EUROPEAN HEMATOLOGY ASSOCIATION

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25th Congress of the European Hematology Association

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Initial Results 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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28 May 2020
Aggressive lymphomas: prospective studies

Disclosures and Acknowledgements

C. Carlo-Stella: research support from ADC Therapeutics, Sanofi, Roche; consultant or advisor for Boehringer Ingelheim, Sanofi, ADC Therapeutics, Servier, Roche, Genenta Science; honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Takeda, Novartis, Janssen.

P. L. Zinzani: consultant to Verastem, MSD, Sanofi and Eusapharma; speaker for Verastem, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, Immune Design, Celgene, Portola, Roche, Eusapharma, Kyowa Kirin; advisory boards for Verastem, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, MSD, Immune Design, Celgene, Portola, Roche, Eusapharma, Kyowa Kirin, ADC Therapeutics; research support from ADC Therapeutics.

B. Kahl: research support from ADC Therapeutics; advisor or consultant for ADC Therapeutics, Seattle Genetics, Genentech.

P. F. Caimi: research support from ADC Therapeutics; advisory boards for ADC Therapeutics, Genentech, Kite Pharma; speaker for Celgene.

M. Solh: research support from ADC Therapeutics; speaker bureau for Amgen, Celgene.

K. Ardeshna: supported by the University College London (UCL)/UCL Hospitals (UCLH) Biomedical Research Unit; honoraria/advisory boards for ADC Therapeutics, Celgene, Gilead, Takeda, Roche, Beigene.

A. Stathis: institutional research funding from Roche, Pfizer, Merck, Bayer, Novartis, MEI-Pharma, ADC Therapeutics; other renumeration from Abbvie, PharmaMar.

M. Hamadani: research support from ADC Therapeutics, Otsuka, Takeda, Sanofi Genzyme, MedImmune, Merck; speaker bureau for Sanofi Genzyme; advisor/consultant for MedImmune, Jansen, Celgene, ADC Therapeutics.

W. Ai: research support from Nurix Therapeutics; advisory boards for ADC Therapeutics, Nurix, Kymera.

B. Hess: no relevant disclosures.

J. P. Alderuccio: honoraria from OncLive and Oncinfo; immediate family member has served on advisory boards for Puma Biotechnology, Inovio Pharmaceuticals, Agios Pharmaceuticals, Forma Therapeutics and Foundation Medicine.

J. Feingold, D. Ungar, S. He, and **Y. Qin:** employees of ADC Therapeutics with stock options.

J. Radford: consultant/advisory role for Takeda, ADC Therapeutics, Bristol-Myers Squibb, Novartis, Kite Pharma; speaker for Takeda, ADC Therapeutics, Seattle Genetics; research support from Takeda; provided expert testimony for Takeda and ADC Therapeutics; stocks/shares: AstraZeneca and GSK (spouse).

This study was funded by ADC Therapeutics SA (NCT03589469)

Acknowledgements

The authors would like to thank all the participating patients and their families, all study co-investigators and research coordinators.

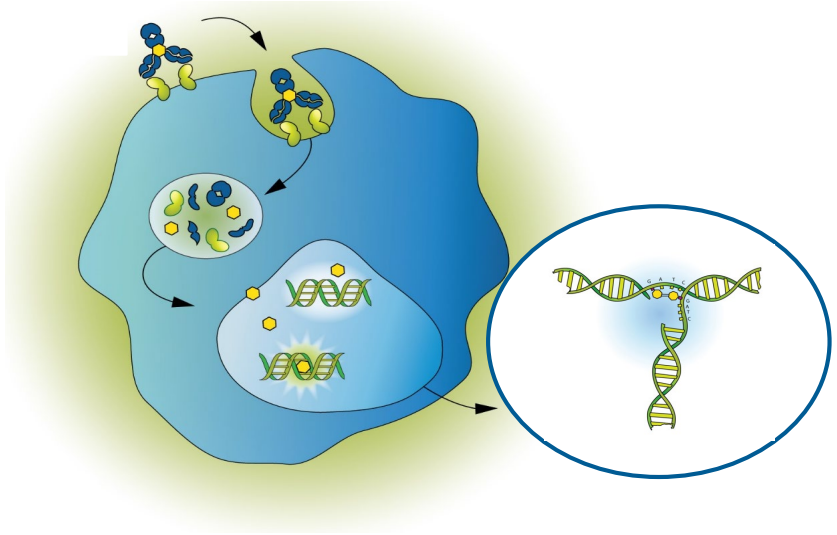
Editorial support was provided by Louise Gildea, PhD, and Becky Salisbury, PhD, at Fishawack Health, funded by ADC Therapeutics.

