ZYNLONTA® (loncastuximab tesirine-lpyl) – LOTIS-1 Study

Summary

- ZYNLONTA is a CD19-directed antibody and alkylating agent conjugate, consisting of a humanized IgG1 kappa monoclonal antibody conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic alkylating agent.[4]
- ZYNLONTA is approved to be administered as an intravenous (IV) infusion over 30 minutes on Day 1 of each cycle (every 3 weeks). Administer intravenous infusion as follows:[4]
    - 0.15 mg/kg every 3 weeks for 2 cycles.
    - 0.075 mg/kg every 3 weeks for subsequent cycles.
    - For patients with a body mass index (BMI) ≥35 kg/m^2, calculate the dose based on an adjusted body weight (ABW) as follows: ABW in kg = 35 kg/m^2 × (height in meters)^2
- LOTIS-1 was a Phase 1, open-label, dose-escalation (Part 1) and dose-expansion (Part 2) study that evaluated the safety and tolerability of ZYNLONTA, used as monotherapy, in 183 adult patients with relapsed or refractory B-cell Non-Hodgkin Lymphoma (R/R B-NHL).[1]
    - The overall response rate (ORR) in all patients with B-NHL (180 evaluable) was 45.6% (95% CI: 38.1, 53.1) and included 48 patients (26.7%) with a complete response (CR) and 34 patients (18.9%) with a partial response (PR).[1]
    - The median duration of response (DoR) in all patients was 5.4 months (95% CI: 4, not reached). The DoR in patients with diffuse large B-cell lymphoma (DLBCL) was 4.5 months (95% CI: 3.9, 9.5).[1]
        - The DoR in patients with mantle cell lymphoma (MCL) or follicular lymphoma (FL) was not reached.
    - The median progression free survival (PFS) in all patients with B-NHL was 3.1 months (95% CI: 2.7, 4.2), 2.8 months (95% CI: 1.9, 3.8) in patients with DLBCL, and 4.8 months (95% CI: 1.1, 7.8) in patients with MCL.[1]
        - The PFS in patients with FL could not be determined due to the low number of events.
    - The median overall survival (OS) in all patients was 8.3 months (95% CI: 6.7, 10.7). The OS in patients with DLBCL was 7.5 months (95% CI: 6-9.8).[1]
        - The OS in patients with MCL or FL was not reached due to the low number of events.
- In the safety analysis set, 181 patients (98.9%) experienced at least one treatment-emergent adverse event (TEAE).[1]
    - Grade ≥3 TEAEs were reported in 141 patients (77%), most commonly hematologic or liver test abnormalities and hypokalemia. See Table 3 and Table 4 for all-grade TEAEs and Grade ≥3 TEAEs, respectively.
- See Relevant Prescribing Information for additional information.

Clinical Data

Study Design

- LOTIS-1 was a phase 1, open-label, dose-escalation (Part 1) and dose-expansion (Part 2) study that evaluated the safety and tolerability of ZYNLONTA, used as monotherapy, in 183 adult patients with relapsed or refractory B-cell Non-Hodgkin Lymphoma (R/R B-NHL).[1]
- The primary endpoints of Part 1 were to evaluate safety and tolerability of ZYNLONTA in patients with R/R B-NHL and determine the maximum tolerated dose (MTD) and recommended doses(s) for Part 2. The primary endpoints of Part 2 were to evaluate the safety and tolerability of ZYNLONTA at the recommended dose(s).
- Key secondary endpoints included ORR, DoR, OS, and PFS.[2]
    - ORR was defined as the number of patients with a best overall response of CR or PR at the time of ZYNLONTA discontinuation, before the start of subsequent anticancer therapy or procedure.[2]
    - DoR was defined among responders (CR and PR) as the time from the earliest date of first response until the first date of either disease progression or death due to any cause. Tumor response was assessed using the 2014 Lugano Classification.[2]
    - OS was defined as the time from the first dose of ZYNLONTA treatment until the date of death due to any cause.[2]
    - PFS was defined among the efficacy population as the time of the first dose of ZYNLONTA until either disease progression or death due to any cause.[2]
- Select inclusion criteria included male or female patients aged 18 years or older with pathologically confirmed R/R B-NHL who failed or were intolerant to established therapy, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, and measurable disease as defined by the 2014 Lugano Classification.[3]
- Select exclusion criteria included autologous or allogeneic transplant within 60 days prior to the screening visit, known history of immunogenicity or hypersensitivity to a CD19 antibody, evidence of myelodysplasia or myeloid leukemia, known history or positive serum human anti-drug antibody (ADA), or active autoimmune disease.[3]

