Interim results of a phase 1/2 study of loncastuximab tesirine (Lonca) combined with ibrutinib in advanced diffuse large B-cell lymphoma (DLBCL) or mantle cell lymphoma (MCL)

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LOTIS-3 LOncastuximab Tesirine CLinIcal AsSessment

INTRODUCTION

- Patients with relapsed or refractory (R/R) DLBCL or MCL have a poor prognosis and limited salvage treatment options.[1-3] Combinations of drugs with different mechanisms of action may provide better outcomes
- Loncastuximab tesirine (Lonca) is an antibody-drug conjugate comprising a humanised anti-CD19 antibody conjugated to a pyrrolobenzodiazepine dimer toxin[4]
- Lonca has shown single-agent activity in phase 1 and 2 trials[5,6]
- Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase, a mediator of the B-cell–receptor signalling pathway, which is implicated in the pathogenesis of B-cell cancers[7]
- Preclinically, the combination of Lonca and ibrutinib has shown synergy and is therefore a rational combination to evaluate in patients[8]
- Here, we present interim phase 1 data from the phase 1/2 trial of Lonca combined with ibrutinib in patients with R/R DLBCL or MCL

OBJECTIVES

Primary objectives for phase 1

- Evaluate the safety and tolerability of Lonca with ibrutinib
- Identify the recommended dose and schedule of this combination for evaluation in phase 2

Secondary objectives for phase 1

- Characterise the treatment combination of Lonca with ibrutinib with respect to:
  - Pharmacokinetic (PK) profile
  - Immunogenicity
  - Preliminary antitumour activity

METHODS

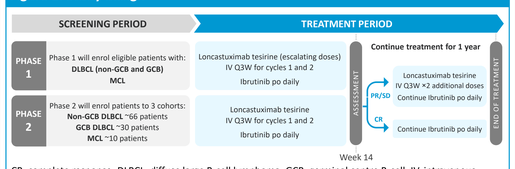
Study design

- This is an open-label, single-arm dose escalation and dose expansion trial (NCT03684694)
- Patients aged ≥18 years with pathologically confirmed R/R DLBCL or MCL are being enrolled
- This study consists of 2 parts: phase 1 and phase 2; this poster reports interim data from phase 1 (**Figure 1**)

Phase 1

- Lonca (60 or 90 µg/kg) is administered as a 30-minute intravenous infusion using a standard 3+3 dose escalation design
- The dose-limiting toxicity (DLT) period is the 21 days following the first dose of ibrutinib during dose escalation
- Patients receive Lonca every 3 weeks for the first 2 doses, with concurrent fixed-dose ibrutinib (560 mg/day, oral) for up to 1 year
  - Patients with a partial response (PR) or stable disease (SD) at the 14-week assessment may receive 2 additional doses of Lonca 4 weeks apart
- Additional patients may be added to evaluate any dose level, provided there is no more than 1 DLT in 6 patients and at least 1 patient has a documented PR or complete response (CR)

Figure 1: Study design



CR, complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell; IV, intravenous; MCL, mantle cell lymphoma; PO, oral; PR, partial response; SD, stable disease; Q3W, every 3 weeks

RESULTS: PHASE 1 INTERIM DATA

Patient characteristics

- As of 6 April 2020, 25 patients have been enrolled: 23 with DLBCL and 2 with MCL
  - Baseline characteristics are shown in **Table 1**
- These patients received a median of 2 cycles of Lonca (range 1–4) at 60 µg/kg (19 patients) or 90 µg/kg (6 patients) and had a median treatment duration of 42 days (range 1–379)

Table 1: Baseline characteristics of patients enrolled up to 6 April 2020

Characteristic	Lonca 60 µg/kg + ibrutinib (n=19)	Lonca 90 µg/kg + ibrutinib (n=6)	All patients (N=25)
Median age, years (range)	72.0 (40–87)	60.5 (39–74)	69.0 (39–87)
Sex, n (%)			
Female	4 (21.1)	2 (33.3)	6 (24.0)
Male	15 (78.9)	4 (66.7)	19 (76.0)
ECOG score, n (%)			
0	12 (63.2)	2 (33.3)	14 (56.0)
1	5 (26.3)	3 (50.0)	8 (32.0)
2	2 (10.5)	1 (16.7)	3 (12.0)
Non-Hodgkin lymphoma subtype, n (%)			
DLBCL (non-GCB)	17 (89.5)	6 (100)	23 (92.0)
Double-hit	1 (5.3)	0	1 (4.0)
Double-expressor	3 (15.8)	0	3 (12.0)
Transformed*	2 (10.5)	0	2 (8.0)
MCL	2 (10.5)	0	2 (8.0)
Disease stage (Ann Arbor criteria), n (%)			
Stage II	1 (5.3)	2 (33.3)	3 (12.0)
Stage III	3 (15.8)	0	3 (12.0)
Stage IV	15 (78.9)	4 (66.7)	19 (76.0)
Number of previous systemic therapies†			
Median (range)	2 (1–5)	3 (1–5)	2 (1–5)
First-line prior systemic therapy response			
Relapsed	14 (73.7)	4 (66.7)	18 (72.0)
Refractory‡	3 (15.8)	2 (33.3)	5 (20.0)
Other¶	2 (10.5)	0	2 (8.0)
Last-line prior systemic therapy response§			
Relapsed	8 (42.1)	3 (50.0)	11 (44.0)
Refractory‡	9 (47.4)	3 (50.0)	12 (48.0)
Other¶	2 (10.5)	0	2 (8.0)
Prior haematopoietic cell transplantation, n (%)			
Autologous	1 (5.3)	0	1 (4.0)
Allogeneic	1 (5.3)	1 (16.7)	2 (8.0)

