LOTIS-1

A Phase 1 Dose-Escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-402 in Patients With Relapsed or Refractory B-cell Lineage Non-Hodgkin Lymphoma (B-NHL)

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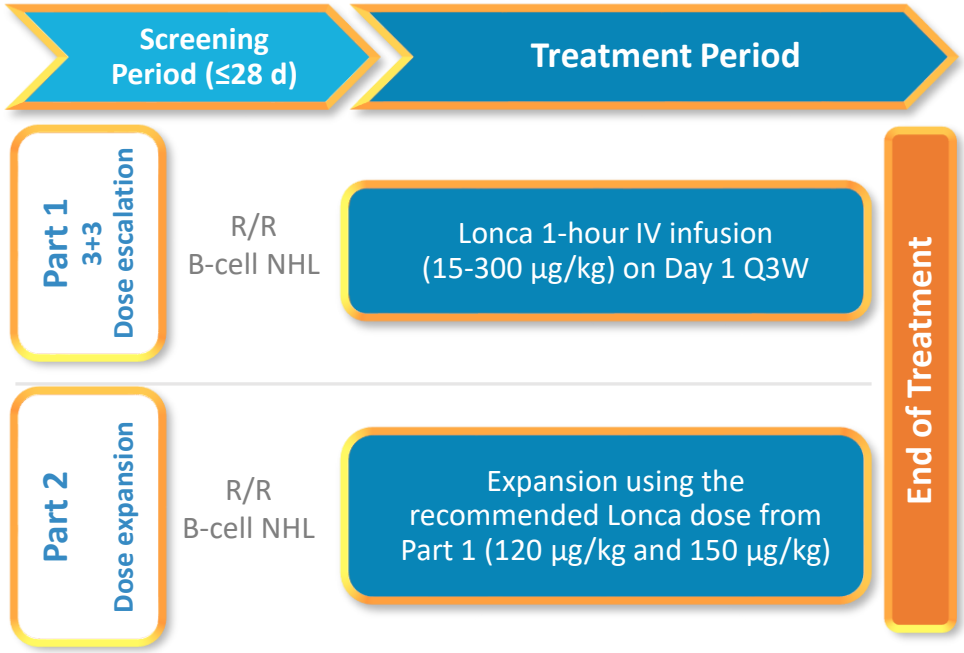
LOTIS-1

Phase 1, Lonca dose-escalation, dose-expansion study[1,2]

- 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 Lonca, used as monotherapy, in 183 adult patients with R/R B-NHL. LOTIS-1 was the first study for the approval of Lonca in patients with R/R large B- cell lymphoma.



PRIMARY ENDPOINTS

- **Part 1 (dose escalation):** Safety and tolerability and determine the recommended dose for dose expansion (Part 2)
- **Part 2 (dose expansion):** Safety and tolerability at recommended doses

SECONDARY ENDPOINTS

- Antitumor activity of Lonca as measured by ORR, DOR, PFS, and OS
- Characterize the pharmacokinetic profile of Lonca
- Evaluate antidrug antibodies in blood before, during, and after treatment with Lonca