Loncastuximab Tesirine (ADCT-402)

Despite recent advances in DLBCL treatment, outcomes for patients with R/R DLBCL remain poor[1]

- Lonca is an ADC comprising a humanised anti-CD19 antibody conjugated to a potent PBD dimer[2]
- Lonca had encouraging antitumour activity and acceptable safety in R/R DLBCL in a Phase 1 first-in-human trial[3]

Lonca targets CD19, which is expressed in the majority of B-cell malignancies[4]



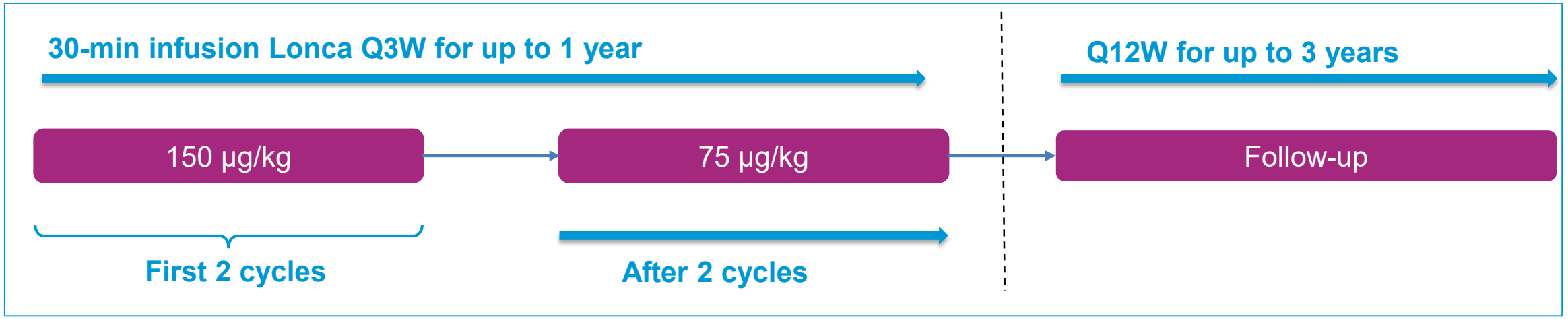
1. Lonca binds to CD19 antigen and is internalised
2. The linker is cleaved and PBD dimers released
3. Cytotoxic DNA cross-links are formed
4. The DNA replication fork stalls
5. The cell goes into apoptosis

1. Crump M. *et al*. *Blood*. 2017;130:1800. 2. Zammarchi F. *et al*. *Blood*. 2018;131:1094; 3. Kahl B.*et al. Clin Cancer Res*. 2019;25:6986; 4. Wang K. *et al*. *Exp Hematol Oncol*. 2012;1:36. ADC, antibody-drug conjugate; DLBCL, diffuse large B-cell lymphoma; Lonca, loncastuximab tesirine; PBD, pyrrolobenzodiazepine; R/R, refractory/relapsed.

Study Design: Single-arm, Open-label Phase 2 Study

Patient population:
Patients with R/R DLBCL following ≥2 lines of prior systemic therapy

Primary objective:
Evaluate efficacy, using ORR (central review), and safety of the full Phase 2 study population



Futility requirements met:
ORR for first 52 patients[1]

Total enrolment:
145 patients

1. Carlo-Stella C, *et al. Blood.* 2019;134(Supp1):757. DLBCL, diffuse large B-cell lymphoma; Lonca, loncastuximab tesirine; ORR, overall response rate; Q3W, every 3 weeks; Q12W, every 12 weeks; R/R, relapsed/refractory.

