ZYNLONTA® (loncastuximab tesirine-lpyl) – LOTIS-2 Study

Summary

- The updated results from LOTIS-2 (data cut-off September 15, 2022) are presented below. In these updated results, an efficacy and safety analysis were performed for the following groups (all treated patients, and patients with complete response (CR) who had been event-free for over a two-year period). The LOTIS-2 primary analysis publication may be accessed online via the following link: http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00139-X/fulltext.
    - Please note frequencies of some treatment-emergent adverse events (TEAEs) reported in the long-term results and LOTIS-2 primary analysis publication may differ from what is reported in the approved labeling for ZYNLONTA. Review of the ZYNLONTA prescribing information is recommended.
- ZYNLONTA, a pyrrolobenzodiazepine (PBD)-based antibody drug conjugate (ADC) comprised of a humanized monoclonal antibody (mAb) directed against CD19+ cells, has been evaluated in both Phase 1 and 2 studies in patients with Non-Hodgkin Lymphoma (NHL), specifically hematologic B-cell malignancies.[1]
- LOTIS-2 evaluated the safety and efficacy of ZYNLONTA in 145 patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) following ≥2 lines of prior systemic therapy at a dose of 150 µg/kg (0.15 mg/kg) every 3 weeks (Q3W) for the first 2 cycles, followed by 75 µg/kg (0.075 mg/kg) Q3W for subsequent cycles.[1]
- In the primary analysis of the LOTIS-2 study, ZYNLONTA demonstrated antitumor activity with an overall response rate (ORR) of 48.3%, a complete response (CR) rate of 24.1%, and durable responses; median duration of response [DOR] of 10.3 months in patients with heavily pretreated R/R DLBCL.[1]
- The long-term follow up analysis (median follow up of 35 months) of LOTIS-2 revealed the following:[4.]
    - In the all-treated population, ORR was consistent at (48.3%, 95% CI: 39.9, 56.7) and included 36 patients (24.8%) with a complete response (CR) and 34 patients (23.4%) with a partial response (PR).[2,4.]
        - The median treatment duration was 45.0 days (1 to 569 days), The median number of treatment cycles was 3.0 (range 1 to 26) in all treated population and 8 (range 1-26) in patients with a CR.
        - Among patients with a CR, 44% (16/36) and 31% (11/36) were event-free for ≥1 and ≥2 years, respectively.[4]
        - Among the subset of patients with CR who were event-free for ≥1 year or ≥2 years, the median duration of time patients remained treatment-free post-Lonca was greater than 24 months, with one patient remaining treatment-free as long as 37 months.[4]
- All-grade treatment emergent adverse events (TEAEs) were reported in 143 patients (98.6%) of the all-treated population.[1]
    - Based on the updated 2-year study results, all-grade TEAEs occurring in ≥30% of all patients included, increased gamma-glutamyltransferase (GGT; 42%), neutropenia (40%), and thrombocytopenia (33%).[4]
    - Grade ≥3 TEAEs were reported in 73.8% of patients and in 75% of patients with a CR.[4]

- Increased GGT was the most common reason for treatment discontinuation, followed by edema and effusions.[4]