Dosing

- ZYNLONTA was administered by IV infusion over 60 minutes once every 3 weeks (day 1 of each 21-day cycle). If well tolerated, the duration could be shortened to 30 minutes per the Investigator's discretion.[1,3]
- In Part 1, the patients were assigned to doses using a 3+3 dose-escalation design overseen by a Dose-Escalation Steering Committee (DESC). No intrapatient dose escalation was permitted.[1]
    - In total of the study, 183 patients received loncastuximab tesirine and in Part 1, 88 patients were assigned to receive doses of 15 to 200 µg/kg every 3 weeks at the following doses; 15 µg/kg (n=4), 30 µg/kg (n=4), 60 µg/kg (n=4), 90 µg/kg (n=5), 120 µg/kg (n=16), 150 µg/kg (n=19), or 200 µg/kg (n=36).[1,3]
- In Part 2, patients received loncastuximab tesirine at the recommended doses identified in Part 1 based on an increase in cumulative toxicities at 200 µg/kg and evidence of activity at 120 and 150 µg/kg doses.[1]
    - The recommended dose of loncastuximab tesirine for Phase 2 was 150 µg/kg every 3 weeks for 2 cycles followed by 75 µg/kg every 3 weeks for subsequent doses.[1]

- During Part 1, the DESC recommended that dexamethasone (8 mg by mouth twice daily) be added for mitigation of toxicity.[3]
- Standard doses of spironolactone could be used at any time for patients with weight gain >1 kg from Cycle 1, Day 1, new or worsening edema and/or new or worsening pleural effusion.[3]
- Additional diuretics could be added if further increases in weight, edema, or pleural effusion occurred and adequate hydration was recommended.[3]

Baseline Demographics

- Baseline characteristics for all patients and those with DLBCL are presented below in Table 1;
  - Patients received a median of 3 prior line systemic therapies (range 1-13 lines), 42 (23%) had received prior hematopoietic cell transplantation (HCT), and 3 (1.6%) had received prior chimeric antigen receptor (CAR) T-cell therapy.[1]
  - Forty-three patients (23.5%) were primary refractory and 109 (59.6%) were refractory to their most recent systemic therapy.[1]

Table 1: Baseline Demographics and Clinical Characteristics of Patients with B-NHL who Received ZYNLONTA (Safety Analysis Set). Adopted from Hamadani, et al.[1]

Characteristic	N (%)	
	All patients with B-NHL (N=183)	Patients with DLBCL (n=139)
Sex		
Female	69 (37.7)	59 (42.2)
Male	114 (62.3)	80 (57.6)
Age (years)		
Median	63	63
Range	20-87	20-86
ECOG score		
0-1	160 (87.4)	119 (85.6)
2	21 (11.5)	18 (12.9)
3	2 (1.1)	2 (1.4)
B-NHL subtype		
DLBCL group		
Double hit[a]		20 (14.4)
Triple hit[a]		3 (2.2)
Transformed		37 (26.6)
Mantle cell lymphoma	15 (8.2)	-
Follicular lymphoma	14 (7.7)[b]	-
Chronic lymphocytic leukemia	6 (3.3)	-
Marginal zone B-cell lymphoma	6 (3.3)	-
Burkitt lymphoma	1 (0.5)	-
Waldenstrom macroglobulinemia	1 (0.5)	-
Other	1 (0.5)[c]	-
No. of lines of prior systemic therapy		
Median	3	3
Range	1-13	1-10
First-line prior systemic therapy response		
Relapsed after initial response	115 (62.8)	90 (64.7)
Refractory to first-line therapy	43 (23.5)	30 (21.6)
Last-line prior systemic therapy response		
Relapsed after initial response	66 (36.1)	49 (35.3)
Refractory to last therapy line	109 (59.6)	83 (59.7)
Prior HCT		
Autologous	31 (16.9)	22 (15.8)
Allogeneic	5 (2.7)	2 (1.4)
Both	4 (2.2)	2 (1.4)
Others[d]	2 (1.1)	1 (0.7)

Prior CAR T-cell therapy		
Yes	3 (1.6)	2 (1.4)
No	180 (98.4)	137 (98.6)
Serum LDH, U/L		
Median	323	
Range	109-9348	

