Loncastuximab Tesirine

Carmelo Carlo-Stella, MD

Department of Biomedical Sciences, Humanitas University, Milano, Italy

Department of Oncology and Hematology, Humanitas Research Hospital, Milano, Italy

AGGRESSIVE LYMPHOMA WORKSHOP, 8 – 9 September 2023, Bologna

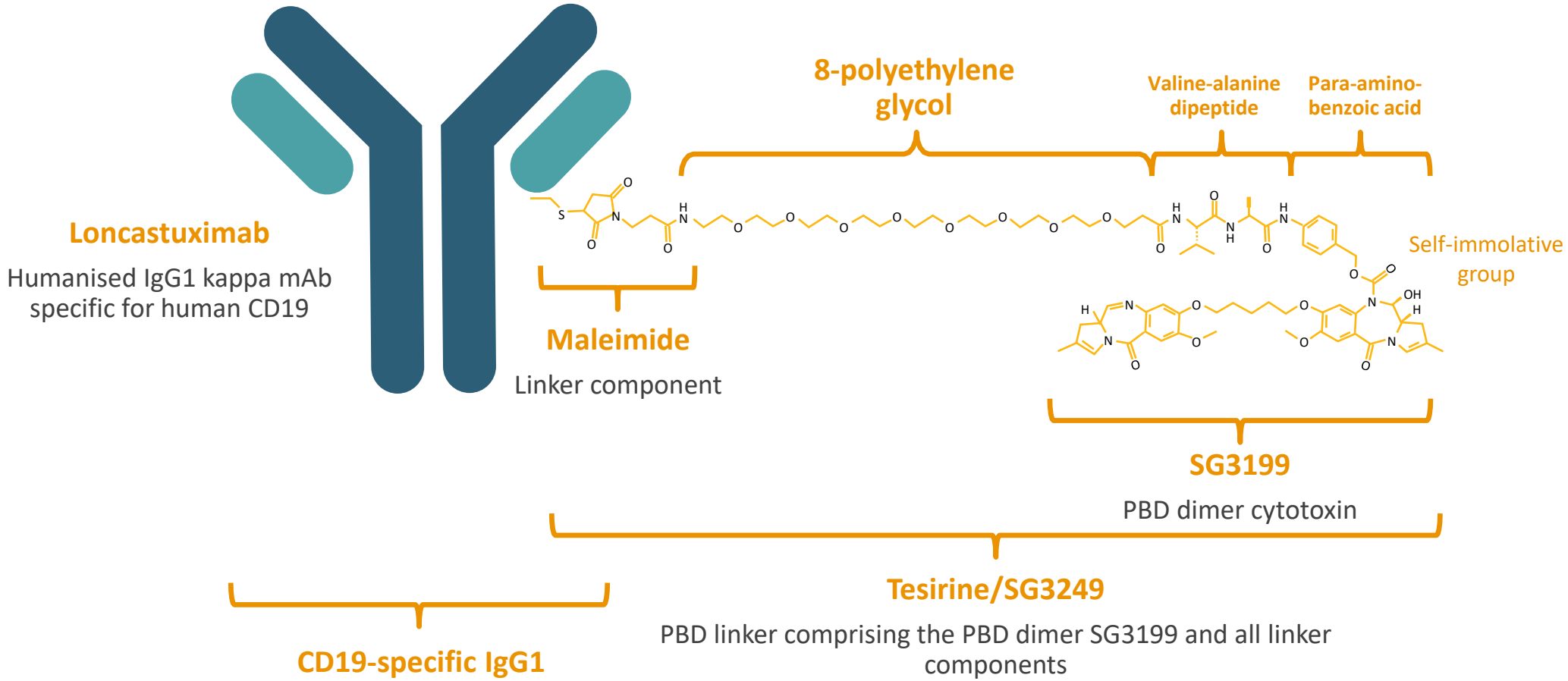
Disclosures

- Advisory Board
  - Genenta Science, ADC Therapeutics, Bristol-Myers Squibb/Celgene, Roche, Karyopharm
- Consultancy
  - Sanofi, ADC Therapeutic
- Honoraria
  - Amgen, Janssen Oncology, AstraZeneca, BMS, MSD, Novartis, Takeda
- Research Support
  - ADC Therapeutics