Clinical Data

Study Design

- LOTIS-2 was a pivotal Phase 2, multicenter, open-label, single-arm study that evaluated the efficacy and safety of ZYNLONTA as monotherapy in 145 adult patients with R/R DLBCL following ≥2 lines of prior systemic therapy.[1]
- The primary endpoint was ORR according to the 2014 Lugano classification in all-treated patients and was assessed by central review.[1,2] ORR was defined as the proportion of patients with a BOR of CR or PR.[1]
- Key secondary endpoints included DoR, CR, relapse-free survival (RFS), PFS, OS, and frequency/severity of adverse events (AEs), and serious adverse events (SAEs) related to the safety profile.[1]
    - DoR was defined as the time from the first documentation of tumor response to disease progression or death. CR rate was defined as the percentage of treated patients with a BOR of CR. RFS was defined as the time from the documentation of CR to disease progression or death. PFS was defined as the time between start of treatment and the first documentation of recurrence, progression, or death. OS was defined as the time between the start of treatment and death from any cause.[3]
- Select inclusion criteria for this study included male or female patients, aged 18 years or older, with pathologic diagnosis of R/R DLBCL following two or more multi-agent systemic treatment regimens, Eastern Cooperative Oncology Group (ECOG) performance status 0–2 and adequate organ function. Additionally, biopsy-proven CD19 expression was required for patients who received prior CD19-targeted therapy.[1]
- Select exclusion criteria included the following: bulky disease (≥ 10 cm in longest dimension); Burkitt lymphoma diagnosis; history of hypersensitivity to a CD19 antibody; prior ZYNLONTA treatment, autologous SCT within 30 days, or allogeneic SCT within 60 days prior to initiation of study drug; major surgery, radiotherapy or anticancer or experimental treatment within 14 days prior to study treatment; active autoimmune disease; active CNS lymphoma; or significant comorbidities.[1]
- Overall, 145 patients with heavily pre-treated R/R DLBCL were enrolled and received at least 1 dose of ZYNLONTA.[1,2] ZYNLONTA was administered as a 30-minute intravenous infusion on Day 1 of each 21-day cycle, at a dose of 150 µg/kg (0.15 mg/kg) every three weeks (Q3W) for the first 2 cycles, followed by 75 µg/kg (0.075 mg/kg) Q3W for subsequent cycles for up to one year or until disease relapse or progression, unacceptable toxicity, death, major protocol deviation, pregnancy, or patient, investigator, or sponsor decision.[1,2] At data cut-off (March 01, 2021), all patients completed treatment.[2]
    - A treatment cycle was defined as 3 weeks (21 days). Patients received premedication with oral dexamethasone unless otherwise contraindicated and were advised to avoid prolonged exposure of skin to sunlight due to reports of light-sensitive skin rashes in the Phase 1 study. Treatment delays of ≤5 weeks and dose reductions were permitted to

manage drug toxicity. Treatment with ZYNLONTA could be continued beyond one year in patients with clinical benefit if agreed with the sponsor.[2]

Baseline Demographics

- In the all-treated patient population of 145 patients with R/R DLBCL, DLBCL not otherwise specified (NOS) was the most common subtype, classified in 127 patients (88%).[1]
    - The median age of the patient population was 66 years (range: 23–94), and the majority of patients were male (59%).[1,4]
    - All patients had an ECOG score of 0 to 2.[1]
    - The median number of previous systemic therapies was 3 (IQR: 2–7), and most patients received ≥2 lines of systemic therapy (43.4%).[1,4.]
        - Among patients with a CR who were event-free ≥1 year, 10/16 had 2 previous systemic therapies, 2/16 had 3 previous systemic therapies, and 4/11 had >3 previous systemic therapies.[4]
        - Among patients with a CR who were event-free ≥2 years, 8/11 had 2 previous systemic therapies, 1/11 had 3 previous systemic therapies, and 2/11 had >3 previous systemic therapies.[4]
    - A total of 21 patients (14%) and 2 patients (1%) received autologous and allogeneic SCT, respectively. One patient (1%) received both autologous and allogeneic SCT.
- A total of 29 patients (20%) and 89 patients (61.4%) were classified as primary refractory or refractory, respectively, to their most recently line of therapy.[1,4.]

Efficacy

Long-term results from LOTIS-2[4]

- This updated results from LOTIS-2 (data cut-off date, September 15, 2022) includes efficacy and safety analysis for all treated patients, patients with CR, patients with CR who had been event-free for over a two-year period.
- The ORR remained the same as in the primary analysis (48.3%), and one patient with a partial response (PR) converted to CR for a final CR rate of 24.8%.
- The median (range) number of treatment cycles was 3.0 (1 to 26) in the all-treated population, 8.0 (1 to 26) in patients with a CR, 12.5 (1 to 26) in patients with a CR who were event free for ≥1 year, and 13.0 (1 to 22) in patients with a CR who were event-free for ≥2 years.
    - Among patients with a CR, 44% (16/36) and 31% (11/36) were event-free for ≥1 and ≥2 years, respectively. All 11 patients with a CR who were event-free for ≥2 years were censored due to patient discontinuation of the study.
- Among patients with a CR (n = 36), the median (range) duration of time patients remained treatment-free post-treatment with ZYNLONTA was 6.1 (1.0 to 37.5) months
    - In the subsets of patients who were event-free for ≥1 year and ≥2 years, the median (range) duration of time patients remained treatment-free after ZYNLONTA was 24.8 (3.4 to 37.5) months and 27.7 (20.7 to 37.5) months, respectively.
- Additional efficacy outcomes for the all-treated population and the subset of patients with CR are summarized in Table 1.

