Interim Futility Analysis of a Phase 2 Study of Loncastuximab Tesirine, a Novel Pyrrolobenzodiazepine-Based Antibody-Drug Conjugate, in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

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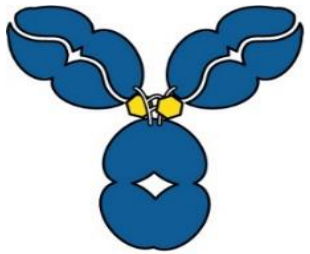
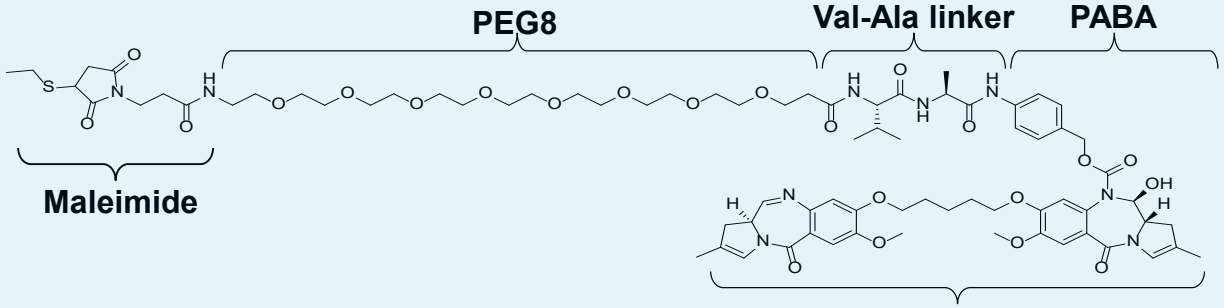
Loncastuximab Tesirine (ADCT-402)



Anti-CD19 Ab

Tesirine/ SG3249



Loncastuximab tesirine comprises a humanized anti-CD19 Ab stochastically conjugated to a potent PBD dimer toxin[1]

The majority of B-cell malignancies express CD19 at normal to high levels[2]

1. **Loncastuximab tesirine binds to CD19 antigen on the tumor cell surface**
2. **ADC is internalized, the linker is cleaved, and PBD dimers are released**
3. **Cytotoxic DNA cross-link formation**
4. **Stalled DNA replication fork**
5. **Cell goes into apoptosis**

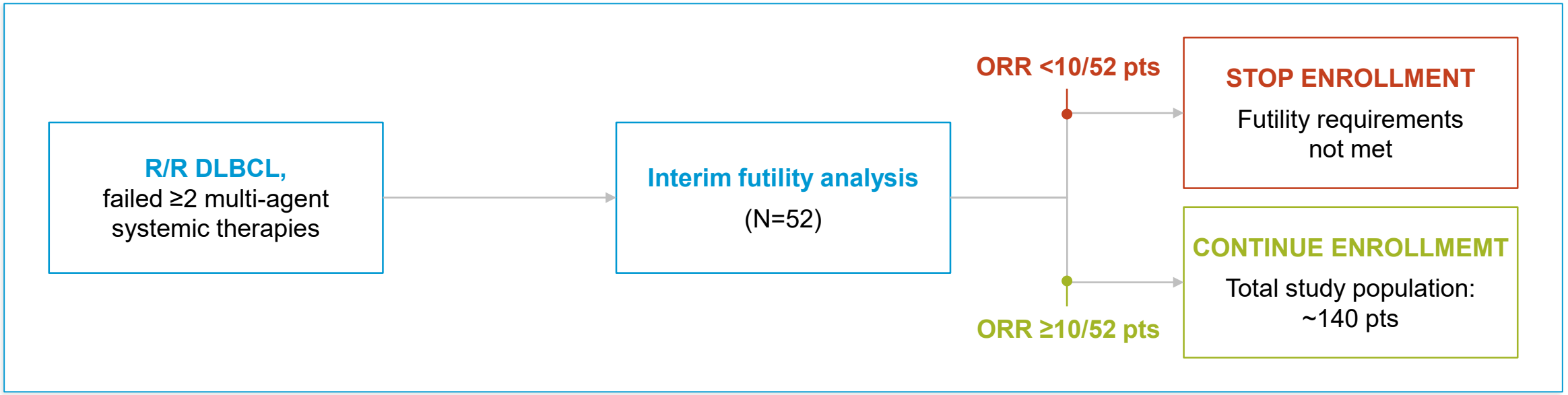
1. Zammarchi F, et al. *Blood*. 2018;131:1094–105. 2. Wang K, et al. *Exp Hematol Oncol*. 2012;1:36.