Loncastuximab Tesirine

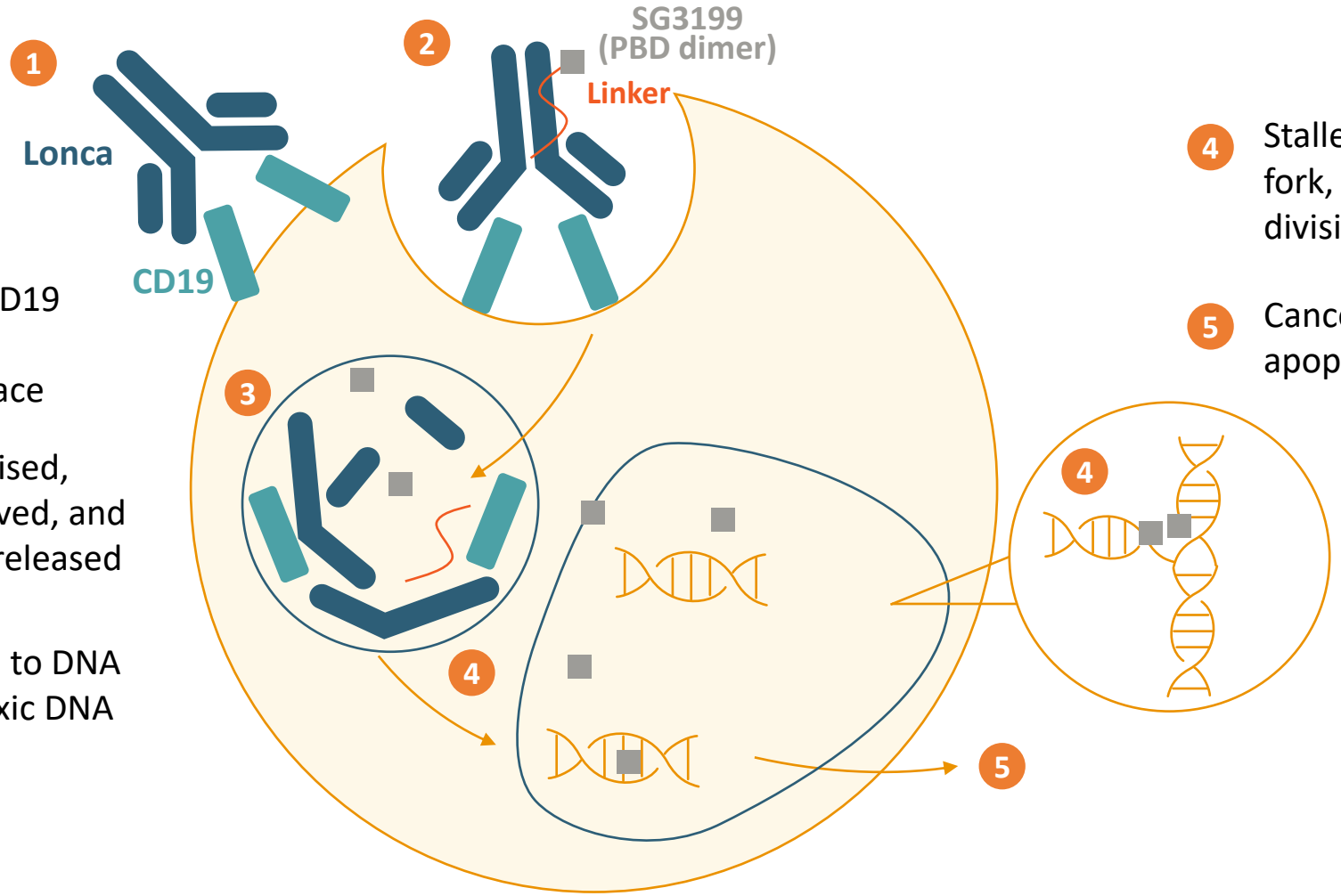
- FDA granted accelerated approval to loncastuximab for adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL NOS, DLBCL arising from low grade lymphoma, and HGBCL
- EMA granted conditional marketing authorisation to loncastuximab for patients with R/R DLBCL

Molecular structure **of Lonca**[1,2]



Lonca, loncastuximab tesirine; IgG1, immunoglobulin G1; mAB, monoclonal antibody; PBD, pyrrolobenzodiazepine.
1. Adapted from Zammarchi et al. *Blood* 2018 **2.** Zynlonta SmPC March 2023.

Mechanism of action **of Lonca**[1,2]



1. Lonca binds to CD19 antigen on the tumour cell surface
2. Lonca is internalised, the linker is cleaved, and PBD dimers are released
3. PBD dimers bind to DNA and form cytotoxic DNA crosslinks
4. Stalled DNA replication fork, blocking cell division
5. Cancer cell undergoes apoptosis

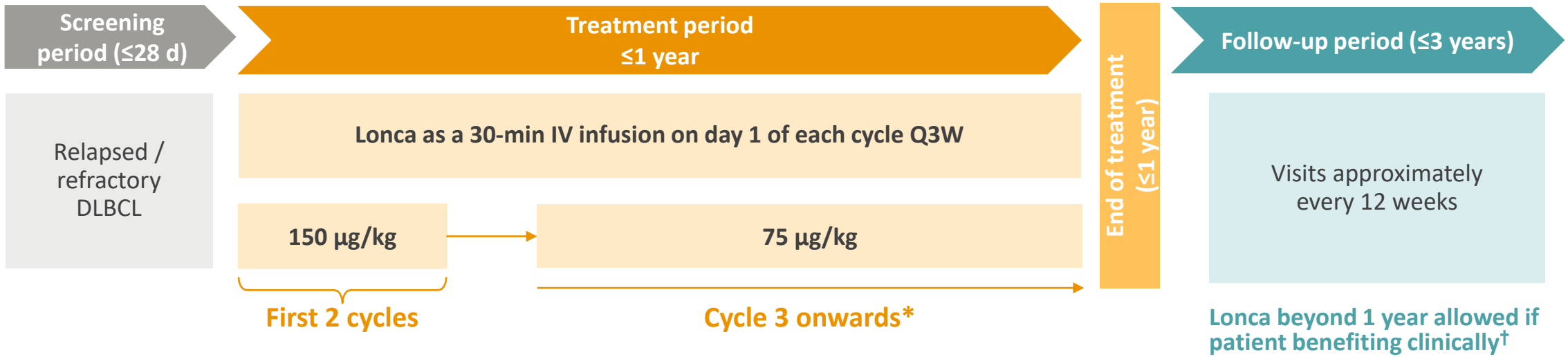
PBD, pyrrolobenzodiazepine.
1. Zynlonta SmPC March 2023 **2.** Calabretta et al. *Blood* 2022.

Study **design**[1-3]

Multicentre, open-label, single-arm, Phase 2 study

145 **patients were enrolled in US, UK, Italy, Switzerland**

Enrolment period: August 2018 – Sept 2019



- **Patients received oral dexamethasone premedication per protocol**
- **Disease assessment by central independent review using PET-CT at baseline, W6, W12, then Q9W until EOT**
  During the follow-up period, patients who discontinued Lonca for reasons other than PD or initiation of other anti-cancer therapy except SCT had imaging performed every 12 weeks until 1 year from EOT, then every 6 months, until progression up to 3 years from EOT
- **Data cut-offs:**
  - **Primary analysis:** April 6, 2020[3], median follow-up of 7.3 months[4]
  - **Follow-up analysis**: March 1, 2021, median follow-up of 7.8 months[5]

* Patients continued on treatment for up to one year **or** until disease relapse or progression, unacceptable toxicity, death, major protocol deviation, pregnancy, or patient, investigator, or sponsor decision. † If agreed with the sponsor. d, days; DLBCL, diffuse large B-cell lymphoma; EOT, end of treatment; IV, intravenous; Lonca, loncastuximab tesirine; PD, progressive disease; PET-CT, positron emission tomography-computed tomography; Q3W, every 3 weeks; Q9W, every 9 weeks; SCT, stem cell transplantation; W, week.

