Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase II LOTIS-2 study

Paolo F. Caimi,[1] Weiyun Z. Ai,[2] Juan Pablo Alderuccio,[3] Kirit M. Ardeshna,[4] Mehdi Hamadani,[5] Brian Hess,[6] Brad S. Kahl,[7] John Radford,[8] Melhem Solh,[9] Anastasios Stathis,[10] Pier Luigi Zinzani,[11,12] Ying Wang,[13] Yajuan Qin,[13] Luqiang Wang,[13] Zhiying Cindy Xu[13] and Carmelo Carlo-Stella[14]

[1]Cleveland Clinic Taussig Cancer Center, Cleveland, OH, USA; [2]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA; [3]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, USA; [4]University College London Hospitals NHS Foundation Trust, London, UK; [5]Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA; [6]Medical University of South Carolina, Charleston, SC, USA; [7]Washington University, St. Louis, MO, USA; [8]NIHR Clinical Research Facility, University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Center, Manchester, UK; [9]Blood and Marrow Transplant Program at Northside Hospital, Atlanta, GA, USA; [10]Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland; [11]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli," Bologna, Italy; [12]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy; [13]ADC Therapeutics America, Inc., Murray Hill, NJ, USA and [14]Department of Biomedical Sciences, Humanitas University, and Department of Oncology and Hematology, Humanitas Research Hospital–IRCCS, Milano, Italy

Correspondence: P.F. Caimi
caimip@ccf.org

Received: May 9, 2023.
Accepted: August 23, 2023.
Early view: August 31, 2023.

https://doi.org/10.3324/haematol.2023.283459

Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase 2 LOTIS-2 study

Paolo F. Caimi,[1] Weiyun Z. Ai,[2] Juan Pablo Alderuccio,[3] Kirit M. Ardeshna, [4] Mehdi Hamadani,[5] Brian Hess,[6] Brad S. Kahl,[7] John Radford,[8] Melhem Solh,[9] Anastasios Stathis,[10] Pier Luigi Zinzani,[11,12] Ying Wang,[13] Yajuan Qin,[13] Luqiang Wang,[13] Zhiying Cindy Xu,[13] Carmelo Carlo-Stella[14]

[1]Cleveland Clinic Taussig Cancer Center, Cleveland, OH, United States

[2]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, United States

[3]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, United States

[4]University College London Hospitals NHS Foundation Trust, London, United Kingdom

[5]Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, United States

[6]Medical University of South Carolina, Charleston, SC, United States

[7]Washington University, St. Louis, MO, United States

[8]NIHR Clinical Research Facility, University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom

[9]Blood and Marrow Transplant Program at Northside Hospital, Atlanta, GA, United States

[10]Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland

[11]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia “Seràgnoli,” Bologna, Italy

[12]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy

[13]ADC Therapeutics America, Inc., Murray Hill, NJ, United States

[14]Department of Biomedical Sciences, Humanitas University, and Department of Oncology and Hematology, Humanitas Research Hospital−IRCCS, Milano, Italy

Corresponding author:

Paolo Caimi

caimip@ccf.org

Running title: LOTIS-2 1-yr/2-yr Long-Term Responses

Acknowledgments

Medical writing support was provided by Adrianne Spencer, PhD (CiTRUS Health Group), and was funded by ADC Therapeutics SA, in accordance with Good Publication Practice 2022 (GPP 2022) guidelines.

Funding

This study was funded by ADC Therapeutics SA.

Contributions

PFC, WZA, JPA, KMA, MH, BH, BSK, JR, MS, AS, PLZ, and CCS were principal investigators who contributed as follows: provision of patient care; data analysis and interpretation; development and critical revision of the manuscript; and provision of final approval of the submitted content. YW, YQ, LW, and ZX contributed as follows: data analysis and interpretation; statistical analyses; development and critical revision of the manuscript; and provision of final approval of the submitted content. All authors had full access to all data in the study and approved the decision to submit for publication.