Ab, antibody; ADC, antibody-drug conjugate; CD19, cluster of differentiation 19; PABA, para-aminobenzoic acid; PBD, pyrrolobenzodiazepine; PEG, polyethylene glycol; Val-Ala, valine-alanine.

Loncastuximab Tesirine Phase 2 DLBCL Study (NCT03589469)

Primary objective:	Evaluate single-agent efficacy in R/R DLBCL
Secondary objectives:	Evaluate safety, PK, immunogenicity and impact on HRQoL

30-min intravenous infusion of 150 µg/kg Q3W×2 cycles, followed by 75 µg/kg Q3W



DLBCL, diffuse large B-cell lymphoma; HRQoL, health-related quality of life; ORR, overall response rate; PK, pharmacokinetics; pts, patients; Q3W, every three weeks; R/R, relapsed/refractory.

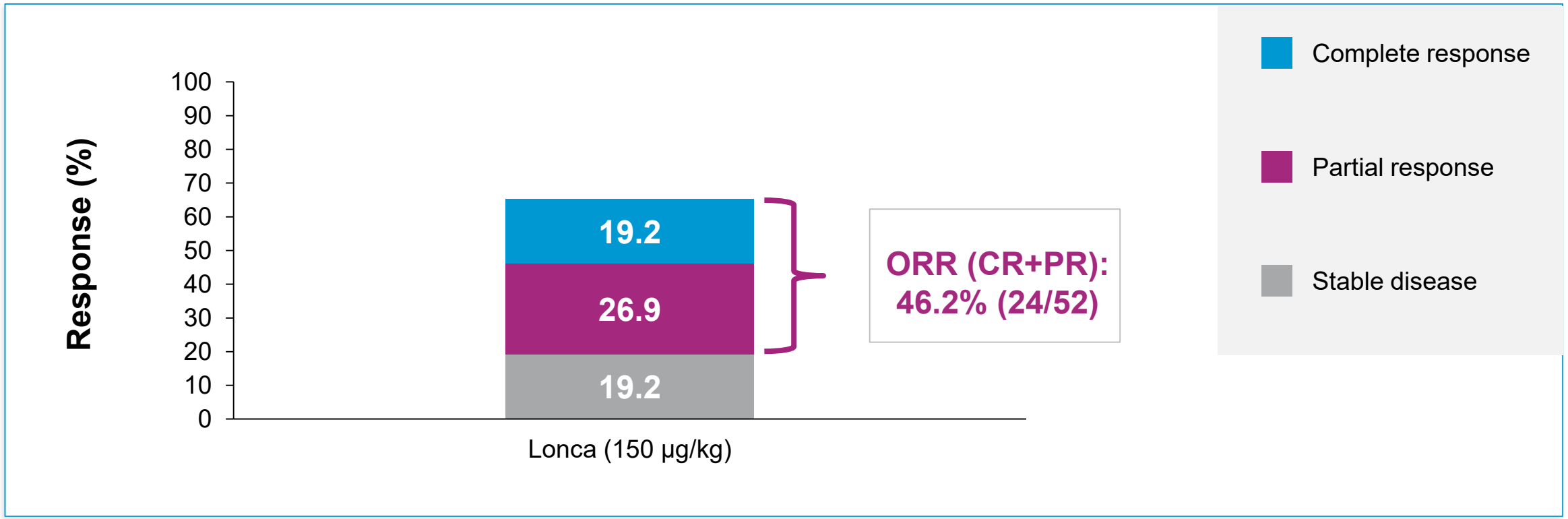
Baseline Characteristics

Patient characteristics		Total (N=52)
Sex, n (%)	Male	38 (73.1)
	Female	14 (26.9)
Race, n (%)	White	48 (92.3)
	Black/African American	2 (3.8)
	Asian	1 (1.9)
	Other	1 (1.9)
Age, years, median (min, max)		63 (24, 84)
Histology, n (%)	**DLBCL**	**45 (86.5)**
	Double/triple hit	3 (5.8)
	Transformed disease	8 (15.4)
	Follicular	*7 (13.5)*
	Richter's	*1 (1.9)*
	HGBCL	**4 (7.7)**
	PMBCL	**3 (5.8)**
Stage, n (%)	I–II	14 (26.9)
	III–IV	38 (73.1)

