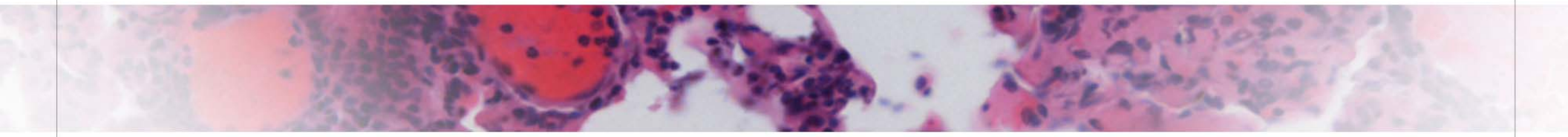
American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

Place video here



Planned Interim Analysis of a Phase 2 Study of Loncastuximab Tesirine Plus Ibrutinib in Patients with Advanced Diffuse Large B-Cell Lymphoma (LOTIS-3)

Oral Presentation, 63rd ASH Annual Meeting and Exposition, December 11–14, 2021

Carmelo Carlo-Stella, MD[1], Pier Luigi Zinzani, MD[2], Murali Janakiram, MD, MS[3], Vivian Dai, MD[4], Xiaomin He, PhD[4], Annette Ervin-Haynes, DO, MPA[4], Julien Depaus, MD[5]

[1]Department of Biomedical Sciences, Humanitas University, and Department of Oncology and Hematology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Humanitas Research Hospital, Milan, Italy; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli," and Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale Università di Bologna, Bologna, Italy; [3]Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA; [4]Clinical Development, ADC Therapeutics America, Inc., Murray Hill, NJ, USA; [5]Department of Hematology, Centre Hospitalier Universitaire (CHU) Université Catholique de Louvain (UCL) Namur Site Godinne, Yvoir, Belgium

Introduction

Place video here

- Patients with R/R DLBCL have a poor prognosis, and the development of an effective and less toxic treatment remains an unmet need[1,2]
- Combined therapy using agents with different MOAs may improve outcomes

- LOTIS-3 is a two-part, open-label, single-arm phase 1/2 study (NCT03684694) evaluating Lonca and ibrutinib in patients with R/R DLBCL and patients with R/R MCL

Loncastuximab tesirine (Lonca): an ADC comprising a monoclonal anti-CD19 antibody conjugated to a PBD dimer cytotoxin, approved for use in patients with R/R DLBCL after ≥2 systemic therapies[3]

Ibrutinib: a small-molecule inhibitor of BTK approved for use in MCL, CLL/SLL, WM, MZL, and cGVHD[4]

- In phase 1, the MTD of Lonca 60 µg/kg Q3W and ibrutinib 560 mg/day was identified[5]
- Lonca plus ibrutinib had encouraging antitumor activity and manageable toxicity in patients with R/R DLBCL and with R/R MCL[6]

- We present the results of a planned phase 2 interim analysis in patients with R/R DLBCL (data cutoff: August 30, 2021)

1. Levin A, Shah NN. *Am J Hematol* 2019;94:S18–S23; 2. Maddocks K. *Blood* 2018;132:1647–56; 3. ADC Therapeutics, Loncastuximab tesirine PI, April 2021; 4. Janssen Biotech, Ibrutinib PI, April 2020; 5. Depaus J, et al. Poster presented at the 25th Annual Congress of EHA (Virtual), June 11–21, 2020. Abstract 1284; 6. Depaus J, et al. Poster presented at the 62nd ASH Annual Meeting and Exposition (Virtual), December 5–8, 2020.
ADC, antibody-drug conjugate; BTK, Bruton's tyrosine kinase; cGVHD, chronic graft-versus-host disease; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; MOA, mechanism of action; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; PBD, pyrrolobenzodiazepine; Q3W, every 3 weeks; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.

