A Phase II Study of Loncastuximab Tesirine as Consolidation Strategy in Patients with LBCL in PR at Day 30 After CAR T-cell Therapy

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Abstract

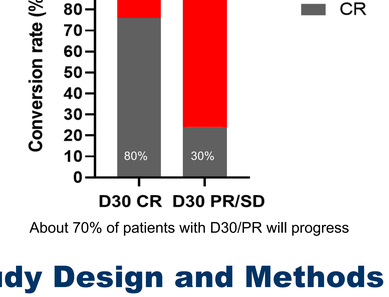
Background and Significance. Approximately 30% of patients with large B-cell lymphoma (LBCL) treated with autologous anti-CD19 CAR T-cell therapy (CART) achieve a partial response (PR) on day 30 (D30) assessment. Of those, up to 30% may spontaneously convert to a complete response (CR) during subsequent restaging. While up to 70% of patients with D30 PR eventually progress, reliable biomarkers that help identify patients at risk are not yet available, and the current standard approach is close monitoring. CD19 expression is retained in most tumors of patients who relapse or progress after CART. Potential reasons for resistance in these tumors include T-cell dysfunction and tumor intrinsic mechanisms that resist T-cell mediated killing. Therefore, targeting such tumors with agents that have an alternative mechanism of action is likely to improve outcomes. To this regard, loncastuximab tesirine (Lonca) is an anti-CD19 antibody conjugated to a cytotoxic pyrrolobenzodiazepine dimer approved by the FDA for LBCL patients who relapse after at least 2 lines of systemic therapy. In the phase 2 LOTIS-2 study, Lonca was associated with an overall response rate of 48% and a CR rate of 24%, and included patients previously treated with CART. Grade 3-4 adverse events were observed in less than one third of patients, and were mainly represented by myelosuppression, skin toxicity and isolated GGT elevation.

Study Design and Methods. This is a phase 2 single center study to investigate the safety and efficacy of Lonca as a consolidation strategy for LBCL patients with D30 PR after standard of care CART (NCT05464719). Patients with LBCL, including diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary mediastinal B-cell lymphoma and transformed follicular lymphoma, treated with standard of care CART (in second line and beyond) and with PET-CT evidence of D30 PR are eligible for this study. Patients with absolute neutrophil count < 1000/μL and/or platelet count < 50,000/μL, and those with previous or active central nervous system involvement are excluded. Tissue biopsy for confirmation of PR will be performed; CD19 expression is not required for eligibility.
Lonca is administered intravenously, on day 1 of a 21-day cycle, at a dose of 150 μg/kg for the first 2 cycles, and 75 μg/kg subsequently, for a total of 6 cycles. Response is assessed by PET-CT, according to 2014 Lugano criteria, after 3 cycles and at the end of treatment. The primary objective is efficacy, measured as conversion from D30 PR to CR. Using a one arm binomial exact test, hypothesizing an increase in conversion rate to CR from 30% to 60%, a sample size of 30 patients has a 90% power to observe a significant difference, with an alpha error of 0.05; a futility analysis, based on efficacy and toxicity, will be performed after the first 10 patients are treated. Secondary objectives are safety and other measurements of efficacy, including duration of CR.

Exploratory objectives include identification of biomarkers of response and resistance. Peripheral blood samples will be collected pre-treatment, after 3 cycles, post-treatment and at time of progression, as well as collection of a pre-treatment tissue biopsy and at time of progression. Blood and tissue samples will be analyzed by multi-parameter flow cytometry and hiplex imaging assays (Phenocycler-Fusion/CODEX) to identify immune signatures of response and resistance to Lonca, and to assess CAR T-cell persistence; blood samples will be analyzed by CAPP-Seq to measure minimal residual disease. Finally, total metabolic tumor volume will be assessed on pre-treatment PET-CT scans, and association with response to consolidation therapy will be analyzed.

Background

- About one third of patients with relapsed or refractory (r/r) large B-cell lymphoma (LBCL) treated with autologous anti-CD19 CAR T-cell therapy achieve a partial response (PR) or stable disease (SD) on day 30 (D30) PET-CT scan
- Among these patients, only 30% will convert later to a complete response (CR), while 70% will eventually progress, experiencing significantly poor outcomes. The current standard approach in patients with D30 PR is observation
- Loncastuximab tesirine (Lonca) is an anti-CD19 antibody conjugated to a cytotoxic pyrrolobenzodiazepine dimer approved for LBCL patients after 2 lines of systemic therapy
- Lonca is the only FDA approved antibody drug conjugate with post CAR T-cell therapy activity with an overall response rate of 48% and a CR rate of 24% independent of baseline CD19 expression