Patient treatment history		Total (N=52)
First-line systemic therapy response, n (%)	Relapsed	32 (61.5)
	Refractory	16 (30.8)
	Other*	4 (7.7)
Last-line systemic therapy response, n (%)	Relapsed	17 (32.7)
	Refractory	28 (53.8)
	Other*	7 (13.5)
No. of previous systemic therapies, median (min, max)		3 (2, 7)
Prior stem cell transplantation, n (%)		**11 (21.2)**
	Allogeneic	1 (1.9)
	Autologous	9 (17.3)
	Both	1 (1.9)

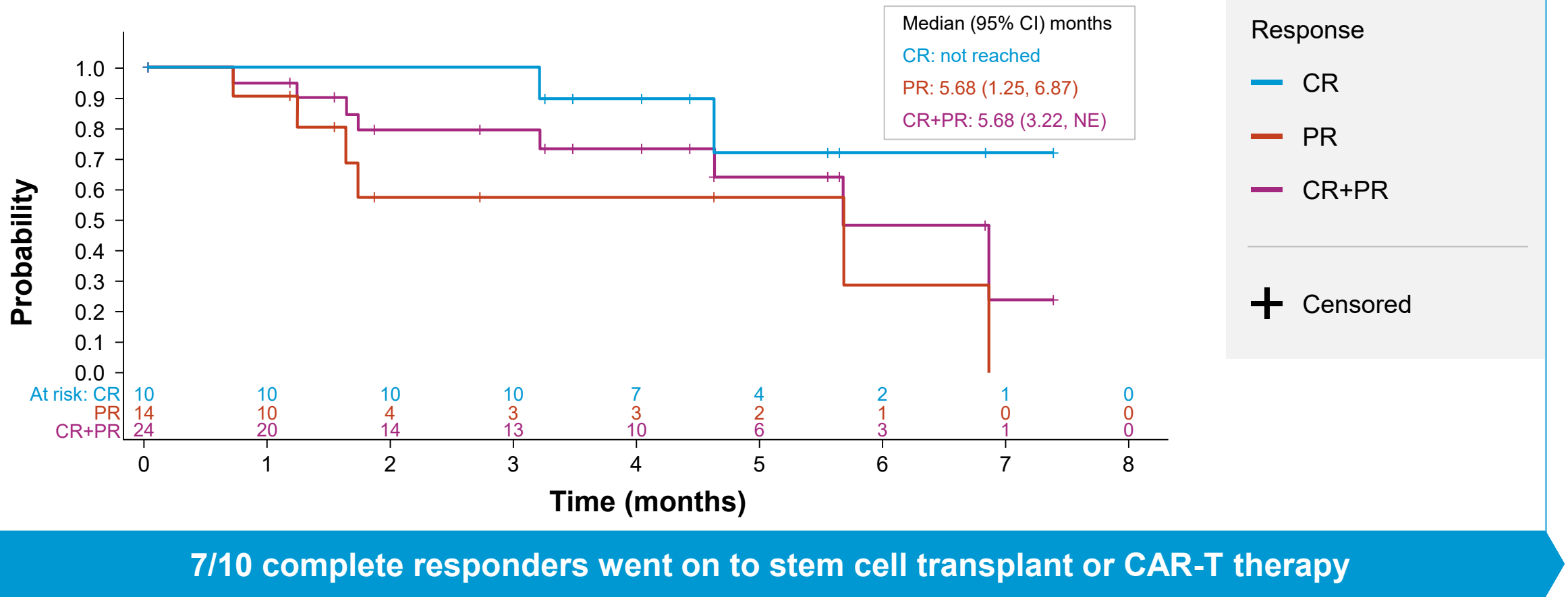
*Other defined as unknown, not evaluable or missing. DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements; PMBCL, primary mediastinal B-cell lymphoma. Data shown as of Oct 14, 2019.

Overall Response Rate (based on independent review)



CR, complete response; Lonca, loncastuximab tesirine; ORR, overall response rate; PR, partial response.
Data shown as of Oct 14, 2019.

Duration of Response



7/10 complete responders went on to stem cell transplant or CAR-T therapy

Includes central radiology review of progression, death, and clinical progression assessed by sites without radiologic confirmation. CAR-T, chimeric antigen T-cell; CI, confidence interval; CR, complete response; NE, not evaluable; PR, partial response. Data shown as of Oct 14, 2019.

