# Trial in Progress (NCT05672173): Phase 2 study of the combination of lisocabtagene maraleucel, nivolumab, and ibrutinib in Richter's transformation

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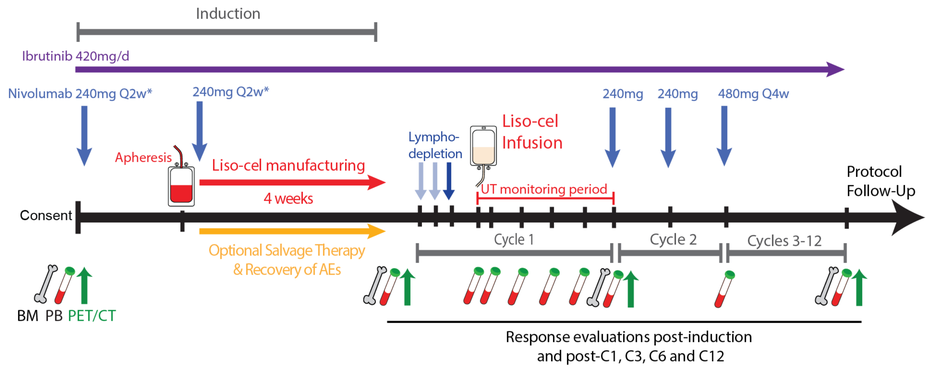
## INTRODUCTION/RATIONALE

- Richter's transformation (RT) is an aggressive transformation of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), typically to large B cell lymphoma (LBCL), that is difficult to treat and has a poor prognosis.
- The goal of treatment is to achieve a complete remission (CR) and proceed to consolidative allogeneic hematopoietic cell transplantation (alloHCT). However, outcomes with standard chemoimmunotherapy are dismal, with median OS < 1year (long-term survival < 20%) and CR rates ranging from 5-38%, most of which are transient. Many patients who achieve durable CR are ineligible for alloHCT due to age, comorbidities and/or lack of a suitable donor.
- Retrospective analyses have shown that chimeric antigen receptor (CAR) T cell monotherapy does not typically yield durable results in RT. Thus, there is an urgent, unmet medical need for well-tolerated, potent treatments for RT.
- The combination of the BTK inhibitor ibrutinib and the PD-1 checkpoint inhibitor nivolumab has shown activity in RT, with an overall response rate (ORR) of 43% and CR rate of 35%.
- The use of ibrutinib and nivolumab as bridging and maintenance therapy may enhance responses to CAR T cell therapy since CAR T cell products that have PD-1 expression and are skewed toward terminally-differentiated effector T cells are associated with inferior efficacy, suggesting that PD-1 inhibition may enhance CAR T cell efficacy.
- The safety and approval of lisocabtagene maraleucel (liso-cel) in relapsed/refractory (r/r) LBCL as well as CLL/SLL makes it the ideal commercial CAR T cell product to use in RT where CLL may also be present.
- We hypothesize that the addition of ibrutinib and nivolumab to liso-cel in patients with r/r RT may enhance responses to CAR T cell therapy.
- Therefore, we propose studying the combination of ibrutinib, nivolumab and liso-cel in patients with r/r RT with a curative intent.

## PROTOCOL SCHEMA (FIGURE 1)




Following consent, patients will be started on daily ibrutinib, or will continue taking ibrutinib if they were already taking it at the time of study entry, and commence nivolumab, 240mg IV every 2 weeks. Patients will receive a minimum of 2 doses of nivolumab prior to apheresis. Patients will undergo apheresis for liso-cel manufacturing at least 2 weeks after the last dose of nivolumab (anticipated to be 4 weeks after commencing study therapy) and nivolumab will be resumed immediately following apheresis. Ibrutinib will continue throughout the induction period (study treatment prior to apheresis through lymphodepletion), as well as during lymphodepletion with fludarabine/cyclophosphamide.during liso-cel infusion (cycle 1), and during the maintenance period (cycles 2-12). Nivolumab will be stopped through day 28 post liso-cel and then restarted at 240mg on days 1 and 15 of cycle 2 followed by 480mg nivolumab on day 1 of cycles 3-12. Disease response assessments (PET/CT, peripheral blood and bone marrow biopsy) will be at the end of induction and cycles 1, 3, 6 and 12. While UT monitoring in the safety lead-in will be from the start of liso-cel infusion through day 28 post liso-cel, patients will be closely monitored for toxicity throughout the study with stopping rules to ensure safety.