About 70% of patients with D30/PR will progress

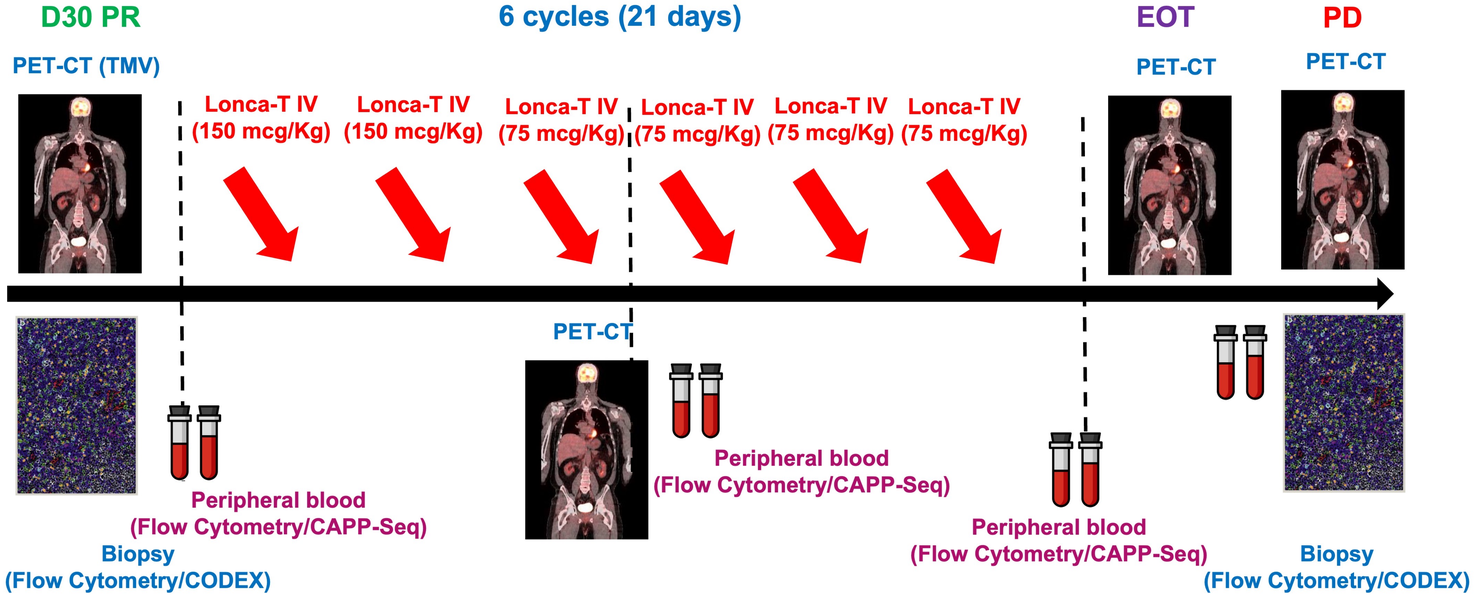
Study Design and Methods

- This is an open label phase 2 single center study to investigate the safety and efficacy of Lonca as a consolidation strategy for LBCL patients with D30 PR after standard of care (SOC) CART
- The study will include 30 patients
- Hypothesis: Lonca will be safe and effective as a consolidation strategy in patients with LBCL in PR at D30 after SOC CAR T-cell therapy
- Primary Objective: To evaluate the efficacy, measured by CR rate, based on Cheson, Lugano classification 2014, on PET-CT performed at the end of consolidation therapy
- Secondary objectives: Duration of response, progression free survival (PFS), overall survival (OS), as well as safety and tolerability
- Exploratory Objectives: To determine the pharmacodynamic effects and investigate biomarkers of response and resistance of this novel consolidation strategy

Statistical Design

- Using a one arm binomial exact test, hypothesizing an increase in conversion rate to CR from 30% to 60%, a sample size of 30 patients has a 90% power to observe a significant difference, with an alpha error of 0.05;
- A futility analysis, based on efficacy and toxicity, will be performed after the first 10 patients are treated.

Trial Schema



- Lonca is administered intravenously over 30 minutes, on day 1 of a 21-day cycle, at a dose of 150 μg/kg for the first 2 cycles, and 75 μg/kg subsequently, for a total of 6 cycles
- Response is assessed by PET-CT, according to 2014 Lugano criteria, after 3 cycles and at the end of treatment

Inclusion Criteria

- Age ≥ 18
- Eastern Cooperative Oncology Group performance statue ≤ 2
- R/R DLBCL, primary mediastinal B-cell lymphoma, transformed indolent B-cell lymphomas and high grade B-cell lymphoma
- Received SOC anti CD19 autologous CAR T-cell therapy (in second line and beyond)
- D30 response of PR according to Lugano 2014 response criteria
- Evidence of CD19 expression (IHC and./or flow cytometry) after CAR T-cell therapy is not required
- Absolute neutrophil count of ≥ 1.o x 10^9/L without growth factor support for 3 days prior to screening
- Platelet count of ≥ 50x10^9/L without transfusion for 3 days prior to screening
- Creatinine clearance (as estimated by Cockroft Gault) ≥ 30mL/min
- Serum alanine transaminase (ALT) or aspartate transaminase (AST) ≤ 2.5 upper limit of normal (ULN)
- Ejection fraction ≥ 45% and no evidence of clinically significant pericardial effusion

Exclusion Criteria

- Prior treatment with Lonca
- Treatment with non SOC CAR T-cell therapy prior to enrollment
- History of Richter's transformation of chronic lymphocytic leukemia (CLL)
- History of malignancy other than nonmelanoma skin cancer or carcinoma in situ, unless disease free for at least 12 months
- History of infection with HIV, hepatitis B, or hepatitis C unless viral loas is undetectable by quantitative PCR
- History of clinically significant deep vein thrombosis or pulmonary embolism within 1 month of enrollment
- Active or previous lymphoma involvement of the central nervous system (CNS)
- Women of child-bearing potential who are pregnant or breastfeeding

Exploratory Analysis

- Peripheral blood samples will be collected pre-treatment, after 3 cycles, post-treatment and at time of progression
- A pre-treatment tissue biopsy will be collected. Additionally, patients may opt to undergo a biopsy at time of progression prior to initiation of next line of therapy
- Blood and tissue samples will be analyzed by multi-parameter flow cytometry and hiplex imaging assays (Phenocycler-Fusion/CODEX) to identify immune signatures of response and resistance to Lonca, and to assess CAR T-cell persistence; blood samples will be analyzed by CAPP-Seq to measure minimal residual disease
- Total metabolic tumor volume will be assessed on pre-treatment PET-CT scans, and association with response to consolidation therapy will be analyzed

References

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