KEY INCLUSION/EXCLUSION CRITERIA

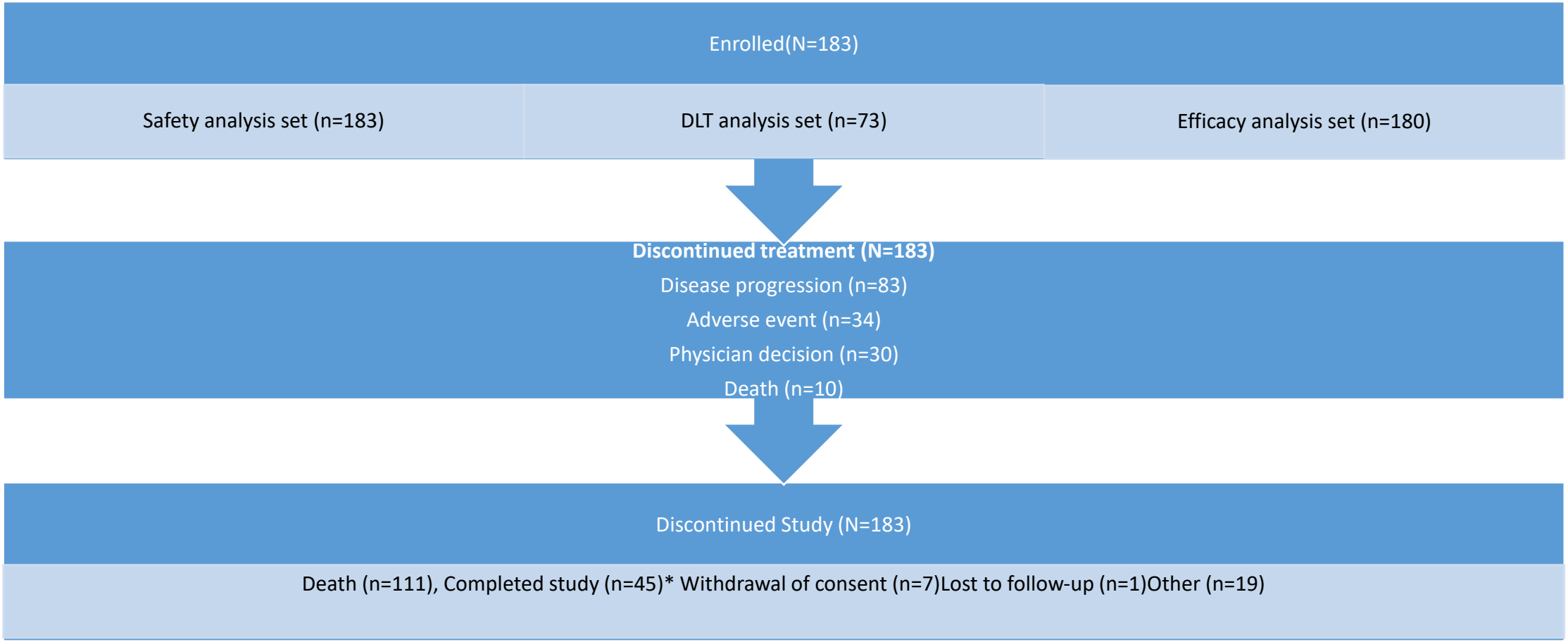
- Adult participants with pathologically confirmed R/R B-cell NHL who have failed or are intolerant to established therapy, or for whom no other treatment options are available
- R/R B-cell NHL (per WHO Classification)
- Measurable disease, as defined by the 2014 Lugano Classification
- ECOG performance status 0 to 2
- Excluded patients with autologous or allogenic transplant within the 60 days prior to the screening visit
- Excluded patients with known history of immunogenicity or hypersensitivity to a CD19 antibody

183 patients were enrolled; 139 of enrolled patients had DLBCL

Cycle 1 dose-limiting toxicity observation period. Disease assessments every other cycle for first 2 evaluations (6 weeks [end of Cycle 2 ± 1 week] and 12 weeks [end of Cycle 4 ± 1 week]) and every third cycle (every 9 weeks [e.g., end of Cycles 7, 10, 13, etc., ± 1 week]) thereafter until progression, or as clinically indicated. Response to treatment determined according to 2014 Lugano Classification Criteria.

REFERENCES

Patient Disposition



*A patient was considered to have completed the study after 12 months posttreatment follow-data were obtained
Hamadani M, et al. Blood. 2020; 137(19):2634-2645.

LOTIS-1: Baseline Demographics (Safety Analysis Set)

Patient characteristics	All Patients with B-NHL (N=183)	Patients with DLBCL (n=139)	Patient characteristics	All Patients with B-NHL (N=183)	Patients with DLBCL (n=139)
Sex, n (%)			**No. of lines of prior systemic therapy**		
Female	69 (37.7)	59 (42.2)	Median	3	3
Male	114 (62.3)	80 (57.6)	Range	1-13	1-10
Age, years, median (range)	63.0 (20-87)	63.0 (20-86)	**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)
ECOG score			**Last-line prior systemic therapy response**		
0-1	160 (87.4)	119 (85.6)	Relapsed after initial response	66 (36.1)	49 (35.3)
2	21 (11.5)	18 (12.9)	Refractory to last therapy line	109 (59.6)	83 (59.7)
3	2 (1.1)	2 (1.4)			
B-NHL subtype			**Prior HCT**		
DLBCL group*			Autologous	31 (16.9)	22 (15.8)
Double hit (MYC plus BCL-2 and/or BCL-6 rearrangement)		20 (14.4)	Allogeneic	5 (2.7)	2 (1.4)
			Both	4 (2.2)	2 (1.4)
Triple hit (MYC plus BCL-2 and BCL-6 rearrangement)		3 (2.2)	Other‖	2 (1.1)	1 (0.7)
Transformed		37 (26.6)			
MCL	15 (8.2)	-			
FL	14 (7.7)**	-			
CLL	6 (3.3)	-			
Marginal zone B-cell lymphoma	6 (3.3)	-	**Prior CAR T-cell therapy**		
Burkitt lymphoma Waldenstrom	1 (0.5)	-	Yes	3 (1.6)	2 (1.4)
macroglobulinemia	1 (0.5)	-	No	180 (98.4)	137 (98.6)
Other	1 (0.5)¶	-			

