A Phase 1/2 Randomized Study of Imvotamab Monotherapy and in Combination with Loncastuximab Tesirine in Relapsed/Refractory Non-Hodgkin Lymphomas

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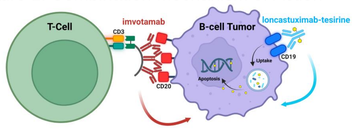
INTRODUCTION

Background

- Imvotamab is a novel CD20 x CD3 bispecific antibody utilizing an IgM backbone. This allows targeting of up to ten CD20 binding sites for every CD3 site. In preclinical models, imvotamab demonstrated encouraging antitumor activity and stimulated T-cells in a more physiologic manner than IgG-based antibodies, which may reduce adverse events typically associated with T-cell engagers and CAR-T, such as cytokine release syndrome (CRS) and neurotoxicity.
- Loncastuximab tesirine is a CD19-targeting antibody-drug conjugate approved by the FDA and EMA for relapsed diffuse large B-cell lymphoma (DLBCL) after two lines of systemic therapy. Loncastuximab tesirine has demonstrated activity in both DLBCL and follicular lymphoma (FL).
- Imvotamab single-agent dose escalation has been completed. There were no dose-limiting toxicities, the maximum tolerated dose was not reached, and no other serious safety signals occurred.

Figure 1: Combination Mechanism of Action



Rationale for Combination

- CD19 and CD20 are well-known, validated targets in lymphoma and have been the focus of many approved agents for use in lymphoma, including NHL.
- Surface expression of B cell markers on tumor cells from patients with B cell lymphomas demonstrate widespread and consistent expression of both CD19 and CD20 (Koksal 2019, Johnson 2009, Horna 2019).
- Combining therapies such as loncastuximab tesirine, which target CD19 and induce apoptosis of cancer cells, with imvotamab's ability to eliminate CD20+ tumor cells by engagement with T cells, may improve treatment outcomes among patients with NHL via potentially synergistic mechanisms of action (Figure 1).
- This combination has the potential to be well-tolerated by patients, given the absence of many overlapping toxicities associated with each drug.
- The most common overlapping toxicities for imvotamab and loncastuximab are fatigue and anemia, which are manageable and not expected to have a significant impact on concurrent administration of these agents.
- The major safety considerations for loncastuximab tesirine are effusion/edema, myelosuppression, infections, cutaneous reactions, and embryo-fetal toxicity, none of which have been serious concerns with imvotamab administration in the ongoing IGM-2323-001 study.

STUDY OBJECTIVES

Phase 1a

- To evaluate the safety and tolerability of imvotamab in patients with R/R NHL
- To determine MTD and/or recommended Phase 2 dose (RP2D) and schedule of imvotamab as a single agent in patients with R/R NHL

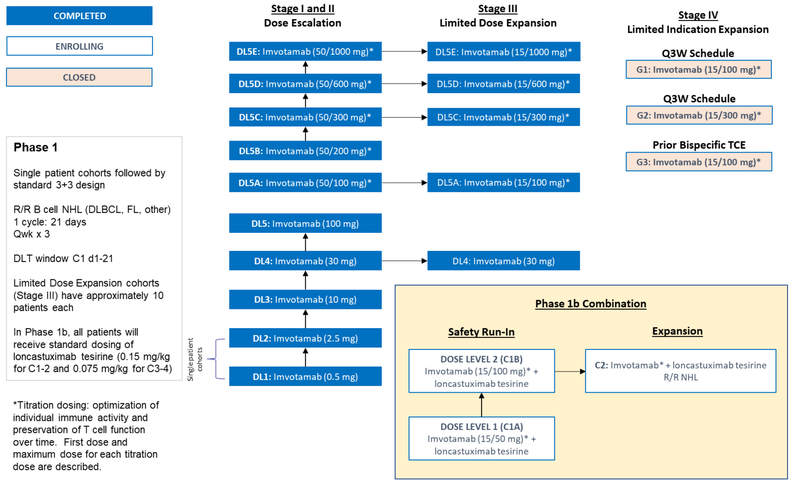
Phase 1b

- To evaluate the safety and tolerability of imvotamab in combination with loncastuximab tesirine in patients with R/R NHL