Objectives and Study Design

Place video here

Primary phase 2 study objective:

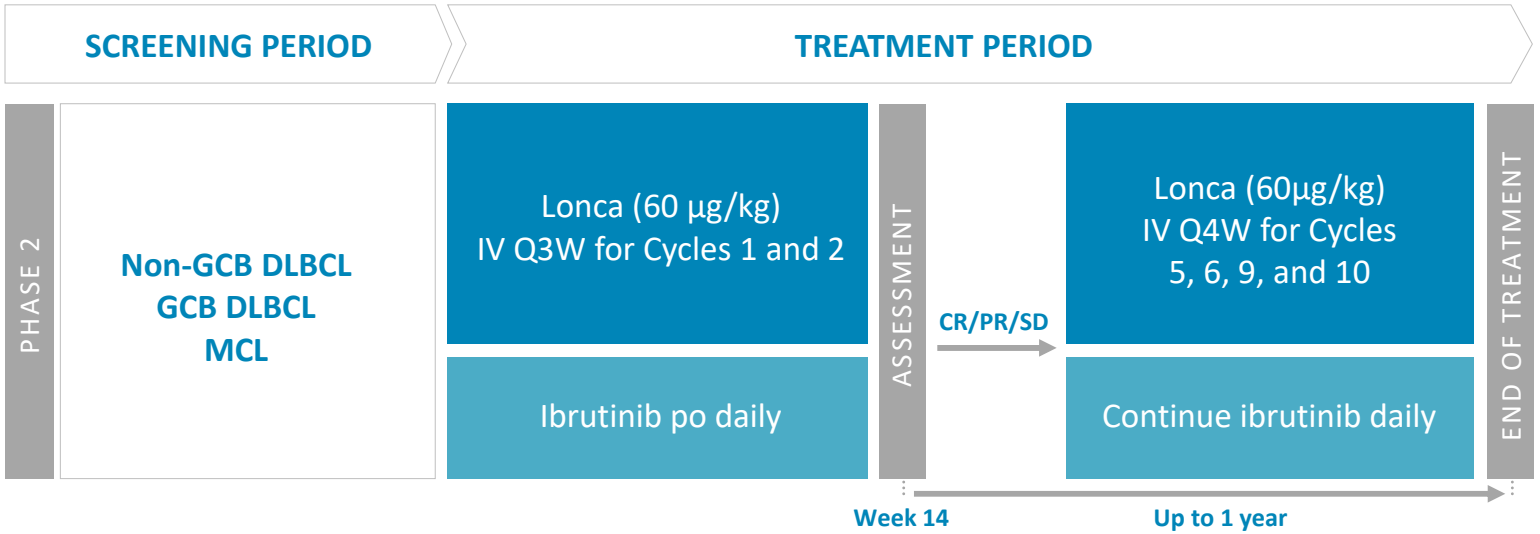
- CRR assessed by central review in R/R non-GCB DLBCL (investigator-determined COO)

Planned interim analysis objective:

- To determine if CRR in the non-GCB DLBCL cohort warranted the continuation of patient enrollment for study completion[a]

KEY INCLUSION CRITERIA:

- R/R DLBCL, measurable disease (2014 Lugano)
- ECOG PS 0–2



[a]A Simon's 2-stage design was used in this study with a planned interim analysis conducted when the 22nd patient in the non-GCB DLBCL cohort had 2 tumor assessments. Futility is defined as ≥6 CRs. Data cutoff: August 30, 2021.

COO, cell of origin; CR, complete response; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma. ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; Lonca, loncastuximab tesirine; MCL, mantle cell lymphoma; Ph, phase; PS, performance status; Q3W, every 3 weeks; R/R, relapsed or refractory.

Baseline Characteristics

As of **Aug 30, 2021**, **35 patients with R/R DLBCL** received Lonca 60 µg/kg plus ibrutinib 560 mg

Median Lonca cycles: 2 (range: 1–6)

Median ibrutinib cycles: 3.5 (range: 1–15)

