ZYNLONTA® (Loncastuximab Tesirine-Ipyl) – LOTIS-2 Subgroup Analysis

Summary

- LOTIS-2 was a pivotal Phase 2, multicenter, open-label single-arm study that evaluated the efficacy and safety of ZYNLONTA used as monotherapy in 145 adult patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) following ≥2 lines of prior systemic therapy.[1]
    - In the as-treated population, the primary endpoint, overall response rate (ORR) was 48.3% (95% CI: 39.9, 56.7).[1.]
    - Secondary end points included duration of response (DOR) progression-free survival (PFS) and overall survival (OS).[1]
- Presently, subgroup analyses that have been conducted from the LOTIS-2 study, include, responses in older vs younger patients, DOR in heavily treated patients, responses in patients with High grade B-cell lymphoma (HGBL), responses in patients post chimeric antigen receptor T-cell (CAR-T) cell therapy, and responses to CAR-T in patients who previously received ZYNLONTA.[2,3,4,5,6,7]
    - March 2021 data cut off from the various subgroups and patient related outcome (PRO) analyses suggest that ZYNLONTA is an effective R/R DLBCL treatment, with a durable response and favorable safety and tolerability profile.[2,3,4.]
    - Patients across all 3 age groups (<65, 65<75, and ≥75 years) had similar responses across nearly all efficacy end points.[3,4.]
    - Patients in the younger (aged <70 years) and older (aged ≥70 years) groups had similar responses across nearly all efficacy measures.[3,4.]
- Patient related Outcomes (PRO) analyses were performed in 130 patients who had a baseline score and ≥1 follow-up score. Comparative analyses between age groups were not performed with statistical testing; instead, numerical trends were noted across age groups on relevant measures.[3,4.]
    - March 2021 data cut off suggest that older age does not have a negative impact on response or safety and tolerability of ZYNLONTA treatment.
    - Data also suggest that ZYNLONTA improves or maintains patient related outcomes (PROs) in younger and older patients respectively.
- A comprehensive breakdown of the baseline demographics, clinical/ disease characteristics, clinical efficacy, safety, and all PRO analyses of all the subgroups in LOTIS-2 study are provided in the supplemental tables below.

Clinical Data

- LOTIS-2 (NCT03589469) was a pivotal Phase 2, multicenter, open-label single-arm study that evaluated the efficacy and safety of ZYNLONTA used as monotherapy in 145 adult patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) following ≥2 lines of prior systemic therapy. The primary endpoint was overall response rate (ORR) according to Lugano classification in all-treated patients. Secondary end points included duration of response (DOR) progression-free survival (PFS) and overall survival (OS).[1]
    - In the all treatment population (N=145), the overall response rate (ORR) was 48.3% (95% CI: 39.9, 56.7) for 70 patients. ORR included 35 patients with a CR of 24.1% (95% CI: 17.4, 31.9) and 35 patients with a PR of 24.1% (95% CI: 17.4, 31.9).

Updated Age Subgroups and PRO analysis from the LOTIS-2 population Data Cut Off March 2021[3,4]

- Baseline characteristics were similar in the all treated population (N = 145) and across all age groups.
    - Patients included in the subgroup analysis were of various age groups (<70 years, and ≥70 years).
    - Table 1 summarizes the baseline characteristics, disease characteristics and patient related outcomes (PRO) from the different age groups.
- PRO analyses were performed in 130 patients who had a baseline score and ≥1 follow-up score. Comparative analyses between age groups were not performed with statistical testing; instead, numerical trends were noted across age groups on relevant measures.
    - The PRO analysis included 130 patients from LOTIS-2 all treated population.
    - EuroQol visual analogue scale (EQ-VAS) and functional assessment of cancer therapy-lymphoma (FACT-Lym) were utilized in the PRO analysis. Overall current health state was measured by the EuroQol visual analog scale (EQ-VAS), with a score of 100 indicating "the best health you can imagine" and a score of 0 indicating "the worst health you can imagine." Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) consists of the Functional Assessment of Cancer Therapy. The FACT-Lym total score (range, 0-168) is the sum of physical well-being (range, 0-28), social/family well-being (range, 0-28), emotional well-being (range, 0-24), functional well-being (range, 0-28), and LymS (range, 0-60). Tolerability was assessed using the FACT-Lym item GP5 ("I am bothered by side effects of treatment"), a single-item scale that provides a measure of overall side effect impact on patients.
    - Change from baseline in EQ-VAS and FACT-Lym total scores were stable or improved over the treatment period in both age groups.
    - A majority of patients in both groups responded, "A little bit" or "Not at all," to the GP5 (FACT-Lym) question on tolerability; however, a higher percentage of patients in the older age group responded, "Not at all," than in the younger age group.
- Patients in the younger (aged <70 years) and older (aged ≥70 years) groups had similar responses across nearly all efficacy measures.
    - Median PFS was longer in the older group ≥ 70 years compared with the younger age groups. (7.36 months vs. 3.81 months)
    - The median DOR was 9.26 months (95% CI, 4.63-NA) in the younger group (< 70 years) and not reached in the older group (≥70 years).
    - Patients <70 years received a median of 3 cycles (range, 1-17), and patients ≥70 years received a median of 4 cycles (range, 1-26) of treatment, with a median (min, max) of 43 (1,358) and 69 (1,569) days of treatment, respectively.
    - The median OS and ORR were similar across both age groups.