Phase 2

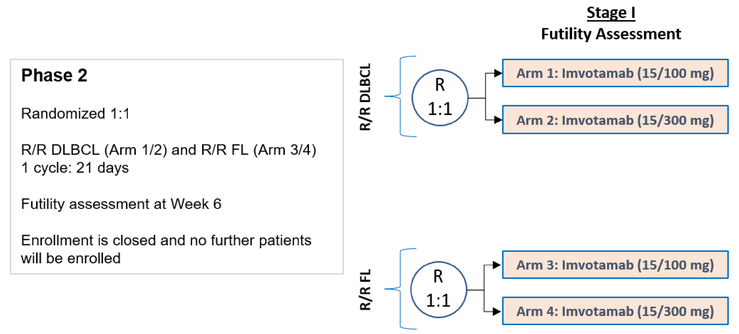
- To select the optimally safe and efficacious dose of imvotamab in patients with R/R DLBCL and R/R FL

STUDY DESIGN



STUDY COMPONENTS

- The Phase 1a component consists of dose escalation and limited dose expansion evaluating multiple titration (or step up) dose levels. Intra-patient dose escalation is allowed for patients in Phase 1a.
- Phase 1b will evaluate the combination of imvotamab with loncastuximab tesirine. Imvotamab will be initiated at 15/50mg and increased to 15/100mg if tolerable. Loncastuximab tesirine will be given at the approved doses for up to 8 total cycles (0.15 mg/kg for 2 cycles, then 0.075 mg/kg for subsequent cycles).
- The Phase 2 component randomizes patients to 2 different dose levels (100 mg and 300 mg plateau dose) in 2 separate indications (R/R DLBCL and R/R FL). This evaluation of multiple dose levels is in line with FDA guidelines (Project Optimus) and is designed to select the optimal dose.
- Patients receive weekly IV dosing on Days 1, 8, and 15 of each 21-day cycle. Dosing in the 15/100 mg cohorts is 15 mg on Day 1, 50 mg on Day 8, and 100 mg on Day 15 (patients in the 15/300 mg cohort will receive an additional step at 300 mg on Day 1 of Cycle 2). Patients then stay at the plateau dose until disease progression or unacceptable toxicity.
- Patients who achieve a response at Week 12 or later may switch to a less frequent dosing interval of every 3 weeks.
- Hospitalization is not required.
- Premedication regimen includes dexamethasone, paracetamol, and diphenhydramine during the first cycle.
- Response assessments are based on Lugano criteria with tumor scans by PET/CT at Weeks 6, 12, and 24, then every 3 months for the first year and every 6 months for the second year, while on treatment.
- Blood and tissue samples for correlative biomarker studies will evaluate the association of clinical benefit with blood and tissue biomarkers.



KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria	
• ≥18 years of age	• ECOG PS 0 or 1
• Relapsed or refractory follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, marginal zone lymphoma (MZL)	• Relapsed or refractory to at least 2 prior systemic treatment regimens (must include anti-CD20 chemo-immunotherapy regimen). FL/MZL may be enrolled with a least 2 prior systemic regimens, which must include an anti-CD20, without the need for a prior chemotherapy regimen
• Measurable disease, per Lugano criteria	• Not eligible for autologous stem cell transplant due to chemoresistant disease, medically unfit (organ function), or unwilling
• Pre-treatment and on-treatment biopsies, where medically feasible	
Key Exclusion Criteria	
• Prior allogeneic transplant	• ASCT within 100 days prior to the first imvotamab administration

STUDY INFORMATION

- The study is currently active in North America and the EU.
- Phase 1a dose (Stages I-IV) and Phase 2 randomized expansion are not currently enrolling.
- Phase 1b combination enrollment will be initiated in the first half of 2023.
- Clinical trial information: NCT04082936.

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