Table 1. Summary of Efficacy Outcomes (Data Cut-Off September 15, 2022). Adopted from Caimi PF et al.[4]

	All-treated N=145	Best response of CR N=36
Median DOR, months (95% CI)	13.4 (6.9, -)	NR
Probability of maintaining response at 1 year	54.7% (37.9,68.8)	82.8% (59.9,93.3)
Probability of maintaining response at 2 years	44.6% (27.9, 60.0)	72.4% (48.1, 86.8)
Median PFS, months (95% CI)	4.9 (2.9, 8.3)	NR
Probability of maintaining PFS at 1 year	33.5% (23.3, 44.0)	82.9% (60.0, 93.3)
Probability of maintaining PFS at 2 years	25.9% (16.2,36.7)	72.5% (48.2, 86.8)
Median OS, months (95% CI)	9.5 (6.7, 11.5)	NR
Probability of maintaining OS at 1 year	39.0% (30.7, 47.1)	77.1% (59.4, 87.9)
Probability of maintaining OS at 2 years	29.5% (22.0, 37.4)	68.2% (50.0, 81.0)

Follow-up Analysis of LOTIS-2 Study[2]

- A follow-up analysis of LOTIS-2, data cut-off March 01, 2021, revealed the following:[2]
  - In the as-treated population, ORR was realized in 70 patients (48.3%, 95% CI: 39.9, 56.7) and included 36 patients (24.8%) with a CR and 34 patients (23.4%) with a PR.[2]
  - Responders (n=70) received a mean of 6.8 cycles (5.0) and median of 5.0 cycles (1.0–26.0); 24 responders (34.3%) received ≥7 cycles.[2] Most responders had a response after 2 cycles and the median (range) time to response was 41.0 (35 to 247) days for all responders and 42.0 (36 to 247) days for patients with a CR.[4]
  - The median DoR for the 70 responders was 13.37 months (95% CI: 6.87), and the median DoR for patients with a CR was not reached.[2] For patients with a PR, the median DoR was 5.68 months (95% CI: 1.64, 9.26).[2]
  - The median PFS and OS were 4.93 months (95% CI: 2.89, 8.31) and 9.53 months (95% CI: 6.93, 11.47), respectively.[2]
  - At data cut-off, among the 36 patients who experienced complete remission, 16 patients (44.4%) remained in complete response with no further treatment, while 13 patients (36.1%) experienced disease progression or death. Corresponding values, excluding 10 patients who were censored because of transplant were 61.5% (16 of 26 patients) and 34.6% (9 of 26 patients), respectively.[2]
  - Sixteen patients (11%) received CD19-directed CAR-T therapy following treatment with ZYNLONTA, with 7 patients achieving an investigator-assessed ORR of 43.8%.[2]
  - Eleven patients (7.6%) proceeded to receive SCT as consolidation after responding to ZYNLONTA.[2]

Caimi PF et al. Lancet Oncol. 2021 (Data Cut-Off, April 6, 2020)[1]

- The probability of responders maintaining responses for ≥ 9 months was 64%.[1]
- Of the total population (N=145), a total of 22 patients (15%) experienced stable disease, while 30 patients (21%) experienced disease progression.[1] See Table 2 additional information regarding PFS by subgroup.

Table 2. Progression Free Survival by Subgroup (Data Cut-Off April 6, 2020). *Adapted from Caimi PF et al (Appendix). Lancet Oncol.*2021[3]

Subgroup	N (at risk)	Number of Events	PFS (median, months)	95% CI
Histology				
DLBCL, NOS	127	57	6.01	(2.89, 8.31)
PMBCL	7	4	1.35	(1.22, NE)
HGBCL	11	6	9.13	(1.31, NE)
Double/triple hit DLBCL				
Yes	15	8	3.68	(1.28, NE)
No	130	59	5.09	(2.89, 8.31)
Prior Systemic Therapies[a]				
2 lines	63	29	8.31	(2.43, NE)
3 lines	35	18	3.68	(2.66, 7.36)
>3 lines	47	20	6.01	(2.89, NE)
Response to first-line systemic therapy				
Relapsed	99	43	7.36	(2.89, 11.47)
Refractory[b]	29	18	2.66	(1.35, 11.24)
Other[c]	17	6	3.81	(1.25, NE)
Response to most recent line systemic therapy[d]				
Relapsed	43	14	11.47	(3.81, NE)
Refractory	84	44	2.66	(1.64, 7.06)
Other[c]	18	9	6.01	(1.38, NE)

[a]Prior HCT is included. For patients who received an autologous transplant, the mobilization regimen was considered a line of therapy if it was chemotherapy-based and distinct from the other previous lines of treatment. [b] Refractory disease defined as no response to therapy. [c] Other defined as unknown, not evaluable or missing [d] If HCT is most recent line, the variable is defined as response to the therapy immediately preceding HCT. CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HCT, hematopoietic cell transplant; HGBCL, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements; NE, not estimable; NOS, not otherwise specified; PMBCL, primary mediastinal B-cell lymphoma; PFS, progression-free survival

