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704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

A CD19/CD20-Directed Bispecific CAR-T Cell Therapy in Relapsed or Refractory Aggressive B-Cell Non-Hodgkin Lymphoma (NHL)

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Three CD19-directed chimeric antigen receptor (CAR) T cell products are approved in the US for patients with relapsed or refractory (R/R) aggressive B cell lymphoma. Most patients treated in the third or later line will experience disease progression. Resistance to CD19-directed CAR T cell therapy may be due to tumor, T cell, or microenvironmental factors. Tumor-intrinsic causes of relapse include CD19 antigen loss, which is observed in approximately one third of relapsed cases(Spiegel, Dahiya, *et al.*, 2021). Lower pretreatment CD19 antigen density has also been associated with treatment failure(Spiegel, Patel, *et al.*, 2021). Conversely, enrichment of memory CD8+ T cells within the infusion product has been associated with achievement of complete remission (CR)(Deng *et al.*, 2020).

IMPT-314 is an autologous, naïve/memory enriched T cell product transduced by a lentivirus to express a tandem, OR-gate CD19/CD20-directed CAR with a 4-1BB co-stimulatory domain(Zah *et al.*, 2016). IMPT-314 incorporates the same CAR and a highly similar manufacturing process as CART19/20, which was evaluated in a single-institution, Phase 1 study (NCT04007029)(Larson *et al.*, 2023; Puliafito *et al.*, 2023). Eleven patients with R/R B cell NHL have been treated at two dose levels ($50 \times 10^6 \pm 30\%$, n=8; $200 \times 10^6 \pm 30\%$, n=3). Ten patients were evaluable for safety, and eleven patients were evaluable for response. Cytokine release syndrome (CRS) occurred in 60% of patients, however there were no CRS events above Grade 1. No patients experienced immune effector cell associated neurotoxicity syndrome (ICANS) of any grade. The overall response rate (ORR) and CR rate were 91% and 73%, respectively. As of March 6, 2023, with a median follow-up of 20.7 months, median progression-free survival (PFS) was 18.2 months (2.6-not estimable), and the median overall survival (OS) has not been reached (5.7-not estimable). This study of CART19/20 demonstrates the potential of simultaneous targeting of CD19 and CD20 with a bispecific CAR.

Study Design

The MPCT-012L study (NCT05826535) is a Phase 1/2 multicenter, open label study to evaluate the safety and efficacy of IMPT-314 in participants with relapsed/refractory aggressive B-cell NHL, defined as diffuse large B cell lymphoma (DLBCL), transformed follicular lymphoma (tFL), primary mediastinal large B cell lymphoma (PMBCL), and high-grade B-cell lymphoma (HGBL), after 2 or more lines of systemic therapy. Participants who have progressed after prior CD19 CAR-T cell therapy are eligible and are included in a separate cohort. All participants must have received prior anti-CD20 monoclonal antibody and an anthracycline. Patients with tFL must have received at least one line of therapy after transformation to DLBCL. Subjects with active (symptomatic or untreated) CNS involvement are excluded. There is no requirement for demonstration of CD19 or CD20 tumor expression at baseline. Phase 1 will be conducted using a modified 3+3 design with a starting dose of 100×10^6 CAR-T cells. Dose limiting toxicities (DLTs) will be evaluated for 28 days post-dosing. If a dose level is determined to be safe based on the DLT incidence, a total of up to 15 total subjects may be backfilled at that dose, per cohort. The primary objectives for Phase 1 are to evaluate the safety of IMPT-314 and to determine the recommended Phase 2 dose. The primary objective of Phase 2 is to estimate the efficacy of IMPT-314 as measured by CR rate. Secondary endpoints include evaluation of pharmacokinetics and time to event outcomes.

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