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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

Carmelo Carlo-Stella, MD[1], Pier Luigi Zinzani, MD[2], Brad Kahl, MD[3], Paolo F. Caimi, MD[4], Melhem Solh, MD[5], Kirit Ardeshna, MD[6], Anastasios Stathis, MD[7], Mehdi Hamadani, MD[8], Weiyun Ai, MD, PhD[9], Brian Hess, MD[10], Juan Pablo Alderuccio, MD[11], Jay Feingold, MD, PhD[12], David Ungar, MD[12], Shui He, PhD[12], Yajuan Qin, MD, PhD[12], John Radford, MD, FMedSci[13]

[1]Department of Oncology and Hematology, Humanitas Cancer Center, Humanitas University, Milan, Italy; [2]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [3]Department of Medicine, Oncology Division, Washington University, St. Louis, MO, USA; [4]University Hospitals Cleveland Medical Center/Case Western Reserve University, Cleveland, OH, USA; [5]Blood and Marrow Transplant Program at Northside Hospital, Atlanta, GA, USA; [6]Department of Hematology, University College London Hospitals NHS Foundation Trust, London, UK; [7]Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [8]Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA; [9]Division of Hematology and Oncology, Department of Medicine, University of California, San Francisco, CA, USA; [10]Division of Hematology and Medical Oncology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA; [11]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [12]ADC Therapeutics America Inc., Murray Hill, NJ, USA; [13]University of Manchester and The Christie NHS Foundation Trust, Manchester Academic Health Centre, Manchester, UK

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Aggressive lymphomas: prospective studies

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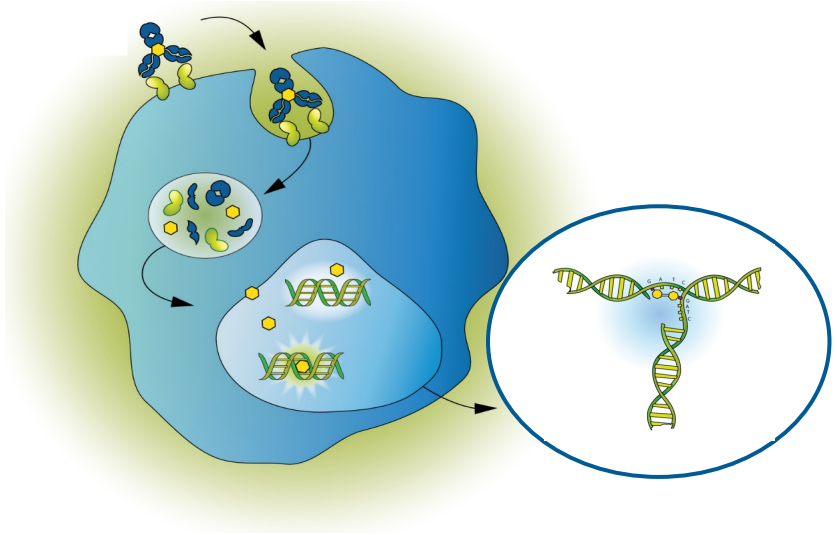
Loncastuximab Tesirine (ADCT-402)

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]



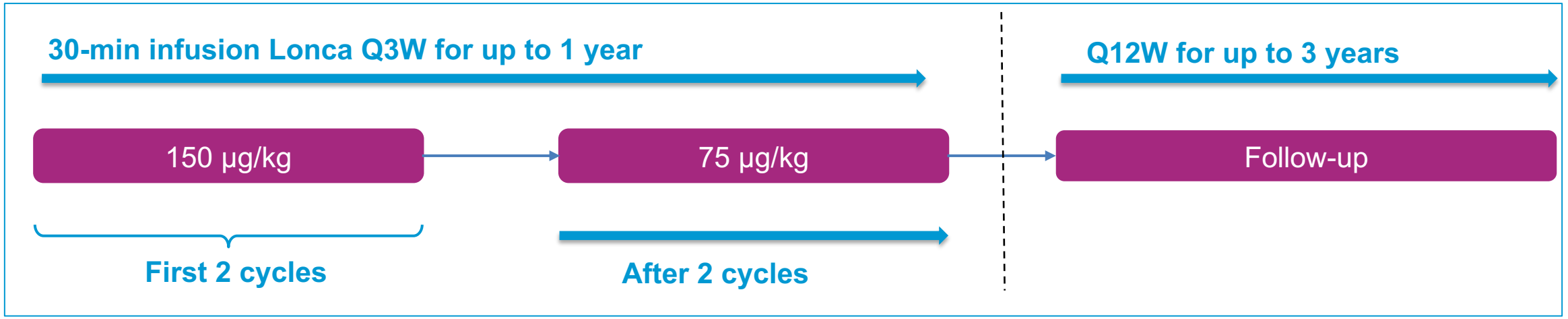
1. Lonca binds to CD19 antigen and is internalised
2. The linker is cleaved and PBD dimers released
3. Cytotoxic DNA cross-links are formed
4. The DNA replication fork stalls
5. The cell goes into apoptosis