- Median relapse-free survival was 13.4 months (10.3, not estimable).[1]
- Median treatment duration was 45 days, reflecting treatment discontinuation for patients with progression at Cycle 2 disease assessments.[1]

Safety

Long-term results from LOTIS-2[4]

- There were no new safety signals identified during the long-term follow-up.
- All-grade TEAEs were reported in 100% of patients with a CR, and Grade ≥3 TEAEs were reported in 75% of patients with a CR.
    - All-grade TEAEs occurring in ≥30% of patients with a CR were increased GGT (50%), neutropenia (42%), anemia (36%), thrombocytopenia (36%), peripheral edema (33%), and nausea (31%).
    - Grade ≥3 TEAEs occurring in ≥10% of patients with a CR were neutropenia (28%), increased GGT (19%), thrombocytopenia (19%), leukopenia (14%), and hypophosphatemia (11%).
    - Increased GGT was the most common reason for treatment discontinuation, followed by edema and effusions.[4]

Follow-up Analysis of LOTIS-2 Study[2]

- A follow-up analysis of LOTIS-2, data cut-off March 01, 2021, revealed the following:[2]
  - Grade ≥3 TEAEs were reported in 107 patients (73.8%). Most common (≥10%) Grade ≥3 TEAEs were as follows: neutropenia (38 [26.2%]), thrombocytopenia (26 [17.9%]), increased GGT (25 [17.2%]), and anemia (15 [10.3%]). Most Grade ≥3 events reflected lab abnormalities rather than clinical symptoms. The rate of febrile neutropenia was low (5 [3.4%]).[2]
  - All-grade TEAEs considered likely related to the PBD warhead included edema or effusion (45 [31.0%]), skin reactions and nail disorders (63 [43.4%]), and liver enzyme abnormalities (76 [52.4%]).[2]
  - Treatment-related TEAEs leading to treatment discontinuation and dose delays were reported in 27 patients (18.6%) and 62 patients (42.8%), respectively; the most common reason for both was increased GGT (17 [11.7%] and 26 [17.9%] patients, respectively).[2]
- Table 3 provides additional information regarding TEAEs reported in the LOTIS-2 follow-up analysis. Please note frequencies of some TEAEs reported in the follow-up analysis may differ from what is reported in the approved labeling for ZYNLONTA. Review of the ZYNLONTA prescribing information is recommended.

Table 3. Overall TEAEs in LOTIS-2 (Data Cut-Off March 01, 2021). *Adapted from Zinzani PF et al, ICML Congress (Virtual), 2021.*[2]

TEAE	All-Treated Population (N=145) n (%)
Patients with any TEAE	**143 (98.6)**
Grade ≥3 TEAE	107 (73.8)
TEAE related to ZYNLONTA[a]	118 (81.4)
TEAE leading to ZYNLONTA dose delay or reduction	75 (51.7)
TEAE leading to ZYNLONTA discontinuation	36 (24.8)
Serious TEAE	57 (39.3)
TEAE with a fatal outcome	8 (5.5)

[a] Related defined as possibly related, probably related, or related including missing relationship;
TEAE, treatment-emergent adverse event

Caimi PF et al. Lancet Oncol.2021, (Data Cut-Off, April 6, 2020)[1]

- During the LOTIS-2 study, patients received a median of 3.0 treatment cycles (IQR: 2.0, 5.0; range: 1–15) of ZYNLONTA.[1] **Table 4** provides additional information regarding TEAEs reported in the LOTIS-2 publication. Please note frequencies of some TEAEs reported in the LOTIS-2 publication may differ from what is reported in the approved labeling for ZYNLONTA. Review of the ZYNLONTA prescribing information is recommended.

Table 4. Most common TEAEs (≥10%) All Grades (Data Cut-Off April 6, 2020). *Adapted from Caimi PF et al. Lancet Oncol*.2021[1]

