PRECISION TCR-T CELL IMMUNOTHERAPY FOR MYD88 L265P MUTATED LYMPHOMA

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Background: Despite progress in adoptive T-cell therapy for aggressive B-cell lymphomas, many patients remain refractory or relapse. CD19-directed CAR-T cells induce durable remissions in only a subset of patients and can cause on-target off-tumor toxicity. Notably, no CAR-T therapy is approved for primary central nervous system lymphoma (PCNSL). T2304-T cells are autologous T cells engineered to express a TCR specific for an HLA-B*07:02-restricted neoepitope derived from the lymphoma-specific MyD88L265P mutation. This mutation occurs in ~50% of PCNSL and ~30% of ABC-type diffuse large B-cell lymphomas (DLBCL). Preclinical studies showed potent anti-lymphoma activity without detectable off-target or alloreactive toxicity. Due to the tumor-restricted expression of the target, no on-tumor, off-target toxicity is expected. A GMP-compliant process for retroviral T2304 transduction has been established.
Trial Objectives: This trial aims to evaluate safety and define the maximum tolerated dose (MTD) of a single infusion of autologous T2304-T cells in patients with MyD88L265P-mutant B-cell lymphoma. Secondary objectives include characterization of pharmacokinetics and preliminary clinical efficacy. Exploratory endpoints assess manufacturing feasibility, product attributes, and anti-TCR immune responses.
Trial Design: This is a multicenter, open-label Phase I trial enrolling adults with relapsed/refractory B-cell lymphomas harboring MyD88L265P and HLA-B*07:02. After lymphodepletion, patients receive a single infusion of T2304-T cells at escalating doses (5×10^7 to 5×10^9 cells) using a Bayesian optimal interval (BOIN) design. At least 18 patients will be evaluable for the primary endpoint.
Trial Status: Study start is planned for Q1/2026 at three sites (Berlin, Würzburg, and Heidelberg), with an 18-month enrolment and 12-month follow-up.
Conclusion: This trial aims to provide first clinical proof-of-concept for neoantigen-specific TCR-T therapy targeting MyD88L265P in high-risk B-cell lymphoma.