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

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OBJECTIVES

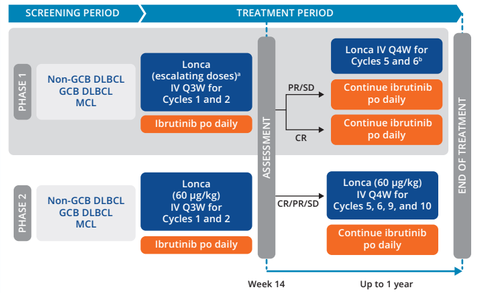
- Prognosis is poor for patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL), and effective, less toxic treatment options are needed[1,2]
- Combination therapy using agents with different mechanisms of action may improve therapeutic outcomes
- We investigated the combination of loncastuximab tesirine (loncastuximab tesirine-lpyl; 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 (po) ibrutinib 560 mg/day[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**)

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.

- 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 had 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
- 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 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

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%])

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)

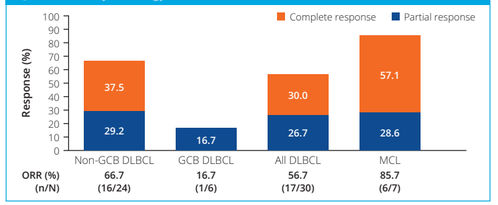
[a]Ann Arbor criteria; [b]Prior SCT is included. For patients who received an autologous transplant, the mobilization regimen was considered a line of therapy if it was chemotherapy based and distinct from the other previous lines of treatment. [c]Systemic therapy; Relapsed: complete or partial response, 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.

- 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 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**)
- 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)

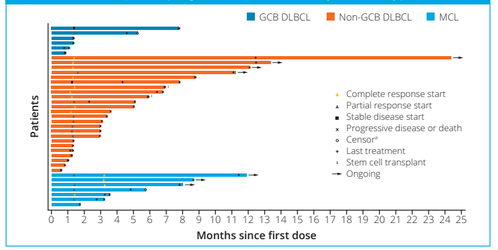
Figure 2. ORR by histology



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

- 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**)

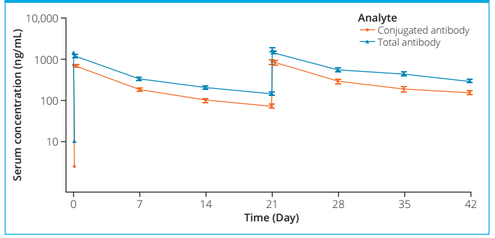
Table 2. Summary of PK parameters of conjugated and total antibody in Cycles 1 and 2

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 to 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.

- Sustained exposure and modest accumulation were seen by Cycle 2 (**Table 2, Figure 4**)

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.

CONCLUSIONS

- Lonca 60 µg/kg plus ibrutinib 560 mg had encouraging antitumor activity in R/R DLBCL or R/R MCL, with an 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 those previously reported[3,4]
- PK profiles exhibit sustained exposure and modest accumulation with the Q3W regimen by Cycle 2

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