TEAE Preferred Term, n (%)	All-Treated Population (N=145) n (%)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Any TEAE	38 (26%)	61 (42%)	36 (25%)	8 (6%)
Fatigue	38 (26%)	2 (1%)	0	0
GGT increased	35 (24%)	22 (15%)	2 (1%)	0
Nausea	34 (23%)	0	0	0
Cough	31 (21%)	1 (1%)	0	0
Blood ALP increase	28 (19)	1 (1)	0	0
Peripheral edema	27 (19)	2 (1)	0	0
Pyrexia	26 (18)	2 (1)	0	0
Anemia	23 (16)	15 (10)	0	0
AST increase	22 (15)	1 (1)	0	0
Decreased appetite	22 (15)	0	0	0
Diarrhea	22 (15)	3 (2)	0	0
Thrombocytopenia	22 (15)	18 (12)	8 (6)	0
Neutropenia	20 (14)	14 (10)	23 (16)	0
Hypomagnesemia	19 (13)	1 (1)	0	0
Vomiting	19 (13)	0	0	0
Constipation	17 (12)	0	0	0
Pruritus	18 (12)	0	0	0
Rash	18 (12)	1 (1)	0	0
Hypokalemia	16 (11)	6 (4)	0	0
Insomnia	16 (11)	0	0	0
Dyspnea	15 (10)	2 (1)	0	0
Hypophosphatemia	15 (10)	7 (5)	1 (1)	0
Headache	14 (10)	1 (1)	0	0
Erythema	14 (10)	1 (1)	0	0

Data are n (%); ALP, alkaline phosphatase; AST, aspartate aminotransferase, GGT, gamma-glutamyl transferase;

- At data cut-off (April 6, 2020), TEAEs leading to dose modifications or treatment discontinuation occurred in 90 patients (62%): treatment discontinuation in 34 patients (23%), dose delays in 74 patients (51%), dose reductions in 11 patients (8%), and infusion interruptions in one patient (1%).[1]
    - Dose delays were mostly short, < 1 week and patients were able to continue treatment. Increase GGT (30 patients [21%]), neutropenia (18 patients [12%]), and thrombocytopenia (13 patients [9%]) were the most common causes of dose delay.
    - Increased GGT was the leading cause of dose reductions (6 patients [4%]). Thrombocytopenia, fatigue, peripheral edema, Klebsiella infection, bacterial urinary tract infection, dyspnea, and skin exfoliation each led to dose reduction in one patient (1%).
    - Most commonly reported (≥2%) AEs leading to treatment discontinuation included the following: GGT increased in 15 patients (10. %), peripheral edema in 4 patients (3%), localized edema and pleural effusion (3 patients [2%] each).

- A total of 77 of 145 patients died during the study period. Most deaths (60 [78%]) were due to disease progression, while 5 patients (6%) died from fatal TEAEs. A total of 12 patients (16%) died following the adverse event reporting period.[1]

Literature Search

- A PubMed biomedical literature search conducted on August 4, 2025, yielded no further information regarding ZYNLONTA's LOTIS-2 study.

Relevant Prescribing Information[4]

Section 6: Adverse Reactions[5]
6.1: Clinical Trials Experience[5]
Relapsed or Refractory Diffuse Large B-Cell Lymphoma: LOTIS-2[5]

- The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including high grade B-cell lymphoma, after at least two prior systemic therapies *[see Clinical Studies (14.1)]*. The trial required hepatic transaminases, including gamma glutamyltransferase (GGT), ≤2.5 times upper limit of normal (ULN), total bilirubin ≤ 1.5 times ULN, and creatinine clearance ≥60 mL/min. Patients received ZYNLONTA 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease or unacceptable toxicity. Among the 145 patients, the median number of cycles received was 3, with 34% receiving 5 or more cycles.
- The median age was 66 years (range 23 to 94), 59% were male, and 94% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian.
- Serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.
- Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.
- Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.
- Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

References

[1] 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 Jun;22(6):790-800. DOI: 10.1016/S1470-2045(21)00139-X.

[2] Zinzani PL, Caimi PF, Carlo-Stella C, et al. LOTIS-2 follow-up analysis: Updated results from a Phase 2 study of loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma. Poster presented at: the International Conference on Malignant Lymphoma (ICML) Virtual Congress; June 18–22, 2021; Virtual.

[3] 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 [supplementary appendix]. *Lancet Oncol*. 2021 Jun;22(6):790-800. DOI: 10.1016/S1470-2045(21)00139-X.

[4] Caimi PF, Ai WZ, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, Kahl BS, Radford J, Solh M, Stathis A, Zinzani PL, Wang Y, Qin Y, Wang L, Xu ZC, Carlo-Stella C. Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase 2 LOTIS-2 study. Haematologica; https://doi.org/10.3324/haematol.2023.283459 [Early view].

[5] ZYNLONTA® (loncastuximab tesirine-lpyl) for injection Prescribing Information, October 2022.

ADC Therapeutics encourages all health care professionals to report any adverse events and product quality complaints to medical information at 855-690-0340. Please consult the ZYNLONTA Prescribing Information.