*DLBCL subtypes comprised DLBCL (n=134), high-grade B-cell lymphoma (BCL; n=2), aggressive BCL with features intermediate between DLBCL and Burkitt lymphoma (n=1), mediastinal BCL (thymic large BCL; n=1), and primary mediastinal BCL (n=1). In the DLBCL category, transformed disease comprised FL (n=26), marginal zone B-cell lymphoma (n=2), lymphoplasmacytic lymphoma (n=1), nodular lymphocyte-predominant Hodgkin lymphoma (n=2), and Richter's transformation (n=6).a= MYC plus BCL-2 and/or BCL-6 rearrangement, b= One patient with FL also had CLL/small lymphocytic lymphoma recurrence, c= This patient had a history of DLBCL and was enrolled based on imaging consistent with recurrence. The patient was subsequently biopsied after enrollment, and the lesion determined to be sarcoid, d= One patient with DLBCL underwent peripheral stem cell harvest transplantation, and 1 patient with FL underwent double cord transplantation
ECOG=Eastern Cooperative Oncology Group
B-NHL=B-cell Non-Hodgkin Lymphoma
DLBCL= diffuse large B-cell lymphoma
HCT=hematopoietic cell transplantation
CAR=chimeric antigen receptor
LDH=lactate dehydrogenase

Efficacy

- The ORR in all patients with B-NHL in 180 evaluable patients was 45.6% (95% CI: 38.1, 53.1), which included 48 (26.7%) CR and 34 (18.9%) PR.[1]
    - The ORR by histology is shown below in Table 2.
- The median DoR in all patients was 5.4 months (95% CI: 4, not reached). The DoR in patients with DLBCL was 4.5 months (95% CI: 3.9, 9.5).[1]
    - The DoR in patients with MCL or FL was not reached.
- The median PFS in all patients was 3.1 months (95% CI: 2.7, 4.2).
    - The PFS in patients with DLBCL was 4.8 months (95% CI: 1.1, 7.8).[1]
    - The PFS in patients with MCL or FL could not be determined due to the low number of events.
- The median OS in all patients was 8.3 months (95% CI: 6.7, 10.7).
    - The OS in patients with DLBCL was 7.5 months (95% CI: 6-9.8).[1]
    - The OS in patients with MCL or FL was not reached due to the low number of events.

Table 2: Overall Response Rate (ORR) in B-NHL Subgroups Treated with ZYNLONTA doses 15 to 200 µg/kg (Efficacy Analysis Set). Adopted from Hamadani, et al.[1]

	N (%)		
	DLBCL (n=137)	MCL (n=15)	FL (n=14)
ORR (95% CI)	58 (42.3) 33.9, 51.1	7 (46.7) 21.3, 73.4	11 (78.6) 49.2, 95.3
Complete response	32 (23.4)	5 (33.3)	9 (64.3)
Partial response	26 (19)	2 (13.3)	2 (14.3)

DLBCL= diffuse large B-cell lymphoma, MCL= mantle cell lymphoma, FL= follicular lymphoma

Safety

- In the safety analysis set shown below in Table 3, 181 patients (98.9%) experienced at least one TEAE.[1]
- Four patients experienced dose-limiting toxicities (DLTs), all hematologic, during Part 1 (shown below).

    - Grade 4 thrombocytopenia in 1 patient receiving 120 µg/kg (1 of 16), Grade 3 febrile neutropenia in 1 patient receiving 150 µg/kg (1 of 16), and Grade 4 thrombocytopenia in 2 patients receiving 200 µg/kg (2 of 25).[1]
    - The maximum tolerated dose (MTD) was not reached.[1]
- The most common nonhematologic TEAEs were fatigue in 78 patients (43.6%), nausea in 59 patients (32.2%), peripheral edema in 58 patients (31.7%), and increased gamma-glutamyl transferase (GGT) in 57 patients (31.1%).[1]
- Dose delays of ≤21 days were used to manage toxicities per protocol, and 68 patients (37.2%) had dose delays because of TEAEs.[1]
    - The most common TEAEs (≥5% of patients) that led to dose delays were increased GGT in 19 patients (10.4%) and neutropenia in 10 patients (5.5%).[1]
    - Eleven patients (6%) had dose reductions because of TEAEs.
    - Thirty-five patients (19.1%) had TEAEs that led to treatment discontinuation, most commonly because of increased GGT in 7 patients (3.8%) and thrombocytopenia in 5 patients (2.7%).[1]
- At least 1 serious TEAE was reported in 85 patients (46.4%).[1]
    - The most common serious TEAEs, excluding disease progression, were febrile neutropenia in 10 patients (5.5%), pyrexia and pleural effusion in 7 patients (3.8%) each, dyspnea in 6 patients (3.3%), sepsis in 5 patients (2.7%), and abdominal pain in 4 patients (2.2%).[1]
    - Thirty-five patients (19.1%) had experienced a TEAE with a fatal outcome during the study. The most common reason being progression of B-NHL in 20 of 35 patients. Six fatal outcomes were related to ZYNLONTA, all of which were infections.[1]