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

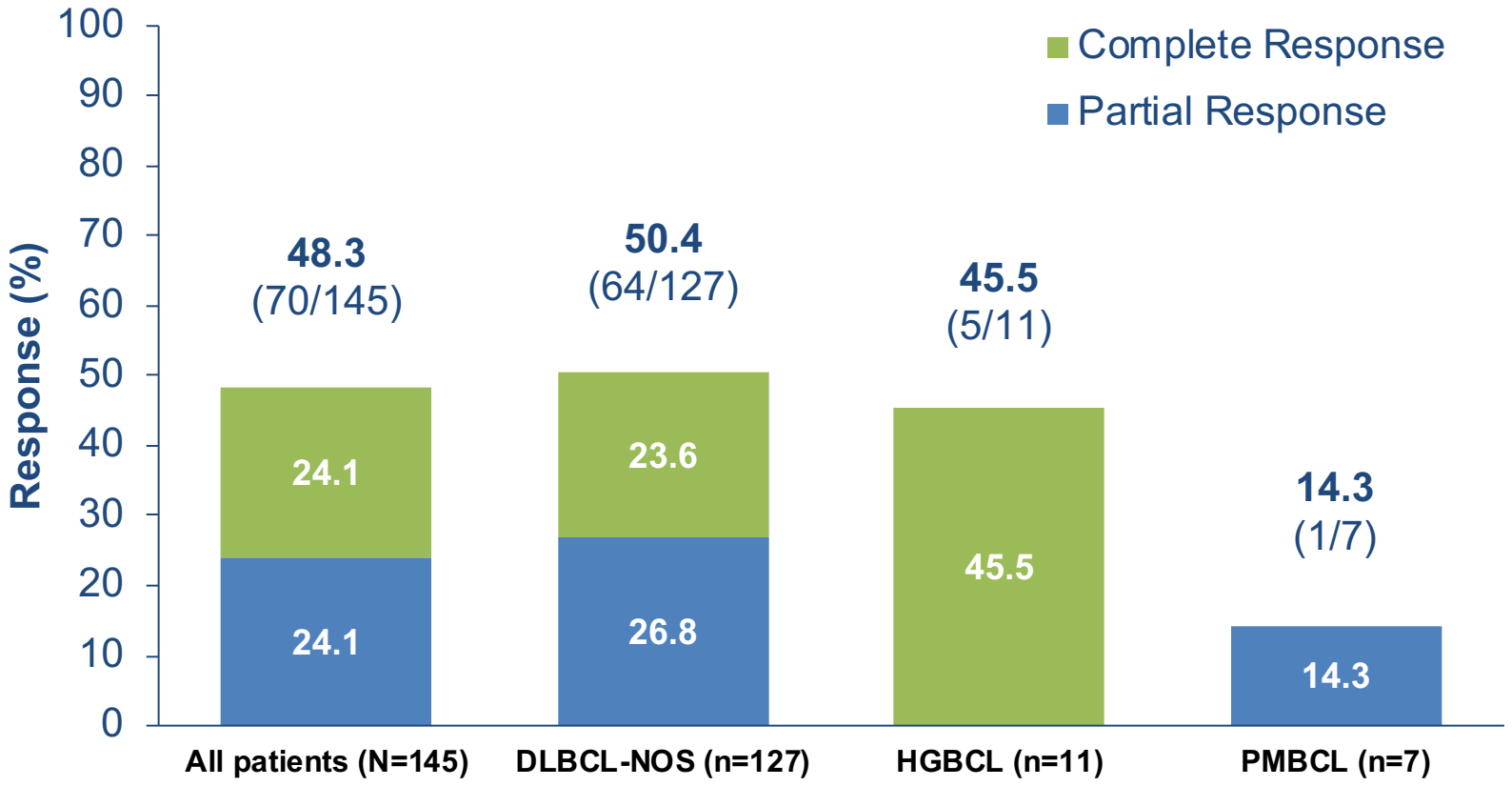
Patient characteristics		Total (N=145)
Sex, n (%)	Female Male	60 (41.4) 85 (58.6)
Age, years, median (min, max)		66.0 (23–94)
Histology, n (%)	DLBCL HGBCL PMBCL	127 (87.6) 11 (7.6) 7 (4.8)
Double/triple hit, n (%)		15 (10.3)
Double/triple expressor, n (%)		20 (13.8)
Transformed disease, n (%)		29 (20.0)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