Place video here

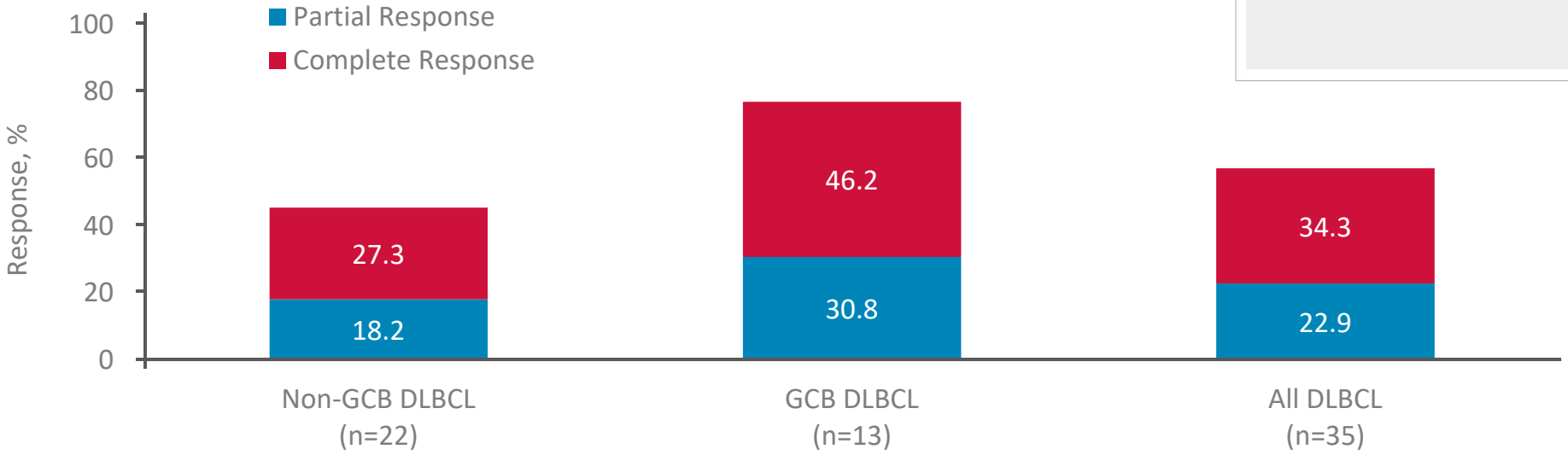
Characteristic	Non-GCB (n=22)	GCB (n=13)	All patients (n=35)
Sex, n (%)			
Male	16 (72.7)	9 (69.2)	25 (71.4)
Age, yrs, median (range)	72 (19–82)	66 (53–82)	72 (19–82)
ECOG status, n (%)			
0	12 (54.5)	9 (69.2)	21 (60.0)
1	9 (40.9)	4 (30.8)	13 (37.1)
2	1 (4.5)	0	1 (2.9)
Disease stage[a], n (%)			
Stage I	1 (4.5)	1 (7.7)	2 (5.7)
Stage II	2 (9.1)	3 (23.1)	5 (14.3)
Stage III	4 (18.2)	0	4 (11.4)
Stage IV	15 (68.2)	9 (69.2)	24 (68.6)

Characteristic	Non-GCB (n=22)	GCB (n=13)	All patients (n=35)
Prior systemic therapies, n[b]			
Median (range)	3 (1–6)	3 (2–5)	3 (1–6)
First-line prior therapy response, n (%)[c]			
Relapsed	11 (50.0)	10 (76.9)	21 (60.0)
Refractory	8 (36.4)	3 (23.1)	11 (31.4)
Other	3 (13.6)	0	3 (8.6)
Last-line prior therapy response, n (%)[c]			
Relapsed	9 (40.9)	7 (53.8)	16 (45.7)
Refractory	11 (50.0)	4 (30.8)	15 (42.9)
Other	2 (9.1)	2 (15.4)	4 (11.4)

Data cutoff: August 30, 2021. [a]Ann Arbor Criteria; [b]Prior SCT is included. For patients who received ASCT, the mobilization regimen was considered a line of therapy if it was chemotherapy-based and distinct from the other previous lines of treatment. [c]Systemic therapy; relapsed: complete or partial response, followed by relapse; refractory: stable disease or progressive disease; other: missing data or not evaluable.
ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; Lonca, loncastuximab tesirine; SCT, stem cell transplant.

Efficacy: Response Rates[a]

