Clinical activity of loncastuximab tesirine plus ibrutinib in non-Hodgkin lymphoma: Updated LOTIS-3 Phase 1 results

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BACKGROUND

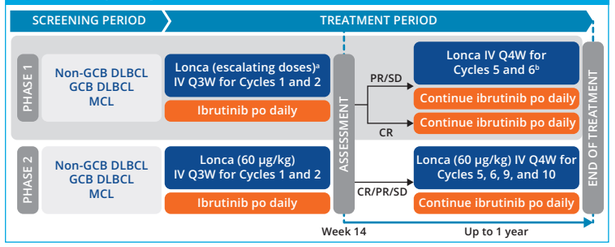
- Prognosis is poor for patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) and effective, less toxic treatment options are needed[1,2]
- Combination therapy using agents with different mechanisms of action may improve therapeutic outcomes
- We investigated the combination of loncastuximab tesirine (Lonca; an antibody-drug conjugate composed of a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer toxin) with ibrutinib (a small-molecule inhibitor of Bruton's tyrosine kinase) in patients with R/R DLBCL or R/R MCL (LOTIS-3)
  - Initial Phase 1 results identified the maximum tolerated dose (MTD) as Lonca 60 µg/kg intravenous every 3 weeks and oral ibrutinib 560 mg/day taken orally[3,4]
- Interim safety, efficacy and pharmacokinetic (PK) data from the Phase 1 portion of the study were previously presented at EHA 2020 and ASH 2020[3,4]
- Enrollment for the Phase 1 portion of the study is now complete
  - Here we present safety and efficacy data (data cut-off March 01, 2021) and PK data (data cut-off August 20, 2020) from the Phase 1 portion of a Phase 1/2 study (NCT03684694)

METHODS

Study design

- The study is an open-label, single-arm, combination study with a dose-escalation phase (Phase 1) and a dose-expansion phase (Phase 2) (**Figure 1**)
- Eligible patients were male or female; aged ≥18 years; had a pathologic diagnosis of R/R DLBCL for whom standard treatment was unsuccessful or who were intolerant to standard therapy, or had a pathologic diagnosis of R/R MCL with ≥1 prior therapy; and an Eastern Cooperative Oncology Group performance status of 0–2
  - Patients previously treated with Lonca or ibrutinib or other Bruton's tyrosine kinase inhibitors were excluded from the study

Figure 1. Study design



[a]Doses of 60 µg/kg and 90 µg/kg. [b]At the discretion of the investigator.

CR, complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; IV, intravenous; Lonca, loncastuximab tesirine; MCL, mantle cell lymphoma; po, taken orally; PR, partial response; SD, stable disease; Q3W, every 3 weeks; Q4W, every 4 weeks.

Objectives

- The primary objectives of Phase 1 were to characterize the safety and tolerability of Lonca plus ibrutinib and identify the MTD/recommended Phase 2 dose and schedule for future studies
- Secondary objectives included evaluation of antitumor effects of Lonca plus ibrutinib and characterization of PK profile of Lonca when combined with ibrutinib

Endpoints

- Primary endpoints included frequency and severity of adverse events
- Secondary endpoints included investigator-determined overall response rate (ORR [complete response or partial response]; according to the 2014 Lugano Classification[5]) and concentrations and PK parameters

RESULTS

Patient demographics and baseline characteristics

- At data cut-off (March 01, 2021), 30 patients with DLBCL (24 with non-germinal center B-cell [non-GCB] DLBCL and 6 with GCB DLBCL) and 7 patients with MCL were included in the study
- Overall, the median patient age was 72 years (range 40–91) and 27 (73.0%) had Stage IV disease (**Table 1**)
- Patients received a median of 2 (range 1–6) prior therapies
  - Eight (21.6%) patients were primary refractory and 18 (48.6%) were refractory to their last line of systemic therapy; 24 (64.9%) and 17 (45.9%) had relapsed with first-line and last-line systemic therapy, respectively

Table 1. Baseline characteristics

Characteristic	DLBCL (n=30)	MCL (n=7)	All patients (n=37)
Sex, n (%)			
Male	21 (70.0)	6 (85.7)	27 (73.0)
Age, years, median (range)	72 (40–91)	69 (54–89)	72 (40–91)
ECOG status, n (%)			
0	16 (53.3)	4 (57.1)	20 (54.1)
1	11 (36.7)	3 (42.9)	14 (37.8)
2	3 (10.0)	0	3 (8.1)
NHL subtype, n (%)			
Non-GCB DLBCL	24 (80.0)	–	24 (64.9)
GCB DLBCL	6 (20.0)	–	6 (16.2)
MCL	–	7 (100)	7 (18.9)
Disease stage[a], n (%)			
Stage I	1 (3.3)	0	1 (2.7)
Stage II	3 (10.0)	1 (14.3)	4 (10.8)
Stage III	4 (13.3)	1 (14.3)	5 (13.5)
Stage IV	22 (73.3)	5 (71.4)	27 (73.0)
Number of prior therapies[b]			
Median (range)	2 (1–6)	2 (1–4)	2 (1–6)
First-line prior systemic therapy response, n (%)[c]			
Relapsed	20 (66.7)	4 (57.1)	24 (64.9)
Refractory	7 (23.3)	1 (14.3)	8 (21.6)
Other	3 (10.0)	2 (28.6)	5 (13.5)
Last-line prior systemic therapy response, n (%)[c,d]			
Relapsed	13 (43.3)	4 (57.1)	17 (45.9)
Refractory	17 (56.7)	1 (14.3)	18 (48.6)
Other	0	2 (28.6)	2 (5.4)
Prior SCT, n (%)			
Autologous	2 (6.7)	1 (14.3)	3 (8.1)
Allogeneic	0	1 (14.3)	1 (2.7)

