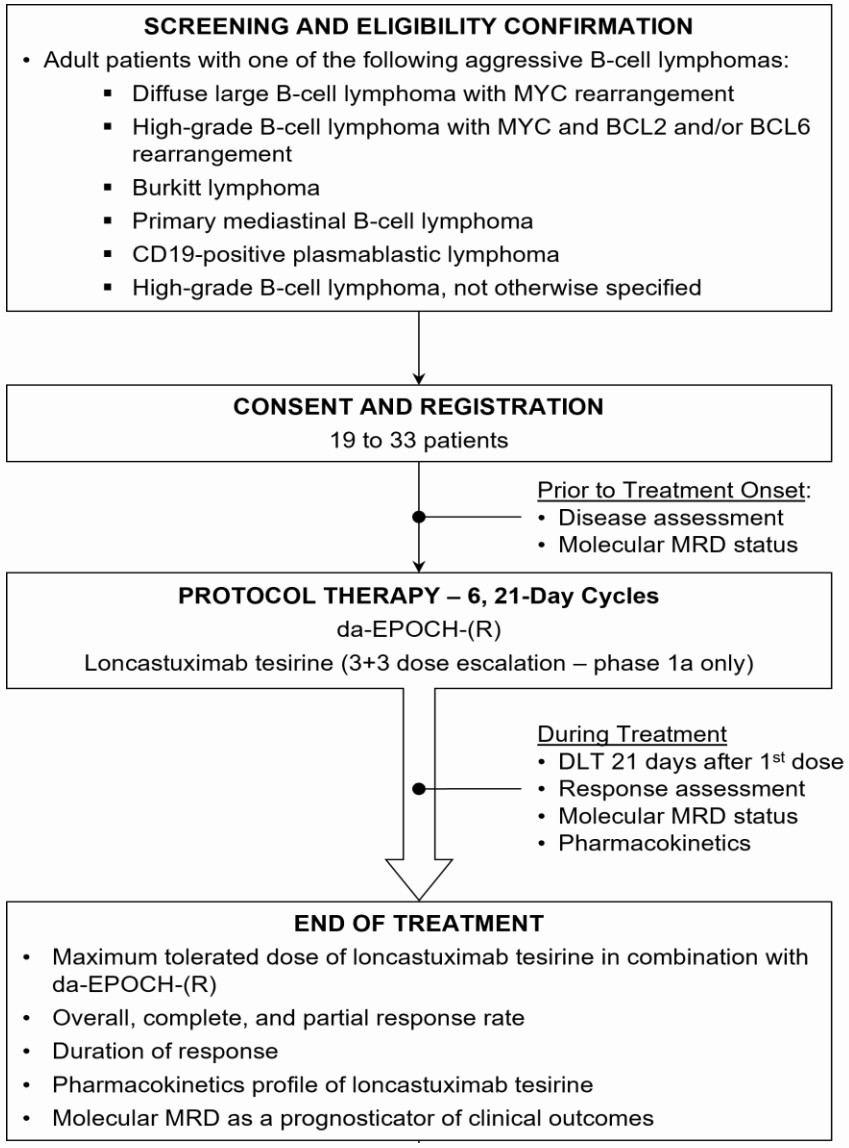
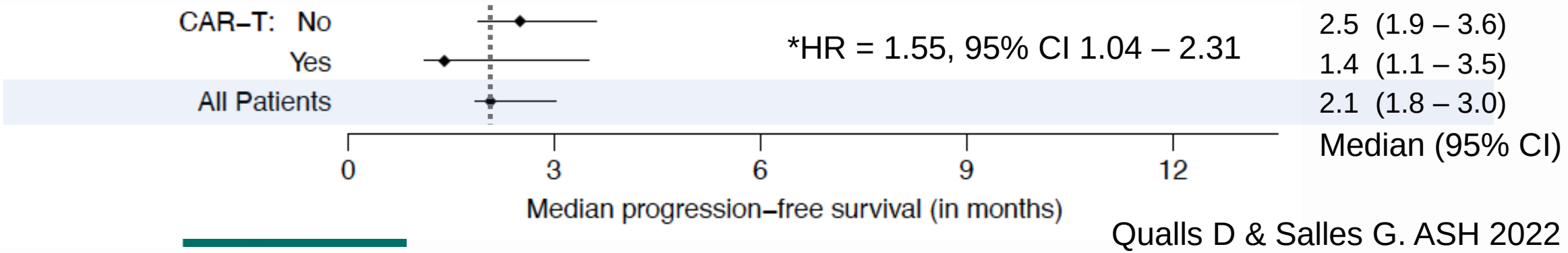