1. ClinicalTrials.gov NCT03589469 **2.** LOTIS-2 study protocol 2019 **3**. Caimi et al. *Lancet Oncol* 2021 **4.** Data on file **5.** Zinzani et al. ICML 2021.

Baseline **characteristics**[1-3]

Patient characteristics* (N=145)	
Sex, n (%)	
Female	60 (41)
Male	85 (59)
Age, years, median (min, max)	66.0 (23, 94)
Histology, n (%)	
DLBCL NOS	127 (88)
HGBL	11 (8)
PMBCL	7 (5)
Double/triple hit DLBCL†, n (%)	15 (10)
Double/triple expressor DLBCL, n (%)	20 (14)
Transformed DLBCL, n (%)	29 (20)
Disease stage‡, n (%)	
I–II	33 (23)
III–IV	112 (77)
ECOG performance status[4], n (%)	
0	58 (40)
1	78 (54)
2	9 (6)

Patient treatment history (N=145)	
No. of previous systemic therapies§, median (range)	3 (2–7)
First-line systemic therapy response, n (%)	
Relapse	99 (68)
Refractory‖	29 (20)
Other¶	17 (12)
Last-line systemic therapy response,# n (%)	
Relapse	43 (30)
Refractory‖	84 (58)
Other¶	18 (12)
Refractory to all prior therapies,‖ n (%)	
Yes	25 (17)
No	115 (79)
Other¶	5 (3)
Prior stem cell transplant, n (%)	
Allogeneic	2 (1)
Autologous	21 (14)
Both	1 (1)
Prior CAR T-cell therapy, n (%)	
Yes	13 (9)
No	132 (91)

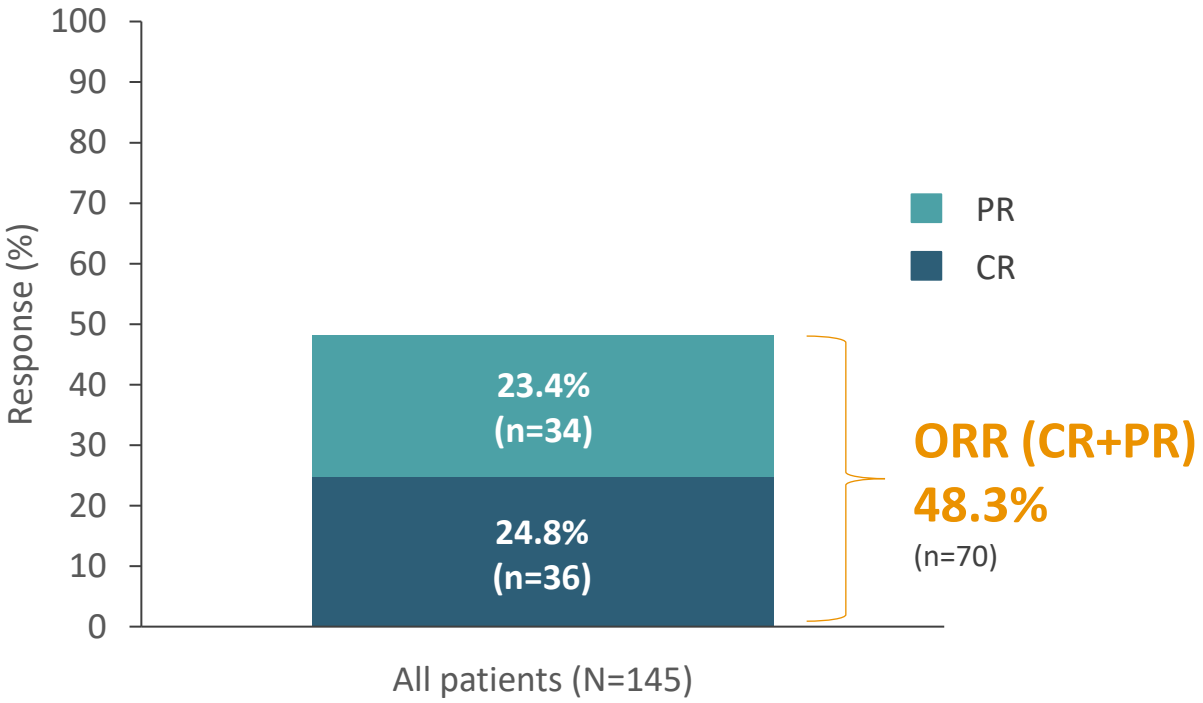
* Data cut-off: March 1, 2021. † Some patients had a diagnosis of double-hit or triple-hit lymphoma based on institutional pathology before the WHO classification of HGBCL with *MYC* and *BCL2* or *BCL6* rearrangements, or with *MYC* and *BCL2* and *BCL6* rearrangements. ‡ Disease stage at study entry. § Prior SCT is included. For patients who received an autologous transplant, the mobilisation regimen was considered a line of therapy if it was chemotherapy based and distinct from the other previous lines of treatment. ‖ Refractory disease defined as no response to therapy. ¶ Other defined as unknown, not evaluable or missing. # If SCT is most recent line, the variable is defined as response to the therapy immediately preceding SCT.

CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HGBL, high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements; NOS, not otherwise specified; PMBCL, primary mediastinal B-cell lymphoma; SCT, stem cell transplant; WHO, World Health Organization.