Disclosures

PFC served as consultant/advisor for ADC Therapeutics, BMS/Celgene, Genentech, Genmab, Kite Pharma, MEI Pharma, Novartis, and Takeda. WZA participated in advisory boards for Acrotech Biopharma, ADC Therapeutics, BeiGene, Kymera Therapeutics, and Nurix Therapeutics; and received research funding from Nurix Therapeutics. JPA received honoraria from Oncinfo and OncLive; consultant and research funding from ADC Therapeutics and Genentech; and served as consultant for Genentech. An immediate family member of JPA served on the advisory boards for Agios Pharmaceuticals, Forma Therapeutics, Foundation Medicine, Inovio Pharmaceuticals, and Puma Biotechnology. KMA received honoraria from BMS, Gilead, and Novartis. MH served as consultant for AbGenomics, ADC Therapeutics, Celgene, Incyte, Janssen R&D, Omeros, Pharmacyclics, TeneoBio, and Verastem; participated in speaker bureaus for AstraZeneca, BeiGene, and Sanofi Genzyme; and received research support from Astellas Pharma, Spectrum Pharmaceuticals, and Takeda. BH served as consultant for ADC Therapeutics, AstraZeneca, and BMS; and participated in a speaker bureau for BMS. BSK served as consultant for AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, Celgene/BMS, Eli Lilly, Epizyme, Genentech, Genmab, Hutchmed, Incyte, Kite, MEI Pharma, Molecular Templates, Pharmacyclics, Takeda, and T G Therapeutics; and received research funding from ADC Therapeutics, AbbVie, AstraZeneca, BeiGene, and Genentech. JR served as consultant/advisor for ADC Therapeutics, BMS, Kite Pharma, Novartis, and Takeda; served as speaker for ADC Therapeutics, Seattle Genetics, and Takeda; owns stock in ADC Therapeutics and AstraZeneca (spouse); provided expert testimony for and received honoraria from ADC Therapeutics and Takeda; and received research funding from Takeda. MS served as consultant/advisor for ADC Therapeutics and Genentech; and served on speaker bureaus for BMS, GSK, and Sanofi. AS served as consultant/advisor for AstraZeneca, Bayer, Eli Lilly, Janssen Oncology, Novartis, and Roche; and received research funding from AbbVie, ADC Therapeutics, Amgen, AstraZeneca, Bayer, Cellestia, Debiopharm Group, Eli Lilly, Incyte, Loxo,

MEI Pharma, Merck/MSD, Novartis, Pfizer, Philogen, and Roche. PLZ served as consultant for EUSA Pharma, MSD, Sanofi, and Verastem; participated in advisory committees for ADC Therapeutics and Sandoz; participated in speaker bureaus/advisory committees for BMS, Celltrion, EUSA Pharma, Gilead, Janssen-Cilag, Kyowa Kirin, MSD, Roche, Servier, Takeda, TG Therapeutics, and Verastem. YW is an employee of ADC Therapeutics with equity and stock options in the company; and has an immediate family member employed by/with stock ownership in Johnson & Johnson. YQ is an employee of ADC Therapeutics with equity and stock options in the company. LW is an employee of ADC Therapeutics with equity and stock options in the company. ZX is an employee of ADC Therapeutics with equity and stock options in the company. CCS served as consultant/advisor for ADC Therapeutics, Celgene/BMS, Karyopharm, MSD, Novartis, Roche, Sanofi, and Scenic Biotech; and received honoraria from AstraZeneca, Celgene, Incyte, Gilead Sciences, Janssen Oncology, MSD, and Roche.

Data-sharing statement: The study protocol was published previously here: Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol.* 2021;22(6):790-800. Summary data for study NCT03589469 are posted at ClinicalTrials.gov, as required. Proposals requesting deidentified participant data collected for the study following publication can be sent to clinical.trials@adctherapeutics.com and will be evaluated on a case-by-case basis.

SUPPLEMENT

Supplemental Appendix 1. Statistical analyses (extended methods)

The overall response rate was assessed as the percentage (with a 95% confidence interval [CI]) of patients with a best overall response of complete response or partial response before starting subsequent anticancer treatments or procedures. All other patients were considered nonresponders, including patients with stable disease, progressing disease, or missing information. The median (with 95% CI) duration of response, progression-free survival, and relapse-free survival were estimated using Kaplan–Meier methods with censoring at the date of the last valid disease assessment for patients who had not progressed or died before starting subsequent anticancer treatments or procedures. The median (with 95% CI) overall survival was estimated using Kaplan–Meier methods with censoring at the date the patient was last known to have been alive if no death was recorded.

All adverse events and serious adverse events were recorded, regardless of relation to the study drug, until 30 days after the last dose of the study drug or the start of new anticancer therapy, whichever was earlier. Thereafter, only serious adverse events related to the study drug were reported, with the exception of patients with subsequent stem cell transplant or chimeric antigen receptor (CAR) T-cell therapy.