Table 3: All-Grade TEAEs Reported in ≥10% of Patients With B-NHL Who Received ZYNLONTA in Order of Incidence by System Order Class (Safety Analysis Set). Adopted from Hamadani, et al.[1]

TEAE, n (%)	N (%)				
	≤90 µg/kg (n=17)	120 µg/kg (n=42)	150 µg/kg (n=88)	200 µg/kg (n=36)	Total (n=183)
Any	16 (94.1)	42 (100)	87 (98.9)	36 (100)	181 (98.9)
Hematologic					
Platelet count decreased*	11 (64.7)	28 (68.3)	62 (71.3)	27 (77.1)	128 (71.1)
Neutrophil count decreased*	10 (58.8)	21 (51.2)	50 (58.1)	25 (71.4)	106 (59.2)
Anemia	4 (23.5)	10 (23.8)	32 (36.4)	14 (38.9)	60 (32.8)
White blood count decreased	0	7 (16.7)	6 (6.8)	9 (25)	22 (12)
General disorders and administration site conditions					
Fatigue	7 (41.2)	22 (52.4)	33 (37.5)	16 (44.4)	78 (42.6)
Edema peripheral	1 (5.9)	12 (28.6)	31 (35.2)	14 (38.9)	58 (31.7)
Pyrexia	2 (11.8)	7 (16.7)	13 (14.8)	11 (30.6)	33 (18)
Gastrointestinal disorders					
Nausea	3 (17.6)	12 (28.6)	28 (31.8)	16 (44.4)	59 (32.2)
Constipation	2 (11.8)	12 (28.6)	20 (22.7)	6 (16.7)	40 (21.9)
Vomiting	1 (5.9)	7 (16.7)	17 (19.3)	7 (19.4)	32 (17.5)
Abdominal pain	1 (5.9)	9 (21.4)	12 (13.6)	7 (19.4)	29 (15.8)
Diarrhea	2 (11.8)	5 (11.9)	16 (18.2)	5 (13.9)	28 (15.3)
Investigations					
GGT increased	5 (29.4)	13 (31)	22 (25)	17 (47.2)	57 (31.1)
Blood ALP increased	4 (23.5)	6 (14.3)	18 (20.5)	9 (25)	37 (20.2)
AST increased	3 (17.6)	5 (11.9)	15 (17)	11 (30.6)	34 (18.6)
ALT increased	3 (17.6)	6 (14.3)	14 (15.9)	9 (25)	32 (17.5)
Skin and subcutaneous tissue disorders					
Rash	2 (11.8)	7 (16.7)	27 (30.7)	9 (25)	45 (24.6)
Erythema	1 (5.9)	5 (11.9)	11 (12.5)	4 (11.1)	21 (11.5)

Pruritus	2 (11.8)	4 (9.5)	7 (8)	7 (19.4)	20 (10.9)
Rash maculopapular	3 (17.6)	4 (9.5)	7 (8)	5 (13.9)	19 (10.4)
Metabolism and nutrition disorders					
Decreased appetite	2 (11.8)	7 (16.7)	13 (14.8)	12 (33.3)	34 (18.6)
Hypokalemia	1 (5.9)	3 (7.1)	15 (17)	4 (11.1)	23 (12.6)
Hyperglycemia	1 (5.9)	3 (7.1)	10 (11.4)	5 (13.9)	19 (10.4)
Respiratory, thoracic, and mediastinal disorders					
Dyspnea	1 (5.9)	11 (26.2)	21 (23.9)	8 (22.2)	41 (22.4)
Pleural effusion	2 (11.8)	10 (23.8)	19 (21.6)	8 (22.2)	39 (21.3)
Cough	0	10 (23.8)	16 (18.2)	8 (22.2)	34 (18.6)
Nervous system disorders					
Dizziness	1 (5.9)	6 (14.3)	9 (10.2)	4 (11.1)	20 (10.9)

*= Platelet count decreased and neutrophil count decreased are based on laboratory abnormality reporting and are reported out of number of patients with postbaseline test values; data for 4 patients (1 at 120 µg/kg, 2 at 150 µg/kg, and 1 at 200 µg/kg) were missing for neutrophil count decreased, and data for 3 patients (1 each at 120, 150, and 200 µg/kg) were missing for platelet count decreased.
GGT=gamma-glutamyl transferase
ALP=alkaline phosphatase
AST=aspartate transaminase
ALT=alanine transaminase

- A total of 141 patients (77%) experienced any Grade ≥3 TEAEs. Table 4 provides additional information regarding Grade ≥3 TEAEs reported in LOTIS-1.