1. Zinzani et al. ICML 2021 **2.** Caimi et al. *Lancet Oncol* 2021 **3.** Caimi et al. ASCO 2021 **4.** Data on file.

Efficacy: ORR data[1]

Follow-up analysis



- **ORR** by central review was 70/145 **48.3%** (95% CI:[2] 39.9–56.7)
- CR rate 24.8% (95% CI:[2] 18.0–32.7)
- PR rate 23.4% (95% CI:[2] 16.8–31.2)

Median follow-up: 7.8 months (range 0.3–31.0)

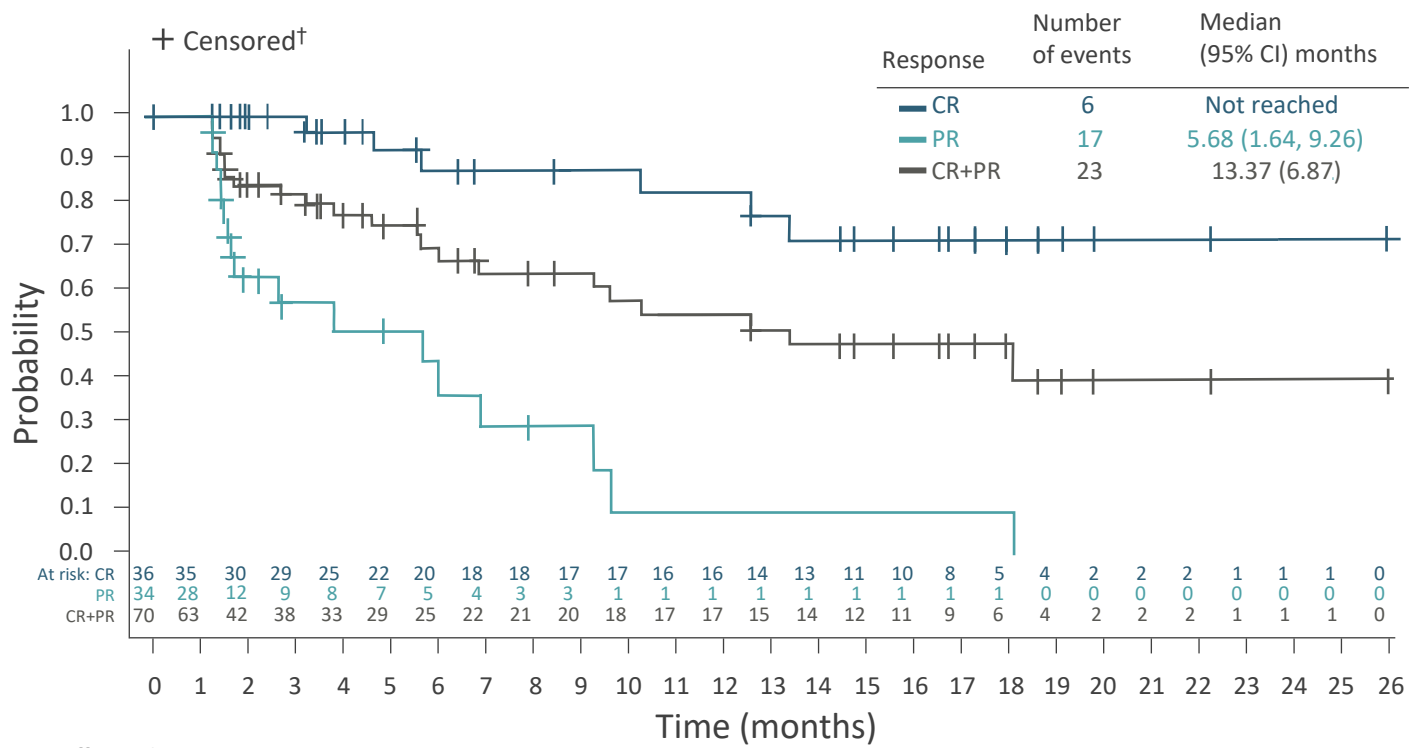
Mean number of Lonca cycles administered: 4.6 (range 1–26)
Median number of Lonca cycles administered: 3 (range 1–26)
Mean number of Lonca cycles in responders (n=70): 6.8 (range 1–26)

Response was assessed by central independent review. Data cut-off: March 1, 2021. Updated results ≥17 months since patients received their first dose.
CR, complete response; Lonca, loncastuximab tesirine; ORR, overall response rate; PR, partial response; SD, stable disease.
1. Zinzani et al. ICML 2021 **2.** Data on file.

Duration of response by best overall response[1]

Follow-up analysis

Duration of response by best overall response* (all-treated population) (N=145)



mDOR for the **70 responders**
13.4 months
(95% CI: 6.9–NE)

mDOR for patients with a **CR**
Not reached

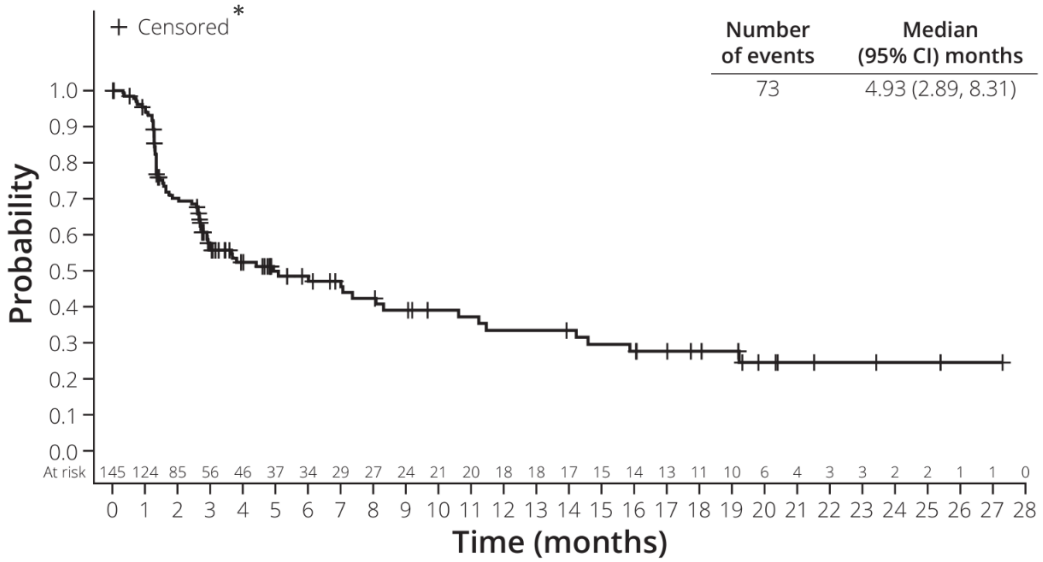
mDOR for patients with a **PR**
5.7 months