Supplemental Table 1. Lonca administration and extent of exposure

	All-treated population (N=145)	**Best response of CR (n=36)**	**Patients with CR who were event-free ≥1 year (n=16)**	**Patients with CR who were event-free ≥2 years (n=11)**
Median duration of treatment, days (range)	45.0 (1-569)	150.0 (1-569)	262.5 (1-569)	316.0 (1-510)
Median number of treatment cycles (range)	3.0 (1-26)	8.0 (1-26)	12.5 (1-26)	13.0 (1-22)
Mean number of treatment cycles (SD)	4.6 (4.26)	8.7 (5.91)	11.6 (7.05)	11.8 (6.32)
Median average weight-adjusted dose per cycle, mg/kg (range)	0.11350 (0.0492-0.1606)	0.09136 (0.0492-0.1500)	0.08679 (0.0492-0.1498)	0.08464 (0.0492-0.1475)
Median relative dose intensity, % (range)	98.16 (41.3-107.1)	95.30 (41.3-102.8)	94.39 (41.3-100.0)	90.67 (41.3-98.3)

CR: complete response; SD: standard deviation.

Supplemental Table 2. Treatment-emergent adverse events occurring in ≥10% of patients with CR who were event-free for ≥1 and ≥2 years

	Patients with CR, event-free ≥1 year (n=16)		Patients with CR, event-free ≥2 years (n=11)	
	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Any TEAE	16 (100)	13 (81.3)	11 (100)	9 (81.8)
Increased GGT	8 (50.0)	2 (12.5)	7 (63.6)	2 (18.2)
Neutropenia	6 (37.5)	6 (37.5)	4 (36.4)	4 (36.4)
Thrombocytopenia	6 (37.5)	2 (12.5)	4 (36.4)	1 (9.1)
Fatigue	4 (25.0)	—	1 (9.1)	—
Anemia	5 (31.3)	2 (12.5)	3 (27.3)	1 (9.1)
Nausea	5 (31.3)	—	4 (36.4)	—
Cough	5 (31.3)	—	2 (18.2)	—
Increased blood ALP	2 (12.5)	—	2 (18.2)	—
Peripheral edema	7 (43.8)	1 (6.3)	5 (45.5)	1 (9.1)
Pyrexia	3 (18.8)	—	2 (18.2)	—
Diarrhea	5 (31.3)	2 (12.5)	3 (27.3)	1 (9.1)
Increased AST	3 (18.8)	—	3 (27.3)	—
Hypokalemia	3 (18.8)	1 (6.3)	2 (18.2)	0
Hypophosphatemia	3 (18.8)	3 (18.8)	2 (18.2)	2 (18.2)
Increased ALT	1 (6.3)	0	1 (9.1)	0
Decreased appetite	4 (25.0)	—	2 (18.2)	—
Leukopenia	4 (25.0)	4 (25.0)	3 (27.3)	3 (27.3)
Hypomagnesemia	2 (12.5)	0	1 (9.1)	0
Pruritus	4 (25.0)	—	3 (27.3)	—
Rash	5 (31.3)	—	4 (36.4)	—
Vomiting	3 (18.8)	—	2 (18.2)	—
Abdominal pain	1 (6.3)	—	1 (9.1)	—
Constipation	3 (18.8)	—	3 (27.3)	—
Dyspnea	4 (25.0)	—	2 (18.2)	—
Pleural effusion	3 (18.8)	0	1 (9.1)	0
Erythema	2 (12.5)	0	2 (18.2)	0
Headache	2 (12.5)	—	2 (18.2)	—
Asthenia	2 (12.5)	—	2 (18.2)	—
Facial edema	3 (18.8)	1 (6.3)	1 (9.1)	1 (9.1)
Arthralgia	2 (12.5)	—	1 (9.1)	—
Back pain	2 (12.5)	—	1 (9.1)	—
Dizziness	2 (12.5)	—	2 (18.2)	—
Lymphopenia	2 (12.5)	1 (6.3)	2 (18.2)	1 (9.1)

Muscle weakness	3 (18.8)	—	1 (9.1)	—
Nasal congestion	3 (18.8)	—	1 (9.1)	—
Hyperglycemia	2 (12.5)	—	2 (18.2)	—
Localized edema	2 (12.5)	—	1 (9.1)	—
Peripheral neuropathy	2 (12.5)	—	2 (18.2)	—
Skin hyperpigmentation	2 (12.5)	—	2 (18.2)	—

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate aminotransferase; CR: complete response; GGT: gamma-glutamyl transferase; TEAE: treatment-emergent adverse event.