Safety in Age Subgroup Data Cut Off March 2021[3,4]

- Overall TEAEs were similar across all age subgroups.[3,4.]
    - Patients with any treatment emergent adverse event (TEAE) leading to dose delay or reduction or any TEAE leading to withdrawal were similar across all age groups.
    - Grade ≥3 AEs in ≥10% of patients showed a lower % of neutropenia in age group ≥75 years as compared to the younger ages, additionally there was a lower % of increased gamma-glutamyltransferase (GGT) in older patients as compared to the younger age groups.

- Additional information regarding adverse events in all age groups are provided in the supplemental table section of this document.

Duration of Response by Age, Response to 1st line Systemic Therapy, Double/Triple Hit disease, and Transformed Disease Data Cut Off March 2021 [5]

- In a subsequent subgroup analysis, it revealed that patients aged (<65, 65 to <75, and ≥75 years) showed similar efficacy, and safety across the 3 age groups.[5]
    - The ORR, median time to CR or PR were similar across the 3 age groups.
    - The shortest median PFS was in (65 <75 years group) at 2.99 months.
    - Median OS was longest in the <65-year group (10.58 months) compared with the other age groups (7.46 months, 8.08 months respectively). Median DOR for older patients was longer than for younger patients (≥75 years, not reached; ≥65 to <75 years, 12.6 months; <65 years, 9.3 months).
    - Patients with DLBCL refractory to first-line systemic therapy had a median DOR of 9.6 months compared with 12.6 months for patients who relapsed after responding to initial therapy.
- Patients with double-/triple-hit (DH/TH) or transformed DLBCL each had a median DOR of not reached.[5]
- Patients with advanced stage disease (Stage III–IV) had a median DOR of 12.6 months.[5]
- Additional efficacy and PRO data in the various age groups are provided in the supplemental table section.

Subgroup Analysis from HGBL-DH/TH population [2]

- A subgroup analysis from the LOTIS-2 study evaluated the outcome of patients with HGBL-DH/TH enrolled in the study at the time of data cut off March 1, 2021.
    - Fifteen patients (10%) with high B cell lymphoma- double hit (DH)/triple-hit (TH) were enrolled in the study, the ORR was 33.3% (95%CI:11.8,61.6).
    - All responding HGBL-DH/TH patients had a DOR of more than 12 months, with a median DOR not reached at the time of data cut off.
    - Five patients achieved a CR, the median time to first CR was 43 days.
    - Among HGBL-DH/TH patients treated with ZYNLONTA after chimeric antigen receptor (CAR) T-cell progression (n = 4), one patient achieved CR.
    - The median follow up was 5.8 months, the median PFS and OS were 3.7 (95%CI 1.28-not reached), and 9.2 (95%CI 1.84-not reached), respectively.
- Pertinent information regarding the baseline characteristics of the patients enrolled with HGBL-DH/TH are as follows:[2.]
    - Of the 15 patients, 12 patients were DH, and 3 patients were TH.
    - Of the 15 patients, there were 10 women (66.7%), with a median age of 74 (range 27-85) years, including 6 patients who were ≥75 years of age.
    - Eleven patients (73%) received three or more lines of therapy, 3 patients (20%) had prior ASCT, 1 patient received polatuzumab vedotin containing regimen prior to enrollment, and 4 patients (26.7%) had prior CAR modified T-cell therapy with new biopsy demonstrating persisting CD19 expression by immunohistochemistry.
- Additional data on this subgroup is provided in the supplemental table section.

LOTIS-2 Subgroup Analysis: Characteristics and Reponses in patients with prior CAR-T therapy[6]

- At Data Cut Off April 6, 2020, 13 (9.0%) patients from LOTIS-2 had received prior CAR-T cell therapy.
    - Patients were required to have a biopsy demonstrating persistence of CD19 expression.
    - Two Patients achieved a CR, 4 patients achieved PR to ZYNLONTA, patients received a median of 2 cycles of Lonca (range 1–9).
        - The median follow up was 8 months; median DoR to ZYNLONTA was also 8 months.
    - The median time from treatment with CAR-T to ZYNLONTA treatment was 7 months.
        - ZYNLONTA was the first treatment after CAR-T in 10 patients, 3 patients received other treatments prior to receiving ZYNLONTA, including chemoimmunotherapy (n=1, R-GemOx) and allogeneic SCT (n=1), and one patient received chemoimmunotherapy (R-GemOx) followed by a clinical trial with venetoclax and a bromodomain inhibitor.