Data cut-off: March 1, 2021.
* DOR was defined as the time from earliest date of first response until the first date of either disease progression or death due to any cause.[2] † Patients with events after start of subsequent anticancer therapy or procedure, or progression free and alive at data cut-off, or who had unknown status were censored at last valid tumour assessment on or before start of subsequent anticancer therapy or procedure or data cut-off.[2]
CI, confidence interval; CR complete response; DOR, duration of response; NE, not estimable; m, median; ORR, overall response rate; PR, partial response.
1. Zinzani et al. ICML 2021 **2.** Caimi et al. *Lancet Oncol* 2021.

OS and PFS[1]

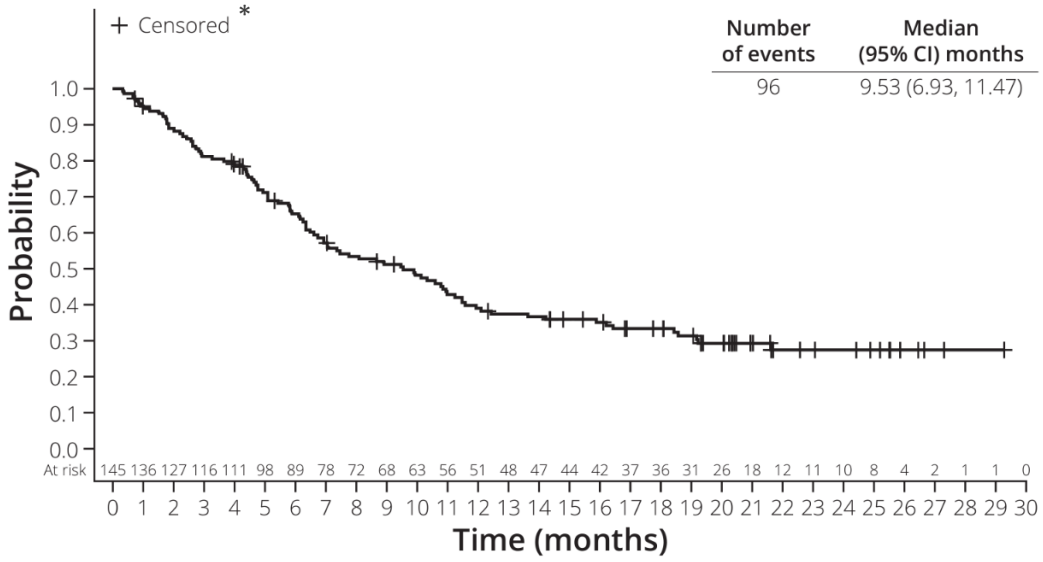
Follow-up analysis

PFS (all-treated population) (N=145)



mPFS was 4.9 months

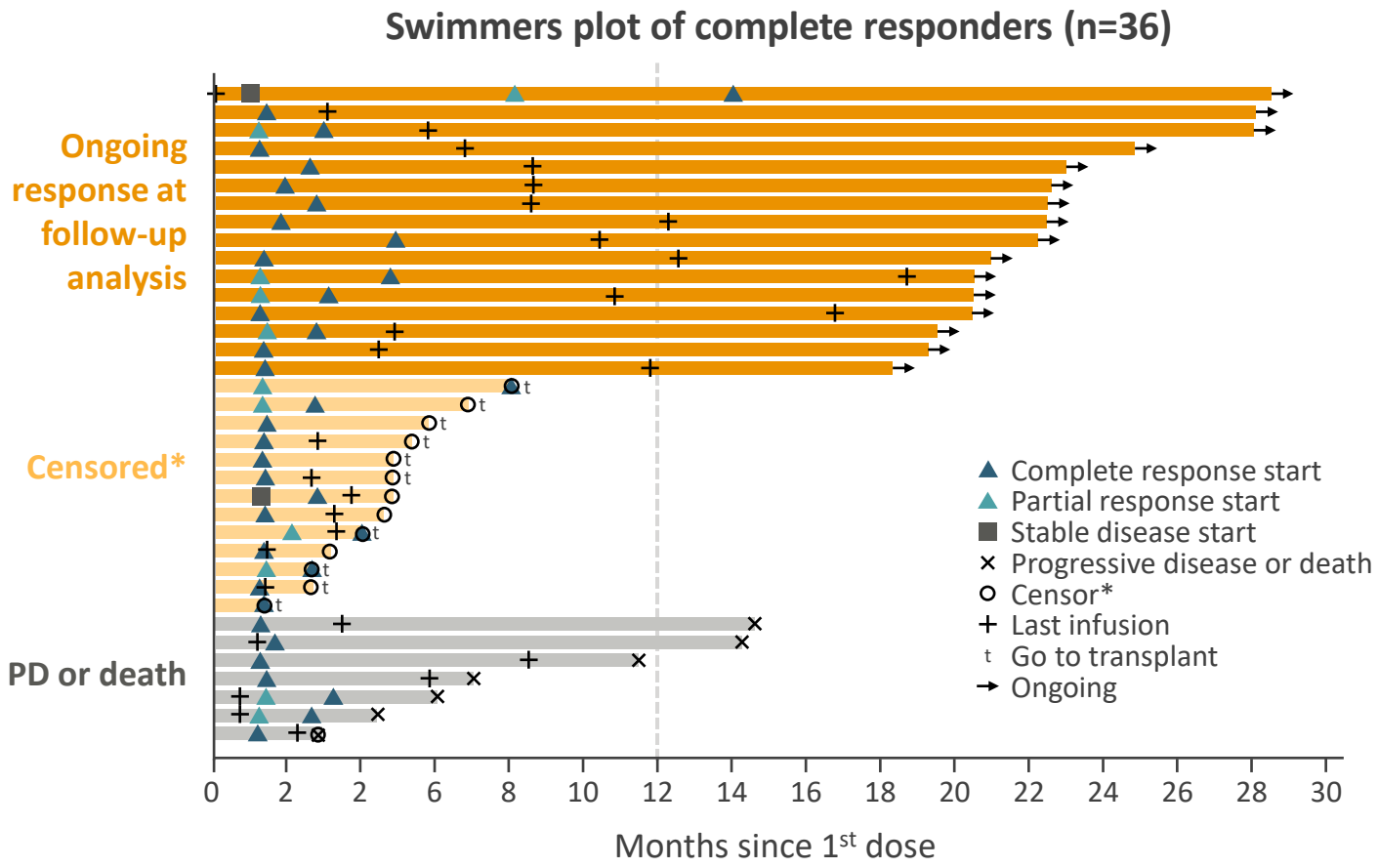
OS (all-treated population) (N=145)