CLL, chronic lymphocytic leukemia; ECOG, Eastern Oncology Cooperative Group; LDH, lactate dehydrogenase; U/L, upper/lower.*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), mediastinalBCL (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). **One patient with FL also had CLL/small lymphocytic lymphoma recurrence.

¶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. ‖Onepatient with DLBCL underwent peripheral stem cell harvest transplantation, and 1 patient with FL underwent double cord transplantation. Hamadani M, et al. Blood. 2020; 137(19):2634-2645.

LOTIS-1 Part 1: Dose escalation

	Dose (µg/kg)					
	≤90	120	150	200	≥120	Total
Response, n (%)	**All patients (N=86)**					
	17	16	19	34	69	86
CR	3	6	7	15	28	31 (36.0)
PR	2	3	5	5	13	15 (17.4)
SD	4	4	1	2	7	11 (12.8)
PD	8	3	6	12	21	29 (33.7)
ORR	5 (29.4)	9 (56.3)	12 (63.2)	20 (58.8)	41 (59.4)	**46 (53.5)**
	DLBCL subgroup (n=61)					
	10	**11**	**15**	**25**	**51**	61
CR	1	4	5	10	19	20 (32.8)
PR	1	2	4	3	9	10 (16.4)
SD	2	3	0	2	5	7 (11.5)
PD	6	2	6	10	18	24 (39.3)
ORR	2 (20.0)	6 (54.5)	9 (60.0)	13 (52.0)	28 (54.9)	**30 (49.2)**

[a]Best visit response based on the 2014 Lugano Classification Criteria; [b]Based on laboratory abnormality; [c]One patient had missing data post-baseline. TEAE, treatment-emergent adverse event; Tx, treatment.

Kahl BS, et al. Clin Can Res. 2019;25(23):6986-6994.

Antitumor Activity Was Observed in Patients With B-NHL including DLBCL, MCL, and FL

- ORR in all 180 evaluable patients with B-NHL was 45.6% (95% CI 38.1, 53.1), including 48 (26.7%) CRs and 34 (18.9%) PRs
  - ORR for Lonca doses of 15-90 µg/kg was 29.4% compared with 47.2% for doses of 120-200 µg/kg
  - ORR for lonca doses of 15-200 µg/kg in DLBCL was 42.3%, in MCL was 46.7%, in FL was 78.6%
- Median time to tumor response for all patients with B-NHL who achieved CR or PR was 43.0 days (range 31-323)
- Median DOR with Lonca in all patients with B-NHL was 5.4 months (95% CI 4.0, not reached)
  - Median DOR was 4.5 months (95% CI 3.9, 9.5) in patients with DLBCL and not reached in patients with MCL or FL
- Median PFS and OS was 3.1 months (95% CI 2.7, 4.2) and 8.3 months (95% CI 6.7, 10.7), respectively, in all patients with B-NHL

Based on cumulative safety, PK, and efficacy data, the recommended dose of Lonca for phase 2 is 150 µg/kg Q3W for 2 doses, followed by 75 µg/kg Q3W for subsequent doses[a]

[a]The initial 150 µg/kg dose level was selected based on the increased frequency of AEs observed with the 200 µg/kg dose. As onset of response was generally rapid (median 2 cycles), reducing the dose after 2 cycles of treatment is intended to mitigate the onset of late-developing and difficult-to-manage toxicities, such as edema, while optimizing the frequency of objective response; 180 patients were included in the efficacy analysis data set.

B-NHL, B-cell non-Hodgkin lymphoma; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; Lonca, loncastuximab tesirine; MCL, mantle cell lymphoma; ORR, overall response rate; PR, partial response

Hamadani M, et al. Blood. 2020; 137(19):2634-2645.

B-NHL subgroups treated with lonca at doses 15 to 200 µg/kg (efficacy analysis set)

	DLBCL (n=137)	MCL (n=15)	FL (n=14)
ORR, n (%) (95% CI)	58 (42.3) (33.9, 51.1)	7 (46.7) (21.3, 73.4)	11 (78.6) (49.2, 95.3)
CR, n (%)	32 (23.4)	5 (33.3)	9 (64.3)
PR, n (%)	26 (19.0)	2 (13.3)	2 (14.3)

Median time to tumor response for all patients with B-NHL who achieved CR or PR:
43.0 days (range, 31-323 days).