*Both MZBCL. †Prior SCT is included. For patients who received an autologous transplant, the mobilisation regimen was considered a therapy line if it was chemotherapy-based and distinct from other previous lines of treatment. ‡Refractory disease defined as no response to therapy. ¶Other defined as unknown, not evaluable, or missing. §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 centre B-cell; MCL, mantle cell lymphoma; MZBCL, marginal-zone B-cell lymphoma; SCT, stem cell transplant

PK profile of Lonca

- Slower clearance, increased exposure, and decreased variability for conjugated antibody and total antibody are apparent by cycle 2 relative to cycle 1 (**Table 2**)
- The reasonably long half-life and modest accumulation suggest good exposure coverage throughout the dosing interval (**Table 2**, **Figure 2**)
- All measures for unconjugated warhead SG3199 were below the lower limit of quantification

Immunogenicity

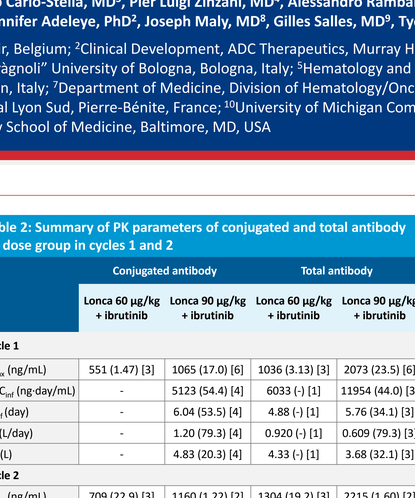
- No confirmed positive antidrug antibody (ADA) responses were detected in patients tested for ADAs prior to dosing or post-dose (9 patients, 38 measurements)
  - Based on currently available data, Lonca did not appear to exert a clinically relevant ADA induction effect

Table 2: Summary of PK parameters of conjugated and total antibody by dose group in cycles 1 and 2

	Conjugated antibody		Total antibody	
	Lonca 60 µg/kg + ibrutinib	Lonca 90 µg/kg + ibrutinib	Lonca 60 µg/kg + ibrutinib	Lonca 90 µg/kg + ibrutinib
Cycle 1				
C_{max} (ng/mL)	551 (1.47) [3]	1065 (17.0) [6]	1036 (3.13) [3]	2073 (23.5) [6]
AUC_{inf} (ng·day/mL)	-	5123 (54.4) [4]	6033 (-) [1]	11954 (44.0) [3]
T_{half} (day)	-	6.04 (53.5) [4]	4.88 (-) [1]	5.76 (34.1) [3]
CL (L/day)	-	1.20 (79.3) [4]	0.920 (-) [1]	0.609 (79.3) [3]
V_{ss} (L)	-	4.83 (20.3) [4]	4.33 (-) [1]	3.68 (32.1) [3]
Cycle 2				
C_{max} (ng/mL)	709 (22.9) [3]	1160 (1.22) [2]	1304 (19.2) [3]	2215 (1.60) [2]
AUC_{tau} (ng·day/mL)	6298 (27.9) [2]	8866 (23.1) [2]	10705 (-) [1]	17865 (27.7) [2]
T_{half} (day)	7.70 (-) [1]	5.20 (-) [1]	10.5 (-) [1]	7.63 (47.4) [2]
CL (L/day)	0.619 (2.24) [2]	0.679 (60.1) [2]	0.350 (-) [1]	0.400 (65.7) [2]
V_{ss} (L)	6.54 (-) [1]	6.59 (-) [1]	5.28 (-) [1]	4.18 (6.90) [2]
AI	1.18 (-) [1]	1.07 (-) [1]	1.33 (-) [1]	1.20 (15.1) [2]

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]; 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; T_{half}, apparent terminal half-life; V_{ss}, apparent steady-state volume of distribution

Figure 2: Semi-log plot of mean (± SE) concentration of (A) PBD-conjugated-antibody concentration, and (B) total antibody concentration, vs time for cycles 1 and 2 by dose cohort



Concentrations below the LLOQ are imputed as 1/2 LLOQ.
LLOQ, lower limit of quantification; PBD, pyrrolobenzodiazepine; SE, standard error