Retrospective Analysis: Characteristics and Reponses to CAR-T in Patients who Previously Received ZYNLONTA[7]

- Fourteen patients with disease relapsing or progressing after treatment with ZYNLONTA were identified from the LOTIS study to have subsequently received CD19-directed CAR-T therapy.
    - 10/14 patients were screened for CD19, and all had positive CD19 expression by IHC prior to CAR-T, 4 patients were not assessed for CD19 expression.
    - The median time between treatment with ZYNLONTA and treatment with CAR-T was 120 days.
        - Six patients received additional lines of therapy between ZYNLONTA treatment and CAR-T cell therapy.
    - Six patients had CR, and 1 patient had PR in response to CAR-T therapy, 1 patient had CR, 5 patients had PR in response to ZYNLONTA therapy.

Supplemental Tables.

Table 1: Baseline demographics and clinical characteristics for younger and older patient age groups. Adopted from Hamadani [3,4,8]

Subgroup	< 65 years (n=65)	65 to <75 years (n=59)	<70years (n=95)	≥70 years (n=50)	≥75 years (n=21)	Total (N=145)
Sex, n (%)						
Female	21 (32.3)	25 (42.4)	34 (35.8	26 (52.0)	14 (66.7)	60 (41.4)
Male	44 (67.7)	34 (57.6)	61 (64.2)	24 (48.0)	7 (33.3)	85 (58.6)
Age (years), median (range)	56 (23-64)	69 (65-74)	59 (23-69)	74 (70-94)	79 (75, 94)	66 (23-94)
ECOG performance status score n (%)						
0	27 (41.5)	24 (40.7)	36 (37.9)	22 (44.0)	7 (33.3)	58 (40.0)
1	38 (58.5)	30 (50.8)	57 (60.0)	21 (42.0)	10 (47.6)	78 (53.8)
2	0	5 (8.5)	2 (2.1)	7 (14.0)	4 (19.0)	9 (6.2)
Primary DLBCL category (WHO 2016), n (%)						
DLBCL, NOS	57 (87.7)	56 (94.9)	87 (91.6)	41 (82.0)	15 (71.4)	128 (88.3)
HGBCL, with MYC and BCL2 and/ or BCL6 rearrangements	2 (3.1)	3 (5.1)	2 (2.1)	8 (16.0)	5 (23.8)	10 (6.9)
DLBCL, primary mediastinal	6 (9.2)	0	6 (6.3)	1 (2.0)	1 (4.8)	7 (4.8)
Transformed DLBCL	11 (16.9)	16 (27.1)	21 (22.1)	9 (18.0)	3(14.3)	30 (20.7)
Transformed follicular	10 (15.4)	13 (22.0)	17 (17.9)	9 (18.0)	3 (14.3)	26 (17.9)
Richter's transformation	1 (1.5)	1 (1.7)	2 (2.1)	0	0	2(1.4)
Transformed lymphoplasmacytic	0	1 (1.7)	1 (1.1)	0	0	1 (0.7)
Transformed MZBCL	0	1 (1.7)	1 (1.1)	0	0	1 (0.7)
DLBCL double/ triple hit	**5 (7.7)**	**4 (6.8)**	**6 (6.3)**	**9 (18.0)**	6 (28.6)	15 (10.3)