Median DoR in all patients with B-NHL was 5.4 months (95% CI: 4, not reached). DoR in patients with DLBCL was 4.5 months (95% CI: 3.9, 9.5)*.
DoR in patients with MCL or FL was not reached

Median PFS in all patients with B-NHL was 3.1 months (95% CI: 2.7, 4.2)
PFS in patients with DLBCL was 2.8 months (95% CI: 1.9, 3.8)
PFS in patients with MCL was 4.8 months (95% CI: 1.1, 7.8). PFS in patients with FL could not be determined due to the low number of events

Median OS in all patients with B-NHL was 8.3 months (95% CI: 6.7, 10.7). OS in patients with DLBCL was 7.5 months (95% CI: 6.0, 9.8). OS in patients with MCL or FL was not reached due to the low number of events

*Similar DORs were achieved in patients with DLBCL receiving 120, 150, and 200 µg/kg doses . Median DOR was not reached in patients with DLBCL (doses ≥120 µg/kg) who achieved CR.
B-NHL, B-cell non-Hodgkin lymphoma; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; FL, follicular lymphoma; MCL, mantle cell lymphoma; TEAE, treatment-emergent adverse event;; OS, overall survival; PFS, progression-free survival; Tx, treatment. Hamadani M, et al. Blood. 2020; 137(19):2634-2645.

LOTIS-1: Safety (N=183)

Four patients experienced DLTs during Part 1:

- Grade 4 thrombocytopenia in 1 patient receiving 120 µg/kg
- Grade 3 febrile neutropenia in 1 patient receiving 150 µg/kg
- Grade 4 thrombocytopenia in 2 patients receiving 200 µg/kg
- MTD was not reached

181 patients (98.9%) reported ≥1 TEAE

- Hematologic TEAEs were common
- Fatigue was the most common nonhematological TEAE (42.6%), followed by nausea (32.2%), peripheral edema (31.7%), and GGT increase (31.1%, all grades; 21.3%, grade ≥3)

All-grades skin- or nail-related toxicities were reported in 98 (53.6%) patients and were generally mild to moderate and reversible

- Rash (24.6%)
- Erythema (11.5%)
- Pruritis (10.9%)
- Maculopapular rash (10.4%)

All-grades edema or effusion were reported in 86 (47%) patients and generally occurred after ≥2 cycles

- Peripheral edema (31.7%)
- Pleural effusion (21.3%)[a]

One patient who received Lonca 120 µg/kg experienced a grade 2 IRR on cycle 1 day 1 in Part 2 that resolved on the same day

- Dosing was not modified, and the patient received 8 further cycles of Lonca

[a]Four patients experienced grade 3 pleural effusion: 1 each at the 120 µg/kg and 200 µg/kg dose, and 2 at the 150 µg/kg dose. DLT, dose-limiting toxicity; GGT, gamma-glutamyl transferase; IRR, infusion related reaction; MTD, maximum tolerated dose; TEAE, treatment-emergent adverse event. Dexamethasone was incorporated mid-study in LOTIS-1 as prophylaxis to mitigate edema and effusion, following observation of fluid-related toxicities. (FDA, 2021)

Hamadani M, et al. Blood. 2020; 137(19):2634-2645. 2. Data on file, ADC Therapeutics SA. 3. U.S. Food and Drug Administration. Multi-Disciplinary Review: Loncastuximab Tesirine-lpyl (Zynlonta). BLA 761271. April 2021. Available at: https://www.accessdata.fda.gov

Serious TEAEs, Dose Modifications, and Treatment Discontinuation (N=183)

- **At least 1 serious TEAE was reported in 85 (46.4%) patients**
  - Excluding disease progression, the most common serious TEAEs were febrile neutropenia (10 patients, 5 .5%), pyrexia and pleural effusion (7 patients, 3.8% each), dyspnea(6 patients, 3.3%), sepsis (5 patients, 2 .7%), and abdominal pain (4 patients, 2.2%)
- **Dose delays of up to 21 days could be used to manage toxicities per protocol**
  - 68 patients (37.2%) had dose delays due to TEAEs, most commonly GGT increase(19 patients, 10.4%) and neutropenia (10 patients, 5.5%)
- **TEAEs led to dose reduction in 11 patients (6.0%) and treatment discontinuation in 35 patients (19.1%)**
  - GGT increase was the leading cause of treatment discontinuation due to TEAEs (7 patients, 3.8%), follow ed by thrombocytopenia (5 patients, 2.7%)

TEAE, treatment-emergent adverse event. Hamadani M, et al. Blood. 2020; 137(19):2634-2645.