mOS was 9.5 months

Data cut-off: March 1, 2021.
Patients with events after start of subsequent anticancer therapy or procedure, or progression free and alive at data cut-off, or who had unknown status were censored at last valid tumour assessment on or before start of subsequent anticancer therapy or procedure or data cut-off.[2]
CI, confidence interval; m, median; OS, overall survival; PFS, progression-free survival.
1. Zinzani et al. ICML 2021 **2.** Caimi et al. *Lancet Oncol* 2021.

Follow-up of complete responders[1]



At data cut-off, 44.4% (16/36) of patients remained in CR with no further treatment

36.1% (13/36) were censored; of them, 10 patients were censored due to transplant while in CR

19.4% (7/36) patients had PD or death

After longer follow-up, durable responses continue to be observed

Data cut-off: March 1, 2021. Each bar represents 1 patient. Patients were treated until progressive disease or unacceptable toxicity. The median number of cycles for CR was 8 (range 1–26).
* Only for censored patients who discontinued the trial due to reasons other than progression or who went onto a different anticancer treatment other than transplant.
CR, complete response; PD, progressive disease.

1. Zinzani et al. ICML 2021.

Exploratory analyses of complete response[1]

Response in select patient subgroups

Subgroup	Patients achieving CR (n/N)	CRR, % (95% CI)
All[2]	35/145	24.1 (17.4, 31.9)
Age		
<65 years	12/65	18.5 (9.9, 30.0)
≥65 to < 75 years	15/59	25.4 (15.0, 38.4)
≥75 years	8/21	38.1 (18.1, 61.6)
WHO classification		
DLBCL NOS	30/127	23.6 (16.5, 32.0)
PMBCL	0/7	0.0 (NE)
HGBL*	5/11	45.5 (16.7, 76.6)
Double/triple hit†		
No	30/130	23.1 (16.1, 31.3)
Yes	5/15	33.3 (11.8, 61.6)
Double/triple expressor		
No	31/125	24.8 (17.5, 33.3)
Yes	4/20	20.0 (5.7, 43.7)
Transformed disease		
Transformed	7/29	24.1 (10.3, 43.5)
De novo	28/116	24.1 (16.7, 33.0)
Cell-of-origin‡		
GCB	12/48	25.0 (13.6, 39.6)
ABC	5/23	21.7 (7.5, 43.7)

Subgroup	Patients achieving CR (n/N)	CRR, % (95% CI)
All[2]	35/145	24.1 (17.4, 31.9)
First-line response		
Relapse	26/99	26.3 (17.9, 36.1)
Refractory	5/29	17.2 (5.8, 35.8)
Prior HSCT		
Yes	7/24	29.2 (12.6, 51.1)
No	28/121	23.1 (16.0, 31.7)
Prior CAR T-therapy		
Yes	2/13	15.4 (1.9, 45.4)
No	33/132	25.0 (17.9, 33.3)
Prior systemic therapies		
2 prior lines	15/63	23.8 (14.0, 36.2)
3 prior lines	5/35	14.3 (4.8, 30.3)
>3 prior lines	15/47	31.9 (19.1, 47.1)

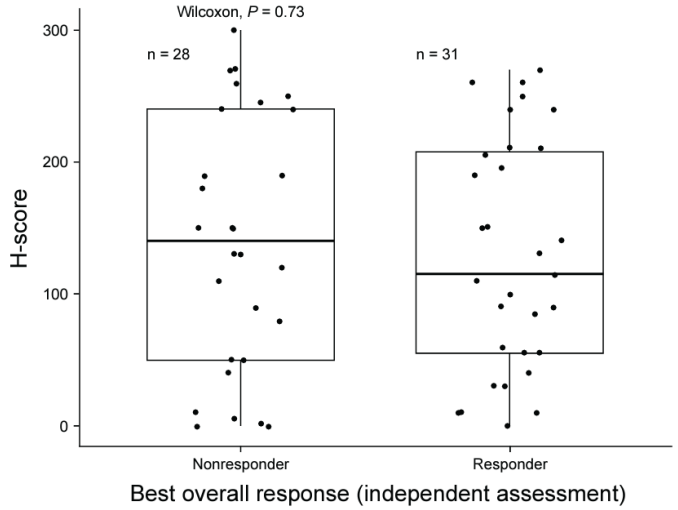
Subgroup analyses were limited in statistical comparison due to small sample size. * HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements defined by the 2016 revision of the WHO classification of lymphoid neoplasms. † Some patients had a diagnosis of double-/triple-hit lymphoma based on institutional pathology prior to the WHO classification of HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements. ‡ ABC and GCB were investigator-reported with no independent testing. ABC, activated B-cell-like; CAR, chimeric antigen receptor; CI, confidence interval; CR(R), complete response (rate); DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell-like; HGBL, high-grade B-cell lymphoma; HSCT, haematopoietic stem cell transplantation; NE, not estimatable; NOS, otherwise specified; ORR, overall response rate; PMBCL, primary mediastinal large B-cell lymphoma; WHO, World Health Organization.