Double hit	4 (4.2)	3 (5.1)	5 (5.3)	7 (14.0)	5 (23.8)	12 (8.3)
Triple hit	1 (1.5)	1 (1.7)	1 (1.1)	2 (4.0)	1 (4.8)	3 (2.1)
Prior systemic therapies n (%)						
2 prior lines	24 (36.9)	29 (49.2)	37 (38.9)	26 (52.0)	10 (47.6)	63 (43.4)
3 prior lines	14 (21.5)	13 (22.0)	20 (21.1)	14 (28.0)	7 (33.3)	34 (23.4)
> 3 prior lines	27 (41.5)	17 (28.8)	38 (40.0)	10 (20.0)	4 (19.0)	48 (33.1)
No of prior systemic therapies, median (min, max)	3.0 (2-7)	3.0 (2-7)	3.0 (2,7)	2.0 (2,5)	3.0 (2,5)	3.0 (2,7)
Any prior SCT, n (%)						
Yes	17 (26.2)	7 (11.9)	21 (22.1)	3 (6.0)	0	24 (16.6)
No	48 (73.8)	52 (88.1)	74 (77.9)	47 (94.0)	21 (100)	121 (83.4)
Response to prior 1st line systemic therapy, n (%)						
Relapse	40 (61.5)	47 (79.7)	63 (66.3)	36 (72.0)	12 (57.1)	99 (68.3)
Refractory	15 (23.1)	11 (18.6)	22 (23.2)	7 (14.0)	3 (14.3)	29 (20.0)
Other	10 (15.4)	1 (1.7)	10 (10.5)	7 (14.0)	6 (28.6)	17 (11.7)
Response to prior last line therapy, n (%)						
Relapse	18 (27.7)	20 (33.9)	29 (20.5)	14 (28.0)	5 (23.8)	43 (29.7)
Refractory	39 (60.0)	36 (61.0)	58 (61.1)	31 (62.0)	14 (66.7)	89 (61.4)
Other	8 (12.3)	3 (5.1)	8 (8.4)	5 (10.0)	2 (9.5)	13 (9.0)
PRO Scores	**n = 57**	**n = 53**	**n = 82**	**n = 48**	**n =20**	**N = 130**
EQ-VAS						
Median (min, max)	72.5 (5, 97)	75 (30, 100)	75 (5, 100	77.5 (30,100)	80 (40,100)	75 (5,100)
Mean (SD)	69.8 (19.38)	71.5 (19.23)	70.5 (19.37)	72.8 (18.74)	75.5 (18.2)	71.4 (19.09)
FACT-Lym total score						
Median (min, max)	116 (60, 156.8)	126 (70, 156)	118 (60, 156.8)	126.5 (41.7, 156)	123 (41.7, 155)	121 (41.7, 156.8)
Mean (SD	111.75 (24.24)	124.49 (21.08)	114.43 (23.07)	125.24 (23.83)	121.32 (25.85)	118.41 (23.84)
GP5 (FACT-Lym), %[a]						
Not at all	56	71.4	63.5	67.4	72.2	64.9
A little bit	22	10.2	14.9	18.6	16.7	16.3
Somewhat	16	12.2	16.2	9.3	11.1	13.7
Quite a bit	2	6.1	2.7	4.7	0	3.4
Very much	4	0	2.7	0	0	1.7

HGBCL, high-grade B-cell lymphoma; NOS, not otherwise specified; MZBCL, marginal zone Bcell lymphoma; SCT, stem cell transplant; WHO, World Health Organization. [a]Some total percentages do not sum to 100% owing to rounding values.

Table 2: Summary of Overall Response Rate (ORR) by Subgroup, as Assessed by Independent Reviewer (All-Treated Population) and Baseline clinical characteristics of Patients with HGBL-DH/TH. Adopted from Alderuccio, Caimi, and Hamadani[1,2,4,8]

Subgroup	N (at risk)	ORR	95% CI
Sex			
Female	60	30 (50)	(36.8, 63.2)
Male	85	40 (47.1)	(36.1, 58.2)
Age group			
<65 years	65	32 (49.2)	(36.6, 61.9)
≥65 to <75 years	59	27 (45.8)	(32.7, 59.2)
< 70 years	90	46 (48.4)	(38.0, 58.9)
≥70 years	50	(24) 48.0	(33.7, 62.6)
≥75 years	21	11 (52.4)	(29.8, 74.3)
Country			
USA	59	29 (49.2)	(35.9, 62.5)
UK	31	13 (41.9)	(24.5, 60.9)
Italy	53	27 (50.9)	(36.8, 64.9)
Switzerland	2	1 (50)	(1.3, 98.7)
Histology			
DLBCL, NOS	128	64 (50.4)	(41.4, 59.4)
PMBCL	7	1 (14.3)	(0.4, 57.9)
HGBCL	10	5 (50.0)	(18.7, 81.3)
Bulky Disease			
Yes	8	2 (25)	(3.2, 65.1)
No	137	68 (49.6)	(41, 58.3)
Double/triple hit HGBCL			
Yes	15	5 (33.3)	(11.8, 61.6)