Baseline Characteristics

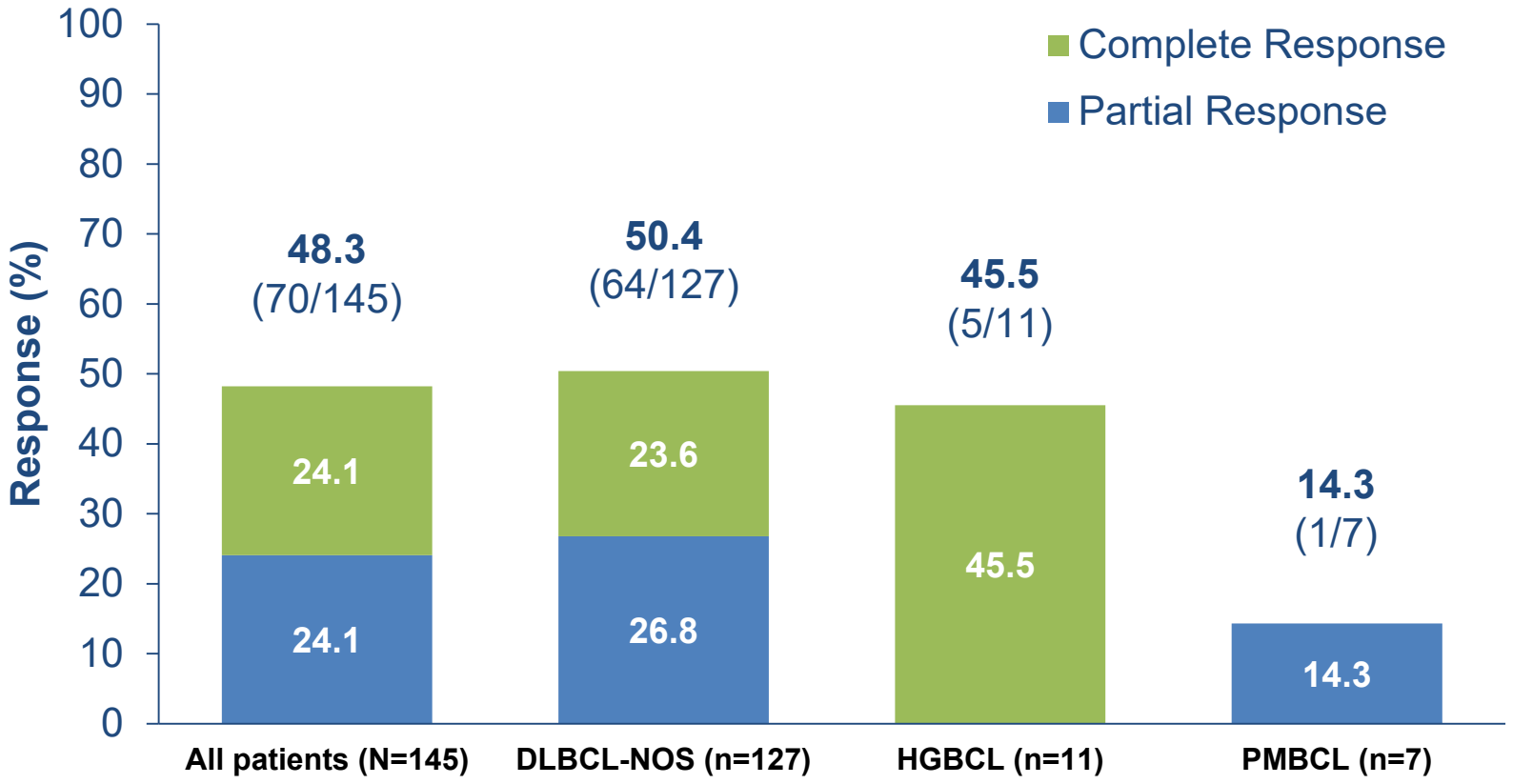
Patient characteristics		Total (N=145)
Sex, n (%)	Female Male	60 (41.4) 85 (58.6)
Age, years, median (min, max)		66.0 (23–94)
Histology, n (%)	DLBCL HGBCL PMBCL	127 (87.6) 11 (7.6) 7 (4.8)
Double/triple hit, n (%)		15 (10.3)
Double/triple expressor, n (%)		20 (13.8)
Transformed disease, n (%)		29 (20.0)
Stage, n (%)	I–II III–IV	33 (22.8) 112 (77.2)