Table 4: Grade ≥3 TEAEs Reported in ≥5% of Patients with B-NHL Who Received ZYNLONTA (Safety Analysis Set). Adopted from Hamadani, et al.[1]

TEAE, n (%)	N (%)				
	≤90 µg/kg (n=17)	120 µg/kg (n=42)	150 µg/kg (n=88)	200 µg/kg (n=36)	Total (n=183)
Any Grade ≥3 TEAE	9 (52.9)	32 (76.2)	69 (78.4)	31 (86.1)	141 (77)
Neutrophil count decreased*	6 (35.3)	12 (29.3)	35 (40.7)	18 (51.4)	71 (39.7)
Platelet count decreased*	1 (5.9)	7 (17.1)	25 (28.7)	15 (42.9)	48 (26.7)
GGT increased	4 (23.5)	9 (21.4)	15 (17)	11 (30.6)	39 (21.3)
Anemia	3 (17.6)	4 (9.5)	16 (18.2)	5 (13.9)	28 (15.3)
Blood ALP increased	4 (23.5)	3 (7.1)	3 (3.4)	2 (5.6)	12 (6.6)
Lymphocyte count decreased	0	4 (9.5)	6 (6.8)	2 (5.6)	12 (6.6)
Progressive disease	0	2 (4.8)	9 (10.2)	0	11 (6)
Febrile neutropenia	1 (5.9)	2 (4.8)	6 (6.8)	1 (2.8)	10 (5.5)
Hypokalemia	0	0	8 (9.1)	2 (5.6)	10 (5.5)

*= Platelet count decreased and neutrophil count decreased are based on laboratory abnormality reporting; data for 4 patients (1 at 120 µg/kg, 2 at 150 µg/kg, and 1 at 200 µg/kg) were missing for neutrophil count decreased, and data for 3 patients (1 each at 120, 150, and 200 µg/kg) were missing for platelet count decreased.
GGT=gamma-glutamyl transferase

Literature Search

- A PubMed biomedical literature search conducted on March 25, 2025, yielded no additional relevant data regarding ZYNLONTA (loncastuximab tesirine-lpyl) – LOTIS-1 Study.

Relevant Prescribing Information

Section 2: Dosage and Administration[4]

2.1: Recommended Dosage

- ZYNLONTA as an intravenous infusion administered over 30 minutes on Day 1 of each cycle (every 3 weeks). Administer intravenous infusion as follows:
  - 0.15 mg/kg every 3 weeks for 2 cycles.
  - 0.075 mg/kg every 3 weeks for subsequent cycles.
  - For patients with a body mass index (BMI) ≥35 kg/m^2, calculate the dose based on an adjusted body weight (ABW) as follows: ABW in kg = 35 kg/m^2 × (height in meters)^2

2.2: Recommended Premedication

- Unless contraindicated, administer dexamethasone 4 mg orally or intravenously twice daily for 3 days beginning the day before administering ZYNLONTA. If dexamethasone administration does not begin the day before ZYNLONTA, dexamethasone should begin at least 2 hours prior to administration of ZYNLONTA.

References

[1] Hamadani M, Radford J, Carlo-Stella C, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. *Blood*. 2021;137(19):2634-2645. doi:10.1182/blood.2020007512.
[2] Study of ADCT-402 in patients with relapsed or refractory B-cell lineage non hodgkin lymphoma (B-NHL). ClinicalTrials.gov Identifier: NCT02669017. Updated May 19, 2021. Accessed March 30, 2023. https://clinicaltrials.gov/ct2/show/NCT02669017
[3] Hamadani M, Radford J, Carlo-Stella C, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma [supplementary appendix]. *Blood*. 2021;137(19):2634-2645. doi:10.1182/blood.2020007512.
[4] ZYNLONTA® (loncastuximab tesirine-lpyl) FDA-approved 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.