## PATIENTS

- Main Inclusion Criteria:
  - Age 18 years or older
  - ECOG performance status 0-2
  - Patients with histologically confirmed RT with radiographically measurable lymphadenopathy (≥1.5 cm) or measurable extra-nodal disease
  - relapsed / refractory disease following initial therapy for RT, or not eligible for alloHCT due to comorbidities or age
  - Eligible to receive liso-cel and ibrutinib per package inserts; prior BTKi is allowed
  - Adequate organ function and counts
  - No active infections
- Main Exclusion Criteria:
  - Patients with de novo RT
  - Received PD1 or PD-L1 inhibitors previously
  - Prior thoracic radiation
  - Prior alloHCT
  - Known bleeding disorder
  - Known HIV

## STUDY DESIGN

- This is an ongoing phase 2 study with a planned sample size of 20 participants who receive all 3 agents on the study (ibrutinib, nivolumab, and liso-cel) and undergo at least 1 response assessment post-CAR T cells.
- Patients will receive ibrutinib and nivolumab prior to lymphodepletion as induction therapy and post CAR T cells as maintenance therapy for up to 1 year post CAR T cells.
- Enrollment is open at 2 sites - City of Hope National Medical Center (CA) and Memorial Sloan Kettering Medical Center (NY).
- Safety lead-in of 6 patients will be to assess the unacceptable toxicity (UT) rate within the first 28 days (during cycle 1) following liso-cel infusion.
- Study accrual will continue after the safety lead-in evaluation of 6 patients if there is at least 1 patient with CR at end of cycle 1 (28 days post CAR T cells) as an early futility criterion.
- ORR with liso-cel in r/r de novo LBCL is approximately 73%, with 54% CR rate. Ibrutinib + nivolumab combination achieves a CR rate of ~35% in RT. We hope that the combination of ibrutinib + nivolumab + liso-cel will achieve a CR rate similar to that achieved in de novo DLBCL treated with single-agent liso-cel and will therefore consider this combination promising if the CR rate after cycle 3 (the primary endpoint) is at least 50%.

## STUDY OBJECTIVES AND ENDPOINTS

**Primary Objective:** Evaluate the complete remission (CR) rate after cycle 3 following liso-cel in combination with nivolumab and ibrutinib in patients with relapsed/refractory RT

Safety lead-in only: Assess the Unacceptable toxicities (UT) rate within the first 28 days (during cycle 1) following liso-cel infusion.

**Primary Endpoint:** CR rate after cycle 3 as assessed using Lugano 2014 criteria;

Safety lead-in only: UT during cycle 1 following liso-cel infusion.

**Secondary Objectives:** Assess the safety of the combination of liso-cel, nivolumab and ibrutinib in patients with RT; estimate the best CR rate; estimate the best overall response rate (ORR); estimate duration of response (DOR) at 2 years; assess minimal residual disease (MRD) status after liso-cel in participants with CLL at baseline; estimate progression free survival (PFS) at 2 years; estimate overall survival (OS) at 2 years.

**Secondary Endpoints:** Toxicity assessed per CTCAE v5.0; for CRS/ICANS, toxicity will be assessed per ASTCT Consensus Criteria; best CR rate; ORR; DOR; MRD; PFS; and OS.

## CORRELATIVE / SPECIAL STUDIES

- MRD analysis (CLL)
  - By Clonoseq and/or CAPPseq analyses of peripheral blood samples
- Immunologic studies
  - Eg, CAR T and immune cell innumeration, immunophenotyping, and gene expression profiling in peripheral blood samples
- Tumor analyses
  - Eg, evaluation of tumor infiltrating lymphocytes and microenvironment in tumor biopsies
  - ctDNA analysis in peripheral blood serum
- Other potential analyses
  - Storage of samples currently

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