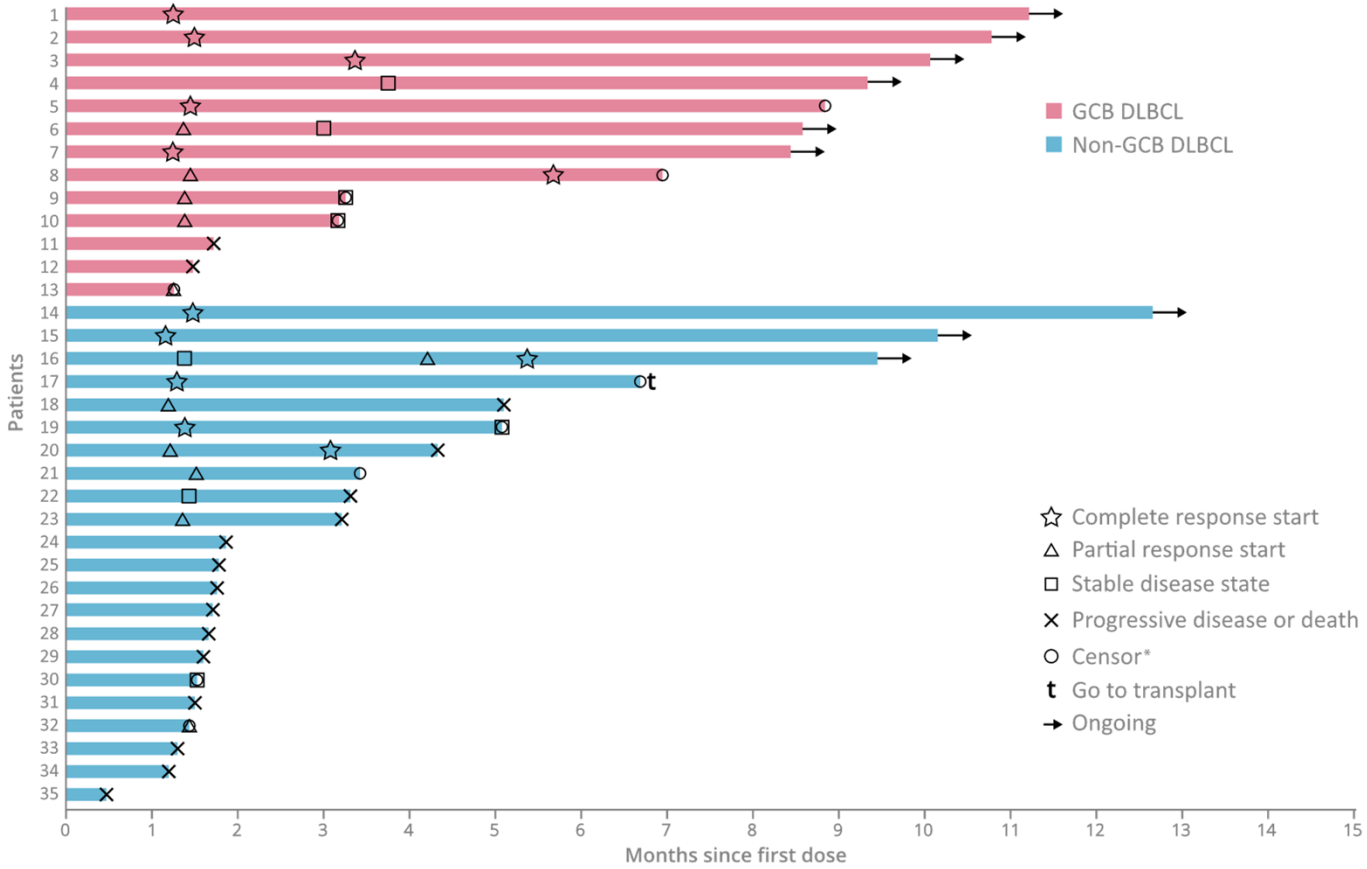
Place video here



ORR (n/N) (95% CI)[b]	**45.5%** (10/22) (24.4, 67.8)	**76.9%** (10/13) (46.2, 95.0)	**57.1%** (20/35) (39.4, 73.7)

Data cutoff: August 30, 2021. Efficacy analysis set consists of patients who received ≥1 dose of study drugs, have a valid BL radiological assessment(s), and have ≥1 valid post-BL radiological assessment.
[a]Overall response rates by IRC assessment; COO designation by local IHC assessment according to the Hans criteria. Patients who do not have a post-baseline radiological assessment due to early clinical progression or death (after receiving study drugs) were also included.
[b]The exact 95% CIs are two-sided and calculated using the Clopper–Pearson method.
BL, baseline; CI, confidence interval; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; IHC, immunohistochemistry; IRC, independent review committee; ORR, overall response rate.

Efficacy: Duration of Response[a]



Place video here

Median treatment duration:

Lonca: 49.0 days (range 1–246)

Ibrutinib: 97.5 days (range 13–386)

Median DoR was not reached (NR) in the non-GCB, GCB, or overall DLBCL cohorts

1st Quartile (95% CI) DoR in the non-GCB DLBCL cohort: **3 (1.9, NR) months**

Data cutoff: August 30, 2021.