Patient treatment history		Total (N=145)
No. of previous systemic therapies,* median (range)		3 (2–7)
First-line systemic therapy response, n (%)	Relapse Refractory† Other‡	99 (68.3) 29 (20.0) 17 (11.7)
Last-line systemic therapy response,¶ n (%)	Relapse Refractory† Other‡	43 (29.7) 84 (57.9) 18 (12.4)
Refractory to all prior therapies, n (%)	Yes No Other‡	25 (17.2) 115 (79.3) 5 (3.4)
Prior stem cell transplant, n (%)	Allogeneic Autologous Both	2 (1.4) 21 (14.5) 1 (0.7)

145 patients were enrolled and received a mean of 4.3 cycles of Lonca (range: 1–15)

Data cut-off: 06 April 2020. *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. 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 SCT, stem cell transplant.

Response to Lonca by Histology



ORR in the total population was 48.3% (95% CI: 39.9, 56.7) and an additional 15.2% (22 pts) had stable disease

Data cut-off: 06 April 2020. Response assessed by independent reviewer. CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements; Lonca, loncastuximab tesirine; ORR, overall response rate; PMBCL, primary mediastinal B-cell lymphoma.

Subgroup Analysis of ORR

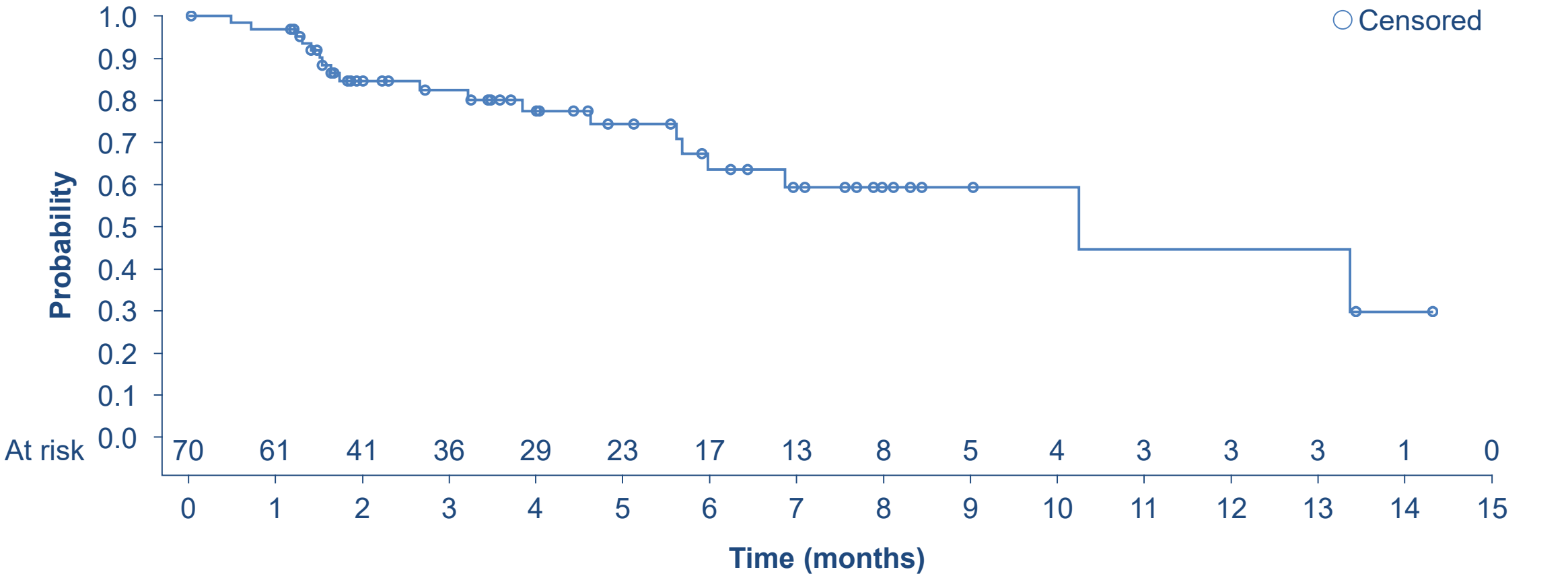
Patients refractory to first-line or last-line prior therapy had ORRs (CRR) of 37.9% (17.2%) and 36.9% (11.9%), respectively