1. Caimi et al. *Lancet Oncol* 2021 (suppl.) **2.** Caimi et al. *Lancet Oncol* 2021.

CD19 expression and Lonca efficacy

- The cohort included **59 patients** with any prior systemic therapies*
  - Median time from biopsy to Lonca was **18 days** (1.5–185 days)

Baseline tumour CD19 H-score by response to loncastuximab†



* Patients who had received previous CD19-directed therapy must have had a biopsy confirming CD19 protein expression after completion of the CD19-directed therapy. † Independent assessment.
CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; H-score, HistoScore; Lonca, loncastuximab tesirine; R/R, relapsed or refractory.

1. Caimi et al. ASH 2022.

Characteristics of patients who previously received CAR-T[1]

13 (9%) patients from LOTIS-2 had received prior CAR T-cell therapy;
CD19 expression was required per protocol, but no prior CAR-T patients failed screening due to a lack of CD19

Patient & disease characteristics			
Patient & disease baseline characteristics	N=13	**CAR T-cell therapy characteristics**	N=13
Sex, male, n (%)	9 (69)	**Time between diagnosis and CAR-T infusion,** median (range), mo	10 (2–79)
Race, n (%)		**No. of LOT prior to CAR-T**, median (range)	3 (1–6)
White	12 (92)	**Time from CAR-T to Lonca**, median (range)	7 mo (45–400 d)*
Pacific Islander	1 (8)	**Type of CAR-T**, n (%)	
Lymphoma subtype, n (%)		Axi-cel	7 (54)
DLBCL, NOS	5 (38)	Liso-cel	2 (15)
Transformed follicular	4 (31)	Investigational CD19	2 (15)
Richter transformation	1 (8)	Investigational CD19/CD20	1 (8)
HGBL—DH/TH	3 (23)	Investigational CD19/CD22	1 (8)
DH/TH, n (%)	5 (38)		
Stage at diagnosis		**Best response to CAR-T**, n (%)	
Stage I–II	2 (15)	Complete response	7 (54)
Stage III–IV	11 (85)	Partial response	2 (15)
Primary refractory, n (%)	10 (77)	No response	4 (31)

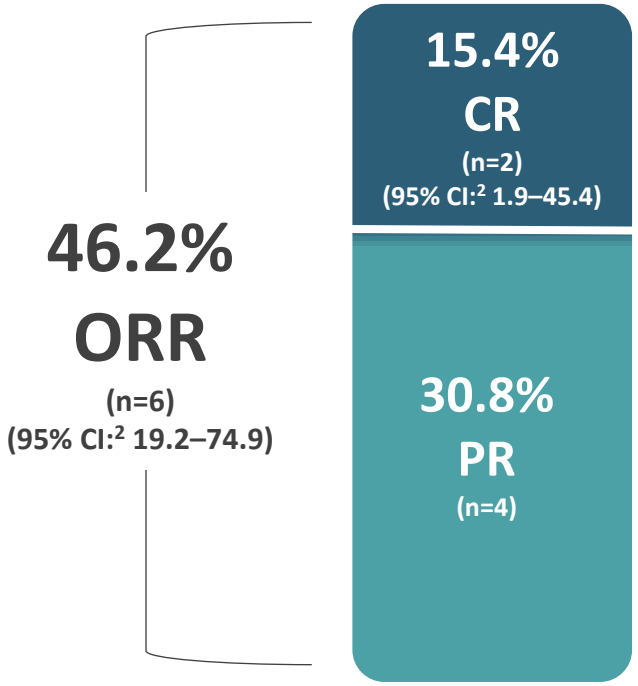
* Lonca was the first treatment after CAR-T in 10 patients; 3 patients received other treatments prior to Lonca, including chemoimmunotherapy (n=1, R-GemOx) and allogeneic SCT (n=1), and one patient received chemoimmunotherapy (R-GemOx), followed by a clinical trial with venetoclax and a bromodomain inhibitor.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; d, days; DH, double-hit; DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; liso-cel, lisocabtagene maraleucel; Lonca, loncastuximab tesirine; LOT, line of therapy; mo, months; NOS, not otherwise specified; R-GemOx, gemcitabine-oxaliplatin plus rituximab; SCT, stem cell transplant; TH, triple-hit.

1. Caimi et al. *Clin Lymphoma Myeloma Leuk* 2022.

Efficacy in patients who previously received CAR-T[1]

After a median follow-up of 8 months, 13 patients received a median of 2 cycles of Lonca (range 1–9)



Median DOR: 8 months
(95% CI: 103 days–NR)

Response to Lonca, based on independent review, was seen in 6/13 (46.2%) patients already treated with CAR-T

Of these, 5 had previously presented response to CAR-T and the sixth patient had prolonged, stable disease for > 1 year after CAR-T

While limited by its small sample size, the response rates observed in this high-risk population are comparable to those observed in other patient subsets

CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; DOR, duration of response; Lonca, loncastuximab tesirine; NR, not reached; ORR, overall response rate; PR, partial response.
1. Caimi et al. *Clin Lymphoma Myeloma Leuk* 2022 **2.** Data on file.

Response to CAR T-cell therapy in patients who previously received Lonca **in LOTIS-2**[1]

Best response, n (%)	N=16 150 µg/kg
Complete response	8 (50.0)
Partial response	1 (6.3)
Stable disease	1 (6.3)
Not evaluable	1 (6.3)
Progressive disease	5 (31.3)

At the September 2022 data cut-off response to subsequent CAR T-cell therapy was evaluated for the 16 patients that underwent CAR T-cell therapy after previously receiving Lonca within the LOTIS-2 study

Investigator-assessed ORR to CAR T-cell therapy after Lonca was 56.3%
(9/16 patients; 95% CI: 29.9–80.2)

Type of subsequent CD19-directed CAR T-cell therapy received is not available.
CAR, chimeric antigen receptor; CI, confidence interval; Lonca, loncastuximab tesirine; ORR, overall response rate, CR complete response.
1. Data on file.