No	130	65 (50)	(41.1, 58.9)
Prior systemic therapies			
2 lines	63	30 (47.6)	(34.9, 60.6)
3 lines	35	17 (48.6)	(31.4, 66)
>3 lines	47	23 (48.9)	(34.1, 63.9)
Response to first-line systemic therapy			
Relapsed	99	53 (53.5)	(43.2, 63.6)
Refractory	29	11 (37.9)	(20.7, 57.7)
Other	17	6 (35.3)	(14.2, 61.7)
Response to most recent line systemic therapy			
Relapsed	43	29 (67.4)	(51.5, 80.9)
Refractory	84	31 (36.9)	(26.6, 48.1)
Other	18	10 (55.6)	(30.8, 78.5)
Transformed DLBCL			
Transformed	29	13 (44.8)	(26.4, 64.3)
De novo	116	57 (49.1)	(39.7, 58.6)
DLBCL stage			
Stage I	10	5 (50)	(18.7, 81.3)
Stage II	23	14 (60.9)	(38.5, 80.3)
Stage I/II	33	19 (57.6)	(39.2, 74.5)
Stage III	19	11 (57.9)	(33.5, 79.7)
Stage IV	93	40 (43)	(32.8, 53.7)
Stage III/IV	112	51 (45.5)	(36.1, 55.2)
Cell-of-origin			
GCB	49	26 (53.1)	(38.3, 67.5))
ABC	23	11 (47.8)	(26.8, 69.4)
Unknown	74	33 (44.6)	(33, 56.6)
Response to any prior line systemic therapy			
Relapsed	115	60 (52.2)	(42.7, 61.6)
Refractory	24	9 (37.5)	(18.8, 59.4)
Relapse within 3 months of first-line therapy			
Yes	35	15 (42.9)	(26.3, 60.6)
Relapse within 6 months of first-line therapy			
Yes	57	26 (45.6)	(32.4, 59.3)
Prior CAR-T therapy			
Yes	14	6 (42.9)	(17.7, 71.1)
No	132	64 (48.5)	(39.7, 57.3)
Prior SCT			
Yes	24	14 (58.3)	(36.6, 77.9)
No	121	56 (46.3)	(37.2, 55.6)
Prior radiotherapy			
Yes	53	28 (52.8)	(38.6, 66.7)
No	92	42 (45.7)	(35.2, 56.4)
Prior surgery			
Yes	27	13 (48.1)	(28.7, 68.1)
No	118	57 (48.3)	(39, 57.7)
Drug formulation			
Frozen liquid	35	17 (48.6)	(31.4, 66)
Lyophilized	110	53 (48.2)	(38.6, 57.9)
Maximal longest tumor diameter			
≤5 cm	82	48 (58.5)	(47.1, 69.3)
>5 to ≤7.5 cm	36	11 (30.6)	(16.3, 48.1)
>7.5 to ≤10 cm	10	4 (40)	(12.2, 73.8)
>10 cm	13	4 (30.8)	(9.1, 61.4)
Missing	4	3 (75)	(19.4, 99.4)
Double/triple expressor DLBCL			
No	125	60 (48)	(39, 57.1)
Yes	20	10 (50)	(27.2, 72.8)

Data Cut off March 1, 2021, and September 15,2022, a Prior stem cell transplant 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 is defined as no response to therapy. c Other defined as unknown, not evaluable, or missing. d Derived from baseline values at time of clinical trial enrollment as previously described DLBCL, diffuse large B-cell lymphoma. PMBCL, primary mediastinal B-Cell lymphoma HGBCL, high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements HGBL-DH/TH, high grade B-Lymphoma double hit/triple hit GCB, germinal center B-cell ABC, activated B-cell; CAR T, chimeric antigen receptor T-cell CAR-T, chimeric antigen receptor T-cell HCT, hematopoietic cell transplant.

Table 3: Summary of Complete Response Rate (CRR) by Subgroup, as Assessed by Independent Reviewer (All-Treated Population). Adopted from Caimi and Hamdani.[1,4.,8]