Grade ≥3 TEAEs Reported in ≥5% of Patients With B-NHL Who Received Lonca

- TEAEs of hematologic abnormalities, peripheral edema, and liver test abnormalities were more common in the 200 µg/kg group than in lower-dose groups.

Grade ≥3 TEAE, 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 (77.0)
Neutrophil count decreased[a]	6 (35.3%)	12 (29.3)	35 (40.7)	18 (51.4)	71 (39.7)
Platelet count decreased[a]	1 (5.9%)	7 (17.1)	25 (28.7)	15 (42.9)	48 (26.7)
GGT increased	4 (23.5)	9 (21.4)	15 (17.0)	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)
Disease progression	0	2 (4.8)	9 (10.2)	0	11 (6.0)
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)

[a]Platelet count decrease and neutrophil count decrease 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 the neutrophil count decrease, and data for 3 patients (1 each at 120, 150, and 200 µg/kg) were missing for the platelet count decrease. ALP, alkaline phosphatase; B-NHL, B-cell non-Hodgkin lymphoma; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event.

Hamadani M, et al. *Blood*. 2021;137(19):2634-2645.

TEAEs DLBCL Population

- 138 patients (99.3%) in the DLBCL cohort (N=139) experienced TEAEs*

Most common (≥20%) TEAEs across all dose cohorts

- Fatigue (42.4%, 59 patients)
- Nausea (33.1%, 46 patients)
- Peripheral edema (33.1%, 46 patients)
- Anemia (31.7%, 44 patients)
- GGT increased (28.1%, 39 patients)
- Rash (25.9%, 36 patients)
- Constipation (23%, 32 patients)
- Neutropenia (23%, 32 patients)
- Dyspnea (22.3%, 31 patients)
- Pleural effusion (21.6%, 30 patients)
- Thrombocytopenia (20.9%, 29 patients)
- Decreased appetite (20.1%, 28 patients)

Most common (≥10%) Grade ≥3 TEAEs

- GGT increased (19.4%, 27 patients)
- Neutropenia (18%, 25 patients)
- Anemia (13.7%, 19 patients)
- Neutrophil count decreased (13.7%, 19 patients)
- Thrombocytopenia (12.9%, 18 patients)
- Platelet count decreased (10.1%, 14 patients)

*200 µg/kg includes patients treated every 3 weeks and every 6 weeks
AE, adverse event; DLBCL, diffuse large B-cell lymphoma; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse events
Data on File, ADC Therapeutics

Safety (Pooled Safety Population)

- The Pooled safety population reflect exposure to lonca as a single agent at an initial dose of 0.15mg/kg in 215 patients with DLBCL in studies ADCT-402-201 (LOTIS-2) and ADCT-402-101 (LOTIS-1).
  - In this pooled safety population of 215 patients, the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea and musculoskeletal pain.

ZYNLONTA® (loncastuximab tesirine-lpyl) for injection Prescribing Information, April 2021

Conclusions

- ORR in all 180 evaluable patients with B-NHL was 45.6% (95% CI: 38.1,53.1), including 48 (26.7%) CRs and 34 (18.9%) PRs
  - ORR for lonca doses of 15 to 90 µg/kg was 29.4% compared with 47.2% for doses of 120 to 200 µg/kg
- Median time to tumor response in patients who achievwed CR or PR was 43.0 days (range 31-323)
- Median DOR (N=180) was 5.4 months (95% CI:4.0, not reached)
  - Median DOR was 4.5 months (95% CI: 3.9, 9.5) in patients with DLBCL and not reached in patients with MCL or FL
- Median PFS and OS were 3.1 months (95% CI 2.7, 4.2) and 8.3 months (95% CI: 6.7, 10.7), respectively (N=180)
- At least 1 serious TEAE was reported in 85 patients (46.4%)
- In the safety analysis set (N=183), 181 patients (98.9%) experienced at least one TEAE
  - Grade ≥3 TEAEs were reported in 141 patients (77%), most commonly hematologic or liver test abnormalities and hypokalemia

Based on cumulative safety, PK, and efficacy data, the recommended dose of Lonca for phase 2 is 150 µg/kg Q3W for 2 doses, followed by 75 µg/kg Q3W for subsequent doses[a]

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