[a]Each bar represents one patient in the study. Response is determined by independent reviewer. DoR is defined among patients with a best response of CR or PR as the time from first documented tumor response to disease progression or death.

*Only for censored patients who discontinued trial due to reasons other than progression, who went on to a different anticancer treatment, or who are ongoing but have no disease assessment yet.

CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; GCB, germinal center B-cell; PR, partial response.

Safety

Place video here

Dose reductions, interruptions, or discontinuations due to TEAEs occurred in 57.1% of all patients

TEAE (all grades) in ≥20% of all patients	Non-GCB (n=22)	GCB (n=13)	All patients (n=35)
Any TEAE, n (%)	20 (90.9)	13 (100)	33 (94.3)
Thrombocytopenia	15 (68.2)	6 (46.2)	21 (60.0)
Neutropenia	10 (45.5)	4 (30.8)	14 (40.0)
Diarrhea	6 (27.3)	5 (38.5)	11 (31.4)
Anemia	6 (27.3)	2 (15.4)	8 (22.9)
Hypophosphatemia	4 (18.2)	4 (30.8)	8 (22.9)
Fatigue	5 (22.7)	2 (15.4)	7 (20.0)

TEAE (grade ≥3) in ≥5% of all patients	Non-GCB (n=22)	GCB (n=13)	All patients (n=35)
Any TEAE, n (%)	16 (72.7)	2 (15.4)	18 (51.4)
Neutropenia	7 (31.8)	1 (7.7)	8 (22.9)
Thrombocytopenia	6 (27.3)	0	6 (17.1)
Coronavirus infection	3 (13.6)	0	3 (8.6)
Febrile neutropenia	2 (9.1)	0	2 (5.7)
General physical health decline	2 (9.1)	0	2 (5.7)

Data cutoff: August 30, 2021.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 and graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Conclusions

Place video here

Lonca plus ibrutinib demonstrated encouraging antitumor activity and a manageable safety profile in patients with R/R DLBCL

CRR for all patients was

34.3%

- Non-GCB DLBCL **27.3%**
- GCB DLBCL **46.2%**

ORR for all patients was

57.1%

- Non-GCB DLBCL **45.5%**
- GCB DLBCL **76.9%**

Safety data were consistent with those reported previously[1,2]

The study protocol will be amended to investigate whether Lonca given at each cycle in combination with ibrutinib improves efficacy outcomes in patients with R/R DLBCL

CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; Lonca, loncastuximab tesirine; ORR, overall response rate; R/R, relapsed/refractory.

1. Depaus J, et al. EHA 2020. Abstract 1284; 2. Depaus J, et al. Poster presented at ASH 2020.

Disclosures and Acknowledgments

Place video here

C. Carlo-Stella: consultancy for Boehringer Ingelheim and Sanofi; research funding from ADC Therapeutics and Rhizen Pharmaceuticals; honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen Oncology, and AstraZeneca; board of directors, speakers' bureau, or advisory committee for Servier, Novartis, Genenta Science SRL, ADC Therapeutics, Roche, and Karyopharm.

P. Luigi Zinzani: consultancy for Verastem, MSD, Eusapharma, Sanofi; board of directors, speakers' bureau, or advisory committee for Verastem, Celltrion, Gilead, Janssen-Cilag, Bristol-Myers Squibb, Servier, Sandoz, MSD, Immune Design, Celgene, Portola, Roche, Eusapharma, Kyowa Kirin, and ADC Therapeutics (advisory board agreement).

M. Janakiram: research funding from ADC Therapeutics, FATE therapeutics, and Takeda pharmaceuticals; speaker bureau from Bristol-Myers Squibb; advisory board for ADC therapeutics and Kyowa Kirin.

V. Dai, X. He, A. Ervin-Haynes: employees of ADC Therapeutics with stock options.

J. Depaus: consultancy for Takeda, Novartis, and Janssen.

This study was funded by ADC Therapeutics SA (NCT03684694), with supply of ibrutinib from Pharmacyclics LLC, an AbbVie company

Acknowledgments

- The authors would like to thank all participating patients and their families, study co-investigators, and research coordinators.
- The authors acknowledge the support of Karuna Bellamkonda, Ruiqi Hao, Sheila Vora, Luqiang Wang, and Eric Yu from ADC Therapeutics.
- Medical writing support was provided by CiTRUS Health Group.