Subgroup	N (at risk)	CRR	95% CI
Sex			
Female	60	21 (35)	(23.1, 48.4)
Male	85	14 (16.5)	(9.3, 26.1)
Age group			
<65 years	65	13 (20.0)	(9.9, 30)
≥65 to <75 years	59	15 (25.4)	(15, 38.4)
<70 years	95	21 (22.1)	(14.2, 31.8)
≥70 years	50	15 (30.0)	(17.9, 44.6)
≥75 years	21	8 (38.1)	(18.1, 61.6)
Country			
USA	59	14 (23.7)	(13.6, 36.6)
Non-USA	86	21 (24.4)	(15.8, 34.9)
Histology			
DLBCL, NOS	128	31 (24.2)	(17.1, 32.6)
PMBCL	7	0 (0)	NE
HGBCL	10	5 (50.0)	(18.7, 81.3)
Double/triple hit DLBCL			
Yes	15	5 (33.3)	(11.8, 61.6)
No	130	30 (23.1)	(16.1, 31.3)
Prior systemic therapies			
2 lines	63	15 (23.8)	(14, 36.2)
3 lines	35	5 (14.3)	(4.8, 30.3)
>3 lines	47	15 (31.9)	(19.1, 47.1)
Response to first-line systemic therapy			
Relapsed	99	26 (26.3)	(17.9, 36.1)
Refractory	29	5 (17.2)	(5.8, 35.8)
Response to most recent line systemic therapy			
Relapsed	43	18 (41.9)	(27, 57.9)
Refractory	84	10 (11.9)	(5.9, 20.8)
Transformed DLBCL			
Transformed	30	7 (23.3)	(10.3, 43.5)
De novo	116	28 (24.1)	(16.7, 33)
DLBCL stage			
Stage I	10	3 (30)	(6.7, 65.2)
Stage II	23	6 (26.1)	(10.2, 48.4)
Stage I/II	33	9 (27.3)	(13.3, 45.5)
Stage III	19	4 (21.1)	(6.1, 45.6)
Stage IV	93	22 (23.7)	(15.5, 33.6)
Stage III/IV	112	26 (23.2)	(15.8, 32.1)
Cell-of-origin			
GCB	49	13 (26.5)	(14.9, 41.1)
ABC	23	5 (21.7)	(7.5, 43.7)
Response to any prior line systemic therapy			
Relapsed	115	30 (26.1)	(18.3, 35.1)
Refractory	24	4 (16.7)	(4.7, 37.4)
Relapse within 3 months of first-line therapy			
Yes	35	9 (25.7)	(12.5, 43.3)
Relapse within 6 months of first-line therapy			
Yes	57	13 (22.8)	(12.7, 35.8)
Prior CAR-T therapy			
Yes	14	3 (21.4)	(4.7, 50.8)
No	132	33 (25)	(17.9, 33.3)
Prior HCT			
Yes	24	7 (29.2)	(12.6, 51.1)
No	121	28 (23.1)	(16, 31.7)
Prior Radiotherapy			
Yes	53	15 (28.3)	(16.8, 42.3)
No	92	20 (21.7)	(13.8, 31.6)
Prior surgery			
Yes	27	6 (22.2)	(8.6, 42.3)

No	118	29 (24.6)	(17.1, 33.4)
Drug formulation			
Frozen liquid	35	8 (22.9)	(10.4, 40.1)
Lyophilized	110	27 (24.5)	(16.8, 33.7)
Double/triple expressor DLBCL			
Yes	20	4 (20)	(5.7, 43.7)
No	125	31 (24.8)	(17.5, 33.3)

Data cut off March 1, 2021 and September 15, 2022

DLBCL, diffuse large B-cell lymphoma PMBCL, primary mediastinal B-Cell lymphoma HGBCL, high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements HGBL-DH/TH, high grade B-Lymphoma double hit/triple hit GCB, germinal center B-cell ABC, activated B-cell; CAR-T, chimeric antigen receptor T-cell CAR-T, chimeric antigen receptor T-cell HCT, hematopoietic cell transplant.

Table 4: Summary of Duration of Response (DOR) by Subgroup (All-Treated Population). Adopted from Caimi and Hamdani.[1,3,4,5]

Subgroup	N (at risk)	Number of Events	DOR (median, months)	95% CI
Age group				
<65 years	32	10	9.63	(3.22, NE)
≥65 to <75 years	27	6	10.25	(3.84, NE)
<70 years	17		9.26	(4.63, NE)
≥70 years	6		NR	NR
≥75 years	11	2	13.37	(5.98, NE)
Histology				
DLBCL, NOS	64	16	9.63	(5.98, NE)
PMBCL	1	1	1.51	NE
HGBCL	5	1	13.37	NE
Bulky Disease				
Yes	2	1	3.22	NE
No	68	17	10.25	(6.87, NE)
Double/triple hit DLBCL				
Yes	5	1	13.37	NE
No	65	17	9.63	(5.98, NE)
Prior systemic therapies				
2 lines	30	8	13.37	(5.68, NE)
3 lines	17	5	5.98	(2.66, NE)
>3 lines	23	5	10.25	(4.63, NE)
Response to first-line systemic therapy				
Relapse	53	12	10.25	(5.98, NE)
Refractory	11	5	9.63	(1.25, NE)
Other	6	1	Not reached	NE
Response to most recent line systemic therapy				
Relapse	29	7	10.25	(5.68, NE)
Refractory	31	8	9.63	(5.98, NE)
Other	10	3	13.37	(3.84, NE)
Transformed DLBCL				
Transformed	13	1	Not reached	NE
De novo	57	17	9.63	(5.68, 13.37)
DLBCL stage				
Stage I/II	19	3	10.25	(4.63, NE)
Stage III/IV	51	15	9.63	(5.98, NE)
Cell-of-origin				
GCB	26	9	9.63	(5.68, 13.37)
ABC	11	3	6.87	(1.31, NE)
Unknown	33	6	Not reached	NE
Response to any prior line systemic therapy				
Relapse	60	14	10.25	(5.98, NE)
Refractory	9	4	9.63	(1.25, NE)
Other	1	0	Not reached	NE

PMBCL, primary mediastinal B-Cell lymphoma HGBCL, high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements GCB, germinal center B-cell