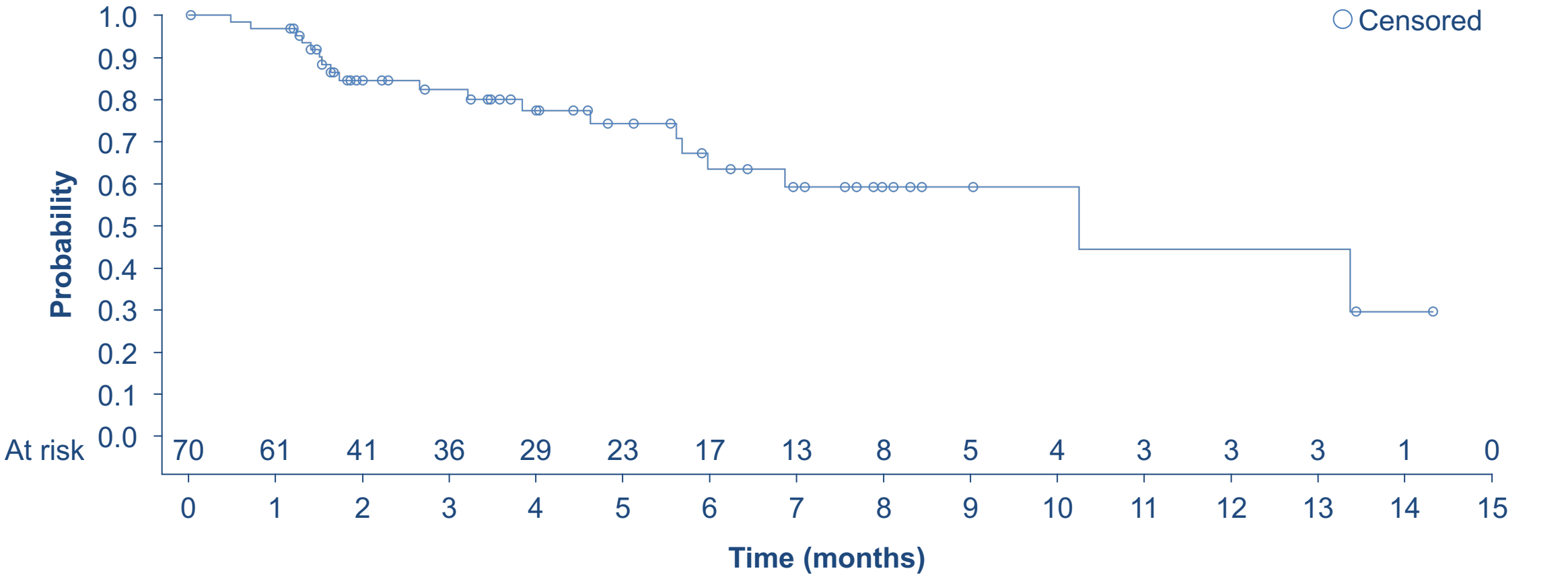
Patients refractory to first-line or last-line prior therapy had ORRs (CRR) of 37.9% (17.2%) and 36.9% (11.9%), respectively

Subgroup	Patients (n/N)	ORR (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 (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.