# A PHASE 2 STUDY OF LONCASTUXIMAB TESIRINE PLUS MOSUNETUZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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## INTRODUCTION

- Despite durable responses of CAR T-cell observed for 30-40% of patients, most patients relapse[1,2,] and effective therapies post-CAR remains an unmet need.
- Loncastuximab (Longa) tesirine is an antibody-drug conjugate targeting CD19, with ORR of 48.3% and CR of 24.1%.
- Mosunetuzumab (Mosun) is a bispecific antibody with ORR 34.9% and CR 19.4% in 3L+ DLBCL.
- Mosunetuzumab-Polatuzumab has demonstrated high response rates even in patients with prior CD19 CAR T-cell therapy and provides rationale for combining CD3/CD20 bispecific antibody and antibody drug conjugate[5]
- With Pola being incorporated into frontline DLBCL treatment[6,] alternate novel antibody-drug conjugate combinations in the relapsed setting are needed.

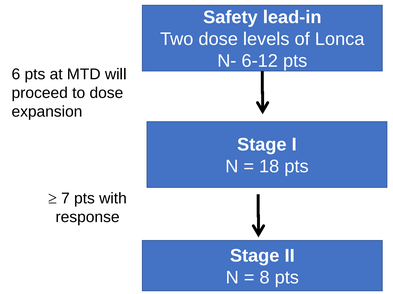
## AIM

- **The primary aim is to evaluate the safety and efficacy (overall response rate) of Longa-Mosun in relapsed-refractory DLBCL.**
- **The secondary aims are to evaluate secondary measures of efficacy , including Complete response, 1-year PFS, 1-year OS, time to response, and duration of response.**

## METHODS

**Study Design**

- Phase II, single institution, open-label, single arm study
- Study phases and stages:
  - Safety lead-in with two dose levels and dose de-escalation of Longa for toxicity
  - Dose expansion at MTD of Longa in two stages via Simon's mini-max design
- Planned enrollment
  - A total sample size of 26 – 32 patients with safety lead-in: 6-12 patients (based on null hypothesis of 35% ORR with alternative hypothesis of 60% ORR)
  - Dose expansion at MTD: Stage 1 with 18 patients, Stage 2 with 8 patients




Inclusion criteria:

- Relapsed or refractory DLBCL, high grade B cell lymphoma, primary mediastinal B cell lymphoma, transformed DLBCL from indolent lymphoma (including Richter's syndrome), or FL grade 3B
- At least two prior lines of therapy (prior CD19-directed therapy and auto-SCT allowed)
- Evidence of CD19 and CD20 positivity
- Blood counts – Plts over 75 (transfusion support allowed), ANC more than 1000 unless related to disease involvement of BM or splenomegaly (G-CSF allowed)
- T bili ≤ 1.5 x ULN (≤3 X ULN for Gilbert's syndrome or documented hepatic involvement by lymphoma)
- AST and ALT ≤ 3 X ULN (if hepatic involvement by lymphoma then ALT and AST ≤ 5 x ULN)
- Creatinine clearance of ≥ 50 ml/min
- ECOG 0-2

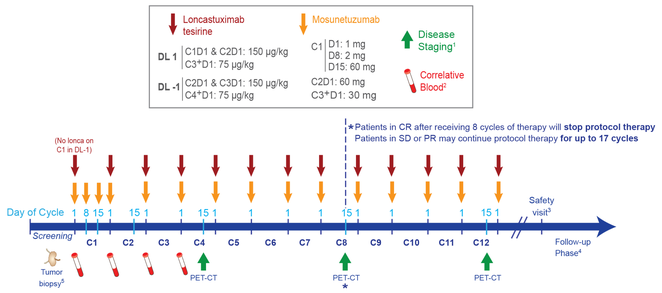
Exclusion criteria:

- Patients previously treated with loncastuximab or CD3/CD20 bispecific therapy
- Prior allogeneic stem cell transplant
- Ongoing treatment with chronic immunosuppressants or systemic steroids > 20 mg of prednisone (or equivalent) once daily
- Any other investigational agent or used an investigational device within 21 days prior to Day 1 of protocol therapy
- Active HIV, Hep B, or Hep C infection
- Concurrent active malignancy requiring active therapy other than nonmelanoma skin cancer, carcinoma in situ of the cervix
- Active infection requiring antibiotics or systemic therapy
- Known central nervous system or meningeal involvement
- Patients with known cardiac problems such as arrhythmia or heart failure

**Study Treatment Dosing**

| | Lonca-T | Mosun |
|---|---|---|
| DL 1 | **D1 C1 - 2**: 150 ug/kg<br>**D1 C3 - 8 (or up to 17):** 75 ug/kg | **C1**: D1 (1 mg), D8 (2 mg), D15 (60 mg)<br>**D1 C2**: 60 mg<br>**D1 C3 - C8 (or up to 17):** 30 mg |
| DL -1 | **D1 C2 - 3**: 150 ug/kg<br>**D1 C4 - 8 (or up to 17):** 75 ug/kg | **C1**: D1 (1 mg), D8 (2 mg), D15 (60 mg)<br>**D1 C2**: 60 mg<br>**D1 C3 - C8 (or up to 17):** 30 mg |

**Study Schema**




**Planned Correlatives**

- Serum samples collected at baseline, C2D1, C3D1, C4D1, EOT/time of progression, and tissue biopsy pre-treatment and at time of progression
- MRD measured via ctDNA using Roche Avenio CAPP-Seq technology
- Immune profiling to evaluate for changes in tumor microenvironment
  - Vectra spatial multispectral immunofluorescence (mIF) from tissue specimens
  - Multicolor flow cytometry from peripheral blood samples
- Mutational profiling with whole exome sequencing

## PRELIMINARY RESULTS

5 patients have been treated thus far:

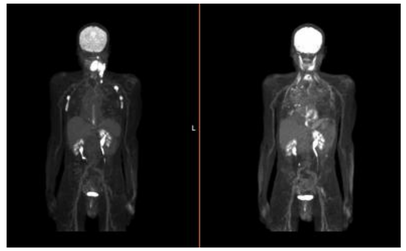
**Efficacy**

- 2 patients with CR
- 1 patient with PD
- 2 patients awaiting first response evaluation.

**Safety**

- Grade 3 or higher treatment-related adverse events: one pt with HTN, 2 patients with cytopenias, one pt with sepsis
- No cases of cytokine release syndrome or ICANS.

76yM with R/R transformed DLBCL s/p autoHCT, CD19 CAR T, and pola-R. **Achieved CR after 4 cycles of Longa-Mosun**



## CONCLUSIONS

- Phase 2 study (with safety lead-in) IIT evaluating preliminary efficacy and safety of Longa-T in combination with mosunetuzumab
- The target goal of 26-32 patients total
- Broad eligibility allowing for multiply relapsed post CAR T patients, a population of unmet need
- Novel correlatives incorporated to better understand the prognostic and predictive value of ctDNA and immune microenvironment
- Future studies include exploring this combination in the frontline setting and assessing other bispecific and ADC combinations.

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## REFERENCES

1. Locke et al. Lancet 2019
2. Locke et al. NEJM 2022
3. Caimi et al. Lancet 2021
4. Budde et al. JCO 2022
5. Budde et al. ASH 2021
6. Tilly etal NEJM 2022

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