Table 5: Subgroup Analysis of Most Common TEAES of all Grades, and Grade ≥3 AEs reported in ≥10% of All Patients by Age in Order of Incidence (All-Treated Population). Adopted from Caimi and Hamadani. [1,4]

TEAE	All patients	Age Subgroup				
	All ages (N=145)	<65 years (N=65)	≥65 to <75 years (N=59)	<70years (n=95)	≥70 years (n=50)	≥75 years (N=21)
Any TEAE	143 (98.6)	65 (100)	58 (98.3)	94 (98.9)	49 (98.0)	20 (95.2)
grade ≥3 AE	107 (73.8)	51 (78.5)	43 (72.9)	73 (76.8)	34 (68.0)	13 (61.9)
Any TEAEs related to treatment	118 (81.4)	53 (81.5)	48 (81.4)	77 (81.1)	41 (82.0)	17 (81.0)
Patients with any TEAE leading to dose delay or reduction	75 (51.7)	36 (55.4)	30 (50.8)	49 (51.6)	26 (52.0)	9 (42.9)
Patients with any TEAE leading to withdrawal	36 (24.8)	16 (24.6)	14 (23.7)	23 (24.2)	13 (26.0)	6 (28.6)
Patients with any serious TEAE	57 (39.3)	26 (40.0)	23 (39.0)	35 (36.8)	22 (44.0)	8 (38.1)
Patients with any TEAE with fatal outcome	8 (5.5)	4 (6.2)	4 (6.8)	6 (6.3)	2 (4.0)	0
Patients with infusion -related reaction	6 (4.1)	5 (7.7)	0	5 (5.3)	1 (2.0)	1 (4.8)
Hematologic TEAEs all grades						
Neutropenia	57 (39.3)	33 (50.8)	20 (33.9)			4 (19)
Thrombocytopenia	48 (33.1)	28 (43.1)	17 (28.8)			3 (14.3)
Anemia	38 (26.2)	23 (35.4)	9 (15.3)			6 (28.6)
Leukopenia	21 (14.5)	9 (13.8)	10 (16.9)			2 (9.5)
Hematologic TEAES grade ≥ 3 AEs						
Neutropenia	38 (26.2)	19 (29.2)	17 (28.8)	28 (29.5)	10 (20.0)	2 (9.5)
Thrombocytopenia	26 (17.9)	13 (20.0)	10 (16.9)	21 (22.1)	5 (10.0)	3 (14.3)
Anemia	15 (10.3)	7 (10.8)	6 (10.2)	11 (11.6)	4 (8.0)	2 (9.5)
Leukopenia	13 (9.0)	5 (7.7)	6 (10.2)	8 (8.4)	5 (10.0)	2 (9.5)
Non-hematologic TEAEs						
Fatigue	40 (27.6)	21 (32.3)	15 (25.4)			4 (19)
Nausea	34 (23.4)	17 (26.2)	13 (22.2)			4 (19)
Cough	32 (22.1)	19 (29.2)	9 (15.3)			4 (19)
Peripheral edema	29 (20)	11 (16.9)	14 (23.7)			4 (19)
Pyrexia	28 (19.3)	15 (23.1)	11 (18.6)			2 (9.5)
Diarrhea	25 (17.2)	10 (15.4)	9 (15.3)			6 (28.6)
Decreased appetite	22 (15.2)	10 (15.4)	10 (16.9)			2 (9.5)
Rash	19 (13.1)	8 (12.3)	8 (13.6)			3 (14.3)
Vomiting	19 (13.1)	15 (23.1)	3 (5.1)			1 (4.8)
Pruritus	18 (12.4)	10 (15.4)	4 (6.8)			4 (19)
Dyspnea	17 (11.7)	6 (9.2)	8 (13.6)			3 (14.3)
Constipation	17 (11.7)	10 (15.4)	6 (10.2)			1 (4.8)
Abdominal pain	16 (11)	11 (16.9)	4 (6.8)			1 (4.8)
Insomnia	16 (11)	9 (13.8)	6 (10.2)			1 (4.8)
Photosensitivity reaction	15 (10.3)	8 (12.3)	7 (11.9)			0
Pleural effusion	15 (10.3)	5 (7.7)	9 (15.3)			1 (4.8)
Erythema	15 (10.3)	9 (13.8)	5 (8.5)			1 (4.8)
Headache	15 (10.3)	11 (16.9)	2 (3.4)			2 (9.5)
Biochemical TEAEs all grades						
Gamma-glutamyltransferase increased	59 (40.7)	33 (50.8)	23 (39)			3 (14.3)
Blood alkaline phosphatase increased	29 (20)	18 (27.7)	10 (16.9)			1 (4.8)
Hypophosphatemia	23 (15.9)	11 (16.9)	9 (15.3)			3 (14.3)
Alanine aminotransferase increased	23 (15.9)	19 (29.2)	4 (6.8)			0
Aspartate aminotransferase increased	23 (15.9)	15 (23.1)	6 (10.2)			2 (9.5)
Hypokalemia	22 (15.2)	9 (13.8)	10 (16.9)			3 (14.3)
Hypomagnesemia	20 (13.8)	10 (15.4)	7 (11.9)			3 (14.3)
Biochemical TEAEs grade ≥ 3						
Gamma-glutamyltransferase increased	25 (17.2)	17 (26.2)	8 (13.6)	22 (23.2)	3 (6.0)	0