[a]Ann Arbor Criteria; [b]Prior SCT 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. [c]Systemic therapy; Relapsed: complete or partial response, followed by relapse; Refractory: stable disease or progressive disease; Other: missing data or not evaluable. [d]If SCT is most recent line, the variable is defined as response to the therapy immediately preceding SCT.

DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; SCT, stell cell transplant.

Treatment

- Patients received a median of 2 cycles (range 1–4) of Lonca and 4 cycles (range 1–15) of ibrutinib
  - Median (range) Lonca treatment duration was 22 (1–127) days
  - Median (range) ibrutinib treatment duration was 105 (18–379) days

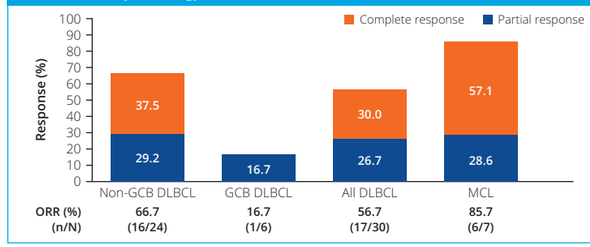
Safety

- Treatment-emergent adverse events (TEAEs) were reported in 37/37 (100%) patients. The most common TEAEs (≥20%) were thrombocytopenia (12 [32.4%]); anemia (9 [24.3%]); diarrhea (9 [24.3%]); and fatigue, nausea, and rash (all 8 [21.6%])
- Grade ≥3 TEAEs were reported in 24/37 (64.9%) patients. The most common (≥5%) were anemia (4 [10.8%]); neutropenia (4 [10.8%]); and thrombocytopenia, fatigue, and acute kidney injury (all 2 [5.4%])
- TEAEs that led to dose delay, reduction, or interruption were reported in 19 (51.4%) patients
- TEAEs that led to treatment discontinuation were reported in 5 (13.5%) patients

Efficacy

- ORR by investigator was 62.2% (35.1% and 27.0% for complete and partial response, respectively)
- ORR for patients with non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL was 66.7%, 16.7%, 56.7%, and 85.7%, respectively (**Figure 2**)

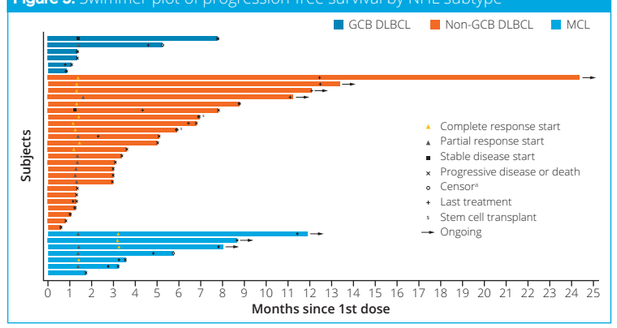
Figure 2. ORR by histology



DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; MCL, mantle cell lymphoma; ORR, overall response rate.

- Median (interquartile range) duration of response was 5.55 months (2.07–not reached)
  - Median duration of response for patients with non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL was 4.65 months (1.92–not reached), not reached (not reached–not reached), 5.55 months (2.07–not reached), and not reached (2.17–not reached)
- Response is ongoing in 4/24 patients with non-GCB DLBCL, and 3/7 patients with MCL (**Figure 3**)

Figure 3. Swimmer plot of progression-free survival by NHL subtype



[a]Only for censored patients who discontinued the trial due to reasons other than progression or who went onto a different anticancer treatment.

DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma.

Pharmacokinetics

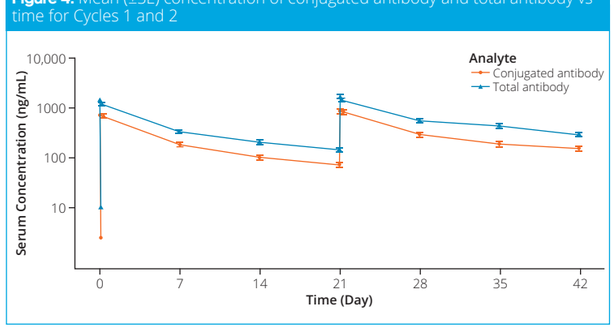
- At data cut-off (August 20, 2020), cycle-related increase in PK exposure was observed and inter-patient exposure variability was moderate (**Table 2**)
- Sustained exposure and modest accumulation were seen by Cycle 2 (**Table 2, Figure 4**)