Safety and tolerability

- DLTs were reported for 2 patients at the Lonca 90 µg/kg and ibrutinib 560 mg/day dose during dose escalation:
  - One patient had a DLT of death, which was due to a cardiac event considered possibly related to ibrutinib per treating physician
  - The other patient's DLT consisted of grade 3 thrombocytopenia and grade 3 anaemia requiring transfusion, all considered probably related to Lonca and ibrutinib per treating physician
- Lonca 60 µg/kg with ibrutinib 560 mg/day was identified as the maximum tolerated dose (MTD)
- TEAEs are shown by grade in **Table 3**
  - The most common all-grade TEAEs, regardless of relationship to treatment, were thrombocytopenia, anaemia, and fatigue
- TEAEs leading to treatment discontinuation occurred in 4 (16.0%) patients

Table 3: Most commonly reported all grade and grade ≥3 TEAEs (≥20% of patients)

TEAE by preferred term	Lonca 60 µg/kg + ibrutinib (n=19) n (%)		Lonca 90 µg/kg + ibrutinib (n=6) n (%)		All patients (N=25) n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any TEAE	**19 (100)**	**9 (47.4)**	**6 (100)**	**5 (83.3)**	**25 (100)**	**14 (56.0)**
Thrombocytopenia	8 (42.1)	2 (10.5)	4 (66.7)	3 (50.0)	12 (48.0)	5 (20.0)
Anaemia	3 (15.8)	1 (5.3)	5 (83.3)	2 (33.3)	8 (32.0)	3 (12.0)
Fatigue	4 (21.1)	1 (5.3)	2 (33.3)	0	6 (24.0)	1 (4.0)
Rash	5 (26.3)	0	1 (16.7)	0	6 (24.0)	0
ALT increase	2 (10.5)	1 (5.3)	3 (50.0)	0	5 (20.0)	1 (4.0)
Diarrhoea	4 (21.1)	0	1 (16.7)	0	5 (20.0)	0
Nausea	4 (21.1)	0	1 (16.7)	0	5 (20.0)	0

ALT, alanine aminotransferase; TEAE, treatment-emergent adverse event

Preliminary antitumour activity

- As of data cut-off, 17 patients with DLBCL and 1 patient with MCL were evaluable for preliminary antitumour activity; outcomes are shown in **Table 4**

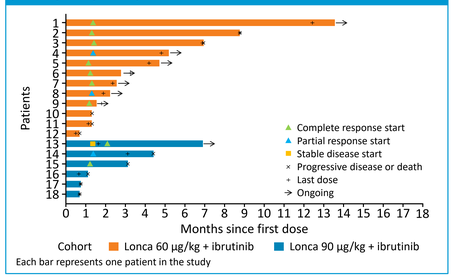
Table 4: Antitumour activity (best overall responses*) by dose level

Response	Lonca 60 µg/kg + ibrutinib (n=12) n (%)	Lonca 90 µg/kg + ibrutinib (n=6) n (%)	Total (N=18) n (%)
CR	7 (58.3)	2 (33.3)	9 (50.0)
PR	2 (16.7)	1 (16.7)	3 (16.7)
SD	0	0	0
PD	3 (25.0)	3 (50.0)	6 (33.3)
ORR	**9 (75.0)**	**3 (50.0)**	**12 (66.7)**
CRR	**7 (58.3)**	**2 (33.3)**	**9 (50.0)**

*Best visit response based on the 2014 Lugano Classification Criteria.
CR, complete response; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; ORR, overall response rate (CR+PR); PD, progressive disease; PR, partial response

- The overall response rate (ORR) in patients receiving Lonca 60 µg/kg (n=12) was 75%; the complete response rate (CRR) was 58.3%
  - Seven out of 11 patients with DLBCL receiving Lonca 60 µg/kg had a CR (63.6%) and 1 patient had a PR (9.1%)
  - One patient with MCL received Lonca 60 µg/kg and had a PR
- ORR in patients receiving Lonca 90 µg/kg (n=6) was 50%, comprising 2 patients with a CR and 1 patient with a PR; CRR was 33.3%
  - All patients receiving Lonca 90 µg/kg had DLBCL
- Time to response is shown for each patient in **Figure 3**

Figure 3: Swimmer plot showing time to response for each patient (efficacy analysis set)



Each bar represents one patient in the study

CONCLUSIONS

- Interim results show encouraging antitumour activity for Lonca in combination with ibrutinib in patients with R/R DLBCL or MCL, with an overall ORR of 66.7% and a CRR of 50%
- The combination has a manageable TEAE and toxicity profile at the MTD of Lonca 60 µg/kg with ibrutinib 560 mg/day
  - ORR at this dose level is 75%, with a CRR of 58.3%
  - In patients with DLBCL treated with Lonca 60 µg/kg, ORR is 72.7% with a CRR of 63.6%
- PK profiles demonstrate good exposure throughout the dosing interval
- This study is continuing to enrol patients

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DISCLOSURES

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