Characteristics of Complete Responders

Patient characteristics				
Patient	**Histology**	**Cycles (N)**	**Study Treatment Status**	**Subsequent Therapy/Outcome**
1	DLBCL	2	Discontinued	CAR-T
2	HGBCL	6	Discontinued	Remains in CR
3	DLBCL	8	Discontinued	SCT
4	DLBCL, transformed follicular	4	Discontinued	SCT
5	DLBCL	2	Discontinued	Progressive disease: death
6	DLBCL, double expressor	10	Ongoing	Remains in CR
7	DLBCL	4	Discontinued	Autologous SCT
8	DLBCL	10	Discontinued	Allogeneic SCT
9	DLBCL, transformed follicular	5	Discontinued	Autologous SCT
10	DLBCL, transformed follicular	5	Discontinued	Allogeneic SCT

CAR-T, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements; SCT, stem cell transplant. Data shown as of Oct 14, 2019.

TEAE Profile

Non-hematological TEAEs (reported in ≥20% patients) (N=52)		
Preferred term, n (%)	**Grade 1–2**	**Grade ≥3**
GGT increased	14 (26.9)	13 (25.0)
Pyrexia	18 (34.6)	-
Cough	15 (28.8)	-
Hypokalemia	12 (23.1)	3 (5.8)
Nausea	15 (28.8)	-
ALP increased	13 (25.0)	1 (1.9)
Fatigue	12 (23.1)	2 (3.8)
Vomiting	11 (21.2)	-

Hematological TEAEs (reported in ≥20% patients) (N=52)		
Preferred term, n (%)	**Grade 1–2**	**Grade ≥3**
Platelet count decreased*	26 (50.0)	11 (21.2)
Neutrophil count decreased*	12 (23.1)	17 (32.7)
Anemia	8 (15.4)	6 (11.5)

*These data are based on laboratory abnormality reporting. ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event. Data shown as of Oct 14, 2019.

TEAEs of Interest

Fatal TEAEs were observed in 3 patients (5.8%)*: pneumonia, septic shock, hemoptysis

- These events were considered **not related** to the study treatment

Overall, 13 (25.0%) patients had **Lonca treatment withdrawal due to TEAEs**

- 7 patients (13.5%) had study **drug-related TEAEs** leading to withdrawal, most commonly GGT increased (4 patients; 7.7%)

No patients had **infusion-related reactions**

Edema or **effusion events** were reported in 15 patients (28.8%)

- 23.1% at grade 1–2 and 5.8% at grade 3

Skin-related TEAEs were reported in 19 (36.5%) patients; **all were grade 1–2**

*A fatal event of DLBCL was also reported but was considered to be disease progression. DLBCL, diffuse large B-cell lymphoma; GGT, gamma-glutamyltransferase; Lonca, loncastuximab tesirine; TEAE, treatment-emergent AE. Data shown as of Oct 14, 2019.

Dose Modifications

Most dose delays were <1 week and few dose reductions were required

Only 2 patients (3.8%) required a dose reduction

31 of 177 dose cycles (17.5%) were delayed (>2 days):

- 16 (9%) cycles were delayed <1 week
- 9 (5%) cycles were delayed 1−2 weeks
- 1 (<1%) cycle was delayed 2−3 weeks
- 5 (3%) cycles were delayed >3 weeks

Data shown as of Oct 14, 2019.

Summary

Lonca has encouraging single-agent antitumor activity and manageable toxicity in R/R DLBCL

ORR was 46.2%, with stable disease in a further 19.2% of patients

- Complete response rate was 19.2%
- Median DoR was not reached for complete responders and was 5.7 months for partial responders
- Following a response to Lonca, 7/10 complete responders went to stem cell transplant or CAR-T therapy

Notable toxicities included GGT increased, thrombocytopenia and neutropenia

- GGT increase was not associated with any evidence of liver dysfunction
- Effusion- and skin-related TEAEs were lower than reported in the Phase 1 trial of Lonca in NHL

- Most patients who required dose modifications had short dose delays and were able to continue treatment

➢ **Futility requirements were met and enrollment in the trial has now been completed**

CAR-T, chimeric antigen T cell; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; GGT, gamma-glutamyltransferase; Lonca, loncastuximab tesirine; NHL, non-Hodgkin lymphoma; ORR, overall response rate; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.