Tafa/Len after CD19-directed CAR T cell therapy (TOLA Study)

- 42 patients (28%) had CAR T before TL
- 19 with biopsy recorded after CAR T
  - 15/19 confirmed CD19 expression
  - 4/19 CD19 expression not reported

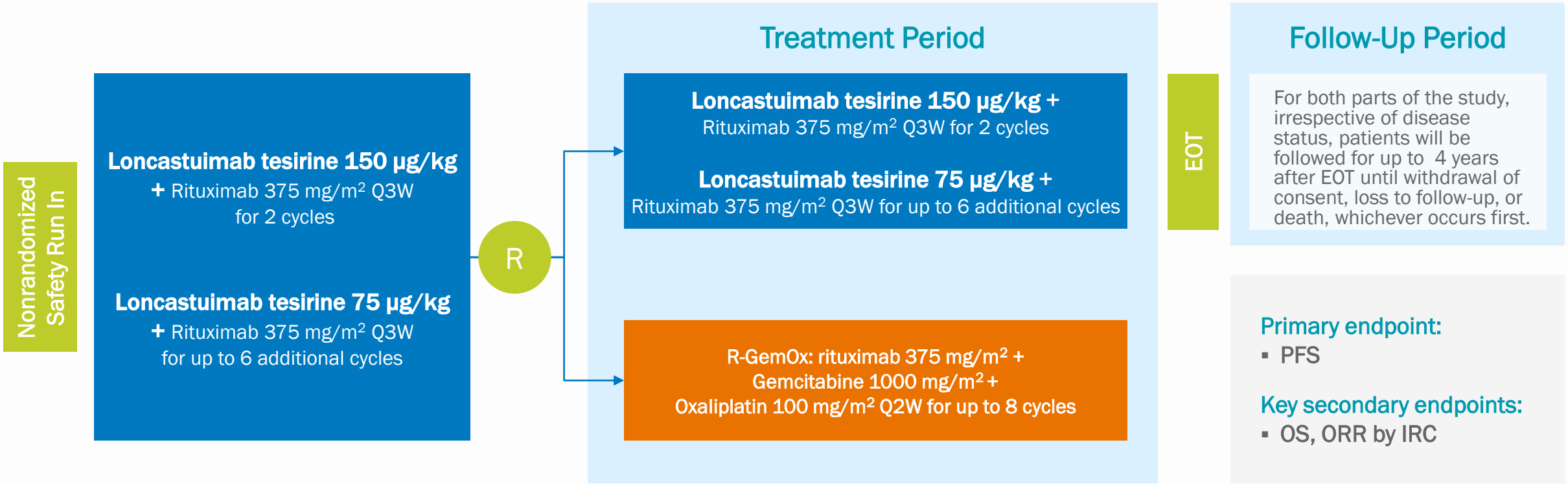
Response to TL according to CAR T Response

DOR after CAR T	≥ 6 months (N = 11)	< 6 months (N = 15)
ORR	36%	7%
CRR	36%	7%



Qualls D & Salles G. ASH 2022 Abs.

LOTIS 5: A Phase 3 Study of Loncastuximab Tesirine With Rituximab vs Immunochemotherapy in R/R DLBCL



Key Inclusion Criteria

- DLBCL or HGBCL with MYC, BCL2, and/or BCL6 rearrangements
- R/R disease following ≥1 multi-agent systemic treatment regimen
- Ineligible for SCT
- ECOG PS 0-2

Froedtert & Medical College of Wisconsin

- 1. ADC Therapeutics. LOTIS-5 Brochure. Accessed 29March2022. https://www.adctherapeutics.com/wp-content/uploads/2020/09/LOTIS-5-Brochure_FINAL.pdf. 2. ClinicalTrials.gov. NCT04384484. Accessed 29March2022. https://www.clinicaltrials.gov/ct2/show/NCT04384484