Table 2. Summary of PK parameters of conjugated and total antibody in Cycles 1 and 2

PK parameters	Conjugated Ab	Total Ab
Cycle 1: Lonca 60 µg/kg and ibrutinib 560 mg		
C_{max} (ng/mL)	659 (45.3) [26]	1280 (41.4) [26]
AUC_{inf} (ng·day/mL)	4364 (61.9) [8]	7449 (54.8) [9]
T_{half} (day)	6.31 (46.7) [8]	5.65 (38.2) [9]
CL (L/day)	0.893 (60.4) [8]	0.590 (50.1) [9]
V_{ss} (L)	5.52 (47.2) [8]	3.43 (43.6) [9]
Cycle 2: Lonca 60 µg/kg and ibrutinib 560 mg		
C_{max} (ng/mL)	761 (91.7) [21]	1461 (80.8) [21]
AUC_{tau} (ng·day/mL)	5582 (65.0) [15]	10,423 (60.1) [13]
T_{half} (day)	7.57 (43.0) [11]	7.79 (33.0) [6]
CL (L/day)	0.705 (63.3) [15]	0.451 (58.8) [13]
V_{ss} (L)	7.85 (64.0) [11]	6.01 (50.0) [6]
AI	1.21 (15.9) [11]	1.20 (10.4) [6]

Blood samples for PK analysis were drawn on Day 1 (pre-dose), Day 8 and Day 15 of treatment Cycles 1 and 2.
Data shown as geometric mean (geometric % coefficient of variation) [n]. Ab, antibody; AI, accumulation index; AUC_{inf}, area under the curve vs time curve from 0 to infinity; AUC_{tau}, area under the curve from 0–21 days; CL, apparent clearance; C_{max}, maximum observed concentration; Lonca, Loncastuximab tesirine; PK, pharmacokinetics; T_{half}, apparent terminal half-life; V_{ss}, apparent steady-state volume of distribution.

Figure 4. Mean (±SE) concentration of conjugated antibody and total antibody vs time for Cycles 1 and 2



Dose: Lonca 60 µg/kg + ibrutinib 560 mg. Concentrations below the LLOQ of 20 ng/mL for conjugated antibody and 5.06 for total antibody are imputed as 1/2 LLOQ.

LLOQ, lower limit of quantification; SE, standard error.

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J Depaus reports consultancy/advisory roles for Takeda, Novartis, and Janssen. **N Wagner-Johnston** reports consultancy/advisory roles for ADC Therapeutics, Regeneron, CALIB-R, Verastem, Karyopharm, Sanofi, SeaGen, Epizyme, and Grunenthal. **PL Zinzani** reports consultancy/advisory roles for Verastem, MSD, Eusapharma, Sanofi, ADC Therapeutics (advisory board agreement), Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, TG Therapeutics, Takeda, Roche, and Kyowa Kirin. **TJ Phillips** reports consultancy/advisory roles for Celgene/BMS, Kite/Gilead, Seattle Genetics, AbbVie/Pharmacyclics, Incyte, and Genentech. **J Maly, S Ferrari, V Delwail, and M Tani** report no conflicts of interest. **E Bachy** reports employment/leadership position for Université Claude Bernard Lyon 1, Lyon, France, consultancy/advisory roles for Roche, and Gilead, and receipt of honoraria from Roche, Celgene, Amgen, Janssen, Gilead, Novartis, and Sanofi. **LJ Bryan** reports employment/leadership position for Augusta University, Augusta, GA. **M Janakiram** reports receipt of research funding from ADC Therapeutics, FATE Therapeutics, and Takeda Pharmaceuticals. **S Guibert** reports employment/leadership position for CHU Pontchaillou, Rennes, France and receipt of honoraria from Janssen, AbbVie, and Gilead. **V Dai** is an employee of ADC Therapeutics and SUNY Research Foundation and has stock and other ownership interests from ADC Therapeutics. **K Havenith, J Boni, X He, and A Ervin-Haynes** are employees of ADC Therapeutics and hold stock and other ownership interests with the company. **C Carlo-Stella** reports consultancy/advisory roles for Sanofi, ADC Therapeutics, Roche, Karyopharm Therapeutics, Celgene/Bristol-Myers Squibb, and Incyte, receipt of honoraria from Bristol-Myers Squibb, Janssen Oncology, and AstraZeneca, receipt of research funding from ADC Therapeutics, Sanofi, and Roche, and receipt of travel grants from Roche, Janssen, Takeda, and ADC Therapeutics.

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CONCLUSIONS

- Lonca 60 µg/kg plus ibrutinib 560 mg had encouraging antitumor activity in R/R DLBCL or R/R MCL, with an investigator-assessed ORR of 62.2%
  - ORR for non-GCB DLBCL was 66.7%, GCB DLBCL was 16.7%, and MCL was 85.7%
- Toxicity was manageable at the MTD, with safety data comparable to that previously reported[3,4]
- PK profiles exhibit sustained exposure and modest accumulation with the Q3W regimen by Cycle 2

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