Literature Search

- A PubMed biomedical literature search conducted on November 3, 2025, yielded no further relevant information regarding subgroup analysis in LOTIS-2 study.

Relevant Prescribing Information

Section 6: Adverse Reactions[9]

6.1: Clinical Trials Experience

- 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.

Section 14: Clinical Studies[9]

14.1: Relapsed or Refractory Diffuse Large B-Cell Lymphoma

- Of the 145 patients enrolled, the median age was 66 years (range 23 to 94), 59% male, and 94% had an 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. The diagnosis was DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low-grade lymphoma), high-grade B-cell lymphoma in 7%. The median number of prior therapies was 3 (range 2 to 7), 63% with refractory disease, 17% with prior stem cell transplant, and 9% with prior chimeric antigen receptor (CAR) T-cell therapy. Efficacy was established on the basis of overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria (Table 6). The median follow-up time was 7.3 months (range 0.3 to 20.2).

Table 6: Efficacy Results in Patients with Relapsed or Refractory DLBCL. Adopted from Prescribing Information.[9]

Efficacy Parameter	ZYNLONTA N = 145
Overall response rate by IRC[a], (95% CI)	48.3% (39.9, 56.7)
Complete response rate (95% CI)	24.1% (17.4, 31.9)
Partial response rate (95% CI)	24.1% (17.4, 31.9)
Duration of overall response[b]	**N = 70**
Median (95% CI), months	10.3 (6.9, NE)

CI=confidence interval, NE=not estimable [a]=independent review committee using Lugano 2014 criteria [b]=of 70 patients with objective response, 25 (36%) were censored prior to 3 months. Twenty-six percent of responders had a duration of response ≥6 months.

References

[1] Caimi PF, Weiyun A, 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 May 11. DOI: 10.1016/S1470-2045(21)00139-X.
[2] Alderuccio JP, Ai WZ, Radford J, Solh MM, et al. Loncastuximab tesirine in relapsed/refractory high-grade B-cell lymphoma: a subgroup analysis from the LOTIS-2 study. Blood Adv. 2022 Jul 5: bloodadvances.2022007782. doi: 10.1182/bloodadvances.2022007782. Online ahead of print.
[3] Hamadani M, Spira AI, Zhou X, et al. Clinical Outcomes of Older and Younger Patients Treated with Loncastuximab Tesirine in the LOTIS-2 Clinical Trial [published online ahead of print, 2023 Oct 23]. Blood Adv. 2023; bloodadvances.2023010636. doi:10.1182/bloodadvances.2023010636
[4] Hamadani M, Spira AI, Zhou X, et al. Clinical Outcomes of Older and Younger Patients Treated with Loncastuximab Tesirine in the LOTIS-2 Clinical Trial Supplemental Material https://ash.silverchaircdn.com/ash/content_public/journal/bloodadvances/jam/10.1182_bloodadvances.2023010636
[5] Caimi PF, et al. Duration of Response to Loncastuximab Tesirine in Relapsed/Refractory Diffuse Large B-cell Lymphoma by Demographic and Clinical Characteristics: Subgroup Analyses from LOTIS-2. Poster presented at the American Society of Clinical Oncology (ASCO) Virtual Congress. June 4–8, 2021. Virtual Meeting.
[6] Caimi PF, Ardeshna KM, Reid E, et al. The antiCD19 antibody drug immunoconjugate loncastuximab achieves responses in DLBCL relapsing after antiCD19 CAR-T cell therapy. Clin Lymphoma Myeloma Leuk. 2021;S2152-2650(21)02437-X. doi:10.1016/j.clml.2021.11.005
[7] Thapa B, Caimi PF, Ardeshna KM, et al. CD19 antibody-drug conjugate therapy in DLBCL does not preclude subsequent responses to CD19-directed CAR T-cell therapy. Blood Adv. 2020;4(16):3850-3852. Blood Adv. 2020;4(19):4606. doi:10.1182/bloodadvances.2020003378
[8] Caimi PF, Ai WZ, Alderuccio JP, et al. Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase 2 LOTIS-2 study. Haematol. Published online August 31, 2023. doi: 110.3324/haematol.2023.283459
[9] 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.