Subgroup	Patients (n/N)	ORR	ORR (95% CI)
All	70/145		48.3 (39.9, 56.7)
Age			
<65 years	32/65		49.2 (36.6, 61.9)
≥65 years	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			
No	60/125		48.0 (39.0, 57.1)
Yes	10/20		50.0 (27.2, 72.8)

Subgroup	Patients (n/N)	ORR	ORR (95% CI)
All	70/145		48.3 (39.9, 56.7)
First-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*			
Relapse	60/115		52.2 (42.7, 61.6)
Refractory†	9/25		36.0 (18.0, 57.5)
Prior stem cell transplant			
Yes	14/24		58.3 (36.6, 77.9)
No	56/121		46.3 (37.2, 55.6)

Data cut-off: 06 April 2020. Response assessed by independent reviewer. *Prior systemic therapies. †Refractory disease defined as no response to therapy.
ABC, activated B-cell–like; CI, confidence interval; CRR, complete response rate; GCB, germinal centre B-cell–like; ORR, overall response rate.

Duration of Response



Median duration of response was 10.25 months (95% CI: 5.98, –)

Data cut-off: 06 April 2020. Based on independent reviewer data, including death and clinical disease progression after last scan assessed by independent reviewer as an event. Number of events: 19. CI, confidence interval.

TEAEs of Any Grade in ≥20% of Patients (Safety Analysis Set; N=145)

Preferred term n (%)	Patients n (%)
Patients with any TEAE	**143 (98.6%)**
GGT increased	59 (40.7)
Neutropenia	57 (39.3)
Thrombocytopenia	48 (33.1)
Fatigue	40 (27.6)
Anaemia	38 (26.2)
Nausea	34 (23.4)
Cough	32 (22.1)
Alkaline phosphatase increased	29 (20.0)
Peripheral oedema	29 (20.0)

The most common grade ≥3 TEAEs (≥10% of patients) were:

- Neutropenia (37 patients; 25.5%)
  - Incidence of febrile neutropenia was low (5 patients; 3.4%)
- Thrombocytopenia (26 patients; 17.9%)
- GGT increased (24 patients; 16.6%)
- Anaemia (15 patients; 10.3%)

Data cut-off: 06 April 2020.
GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event.

Conclusions

Lonca had substantial single-agent antitumour activity in patients with R/R DLBCL who failed established therapies

- ORR was 48.3% (70/145 patients; 95% CI: 39.9, 56.7)
- CRR was 24.1% (35/145 patients; 95% CI: 17.4, 31.9)
- Median duration of response was 10.25 months (95% CI: 5.98, –)
- The toxicity profile was manageable and no new safety concerns were identified
- There is the potential for Lonca to fill a critical unmet need for treatment of heavily pre-treated patients with DLBCL

Data cut-off: 06 April 2020. Response assessed by independent reviewer. CI, confidence interval; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; Lonca, loncastuximab tesirine; ORR, overall response rate; R/R, relapsed/refractory.