Safety results: TEAEs occurring in ≥ 10% of patients[1]

Non-haematological TEAE	Patients, n (%) All grades	Patients, n (%) Grades 3 or 4
Fatigue	40 (27)	2(1)
Nausea	34 (23)	0 (0)
Cough	32 (22)	1 (1)
Peripheral oedema	**29 (20)**	**2 (1)**
Pyrexia	28 (19)	2 (1)
Diarrhoea	25 (17)	3 (2)
Decreased appetite	22 (15)	0 (0)
Vomiting	19 (13)	0 (0)
Rash	**19 (13)**	**1 (1)**
Pruritus	18 (12)	0 (0)
Constipation	17 (12)	0 (0)
Insomnia	16 (11)	0 (0)
Abdominal pain	16 (11)	4 (3)
Dyspnoea	17 (11)	2 (1)
Headache	15 (11)	1 (1)
Erythema	**15 (11)**	**1 (1)**
Pleural effusion	**15 (10)**	**3 (2)**
Photosensitivity reaction	**15 (10)**	**3 (2)**

- TEAEs considered likely to be related to the PBD payload include **oedema or effusion, skin toxicity (e.g., rash, erythema) or photosensitivity, and liver enzyme elevation**[1,2]
- After introduction of dexamethasone premedication, standard spironolactone diuretics, and more stringent recommendations on sun exposure, **PBD-related AEs were generally mild-to-moderate in severity and were generally reversible and manageable** with dose delays as required

Data cut-off: April 6, 2020. AE, adverse event; PBD, pyrrolobenzodiazepine; TEAE, treatment-emergent adverse event. **1.** Caimi et al. *Lancet Oncol* 2021 **2.** Sauber et al. *Regul Toxicol Pharmacol* 2019.

TEAEs occurring in ≥ 10% of patients[1]

Haematological TEAE	Patients, n (%) All grades	Patients, n (%) Grades 3 or 4
Neutropenia	57 (40)	37 (26)
Thrombocytopenia	48 (33)	26 (18)
Anaemia	38 (26)	15 (10)
Leukopenia	21 (14)	13 (9%)
Febrile neutropenia	5 (3)	5 (3)

Laboratory TEAE	Patients, n (%) All grades	Patients, n (%) Grades 3 or 4
GGT increase	**59 (40)**	**24 (16)**
ALP increase	29 (20)	1 (1)
AST increase	23 (16)	1 (1)
ALT increase	23 (16)	4 (3)

- Haematological parameters generally decreased with treatment but tended to partially recover between cycles
- Increased GGT was **not associated with synthetic dysfunction** or severe hepatic events

Data cut-off: April 6, 2020.
ALP, bood alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event.
1. Caimi et al. *Lancet Oncol* 2021.

Safety results **according to age groups**

TEAEs in ≥20% of the all-treated population				
Preferred term	**Patients, n (%)**			
	<65 years (n=65)	**≥65 to <75 years (n=59)**	**≥75 years (n=21)**	**Total (N=145)**
Patients with any TEAE	**65 (100)**	**58 (98.3)**	**20 (95.2)**	**143 (98.6)**
GGT increased	33 (50.8)	23 (39.0)	3 (14.3)	59 (40.7)
Neutropenia	33 (50.8)	20 (33.9)	4 (19.0)	57 (39.3)
Thrombocytopenia	28 (43.1)	17 (28.8)	3 (14.3)	48 (33.1)
Fatigue	21 (32.3)	15 (25.4)	4 (19.0)	40 (27.6)
Anaemia	23 (35.4)	9 (15.3)	6 (28.6)	38 (26.2)
Nausea	17 (26.2)	13 (22.2)	4 (19.0)	34 (23.4)
Cough	19 (29.2)	9 (15.3)	4 (19.0)	32 (22.1)
Alkaline phosphatase increased	18 (27.7)	10 (16.9)	1 (4.8)	29 (20.0)
Peripheral oedema	11 (16.9)	14 (23.7)	4 (19.0)	29 (20.0)

No increase in toxicity observed in elderly patients compared with younger patients

Data cut-off: April 6, 2020. TEAEs were reported for the all-treated population.
GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event.
1. Caimi et al. *Lancet Oncol* 2021 (suppl.).

Conclusions

- LOTIS-2 is a large pivotal, open-label, single-arm, Phase 2 trial that evaluated **single-agent** Lonca in a broad population of 145 heavily pretreated and **difficult-to-treat patients with R/R DLBCL and HGBL** after ≥2 lines of therapy[1]
- Lonca showed efficacy in this population (**ORR 48.3%, CR 24.1%**) including patients with DH/TH, refractory to previous therapies, and who previously received CAR T-cell therapy.[1,2] Responses were confirmed in follow-up analyses and demonstrated a **median duration of 13.4 months**[1-3]
- Lonca **safety and tolerability profile was manageable** and no increase in toxicity was observed in patients aged 65 years or older[1-3]
- Notably, Lonca demonstrated **efficacy in patients treated with previous CAR T-cell therapy**[1,2] and allowed for response to **subsequent CAR T-cell therapy**[4,5]. Also, in an exploratory analysis, responses were demonstrated in patients with low levels of CD19 expression[6]
- The present data suggest single-agent **loncastuximab tesirine as a valuable treatment option** for patients with R/R DLBCL who have received **≥2 lines of systemic therapy**[1]

CAR, chimeric antigen receptor; CR, complete response; DH/TH, double-hit or triple-hit; DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; Lonca, loncastuximab tesirine; ORR, overall response rate; R/R, relapsed or refractory.

1. Caimi et al. *Lancet Oncol* 2021 **2.** Caimi et al. *Lancet Oncol* 2021 (suppl.) **3.** Zinzani et al. ICML 2021 **4.** Data on file **5.** Thapa et al. *Blood Adv* 2020 **6.** Caimi et al. ASH 2022.