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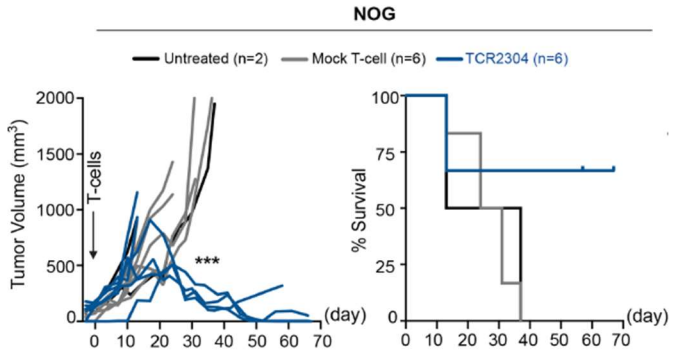
T-cell therapy of MYD88L265P-dependent B-cell lymphoma

Reference Number TO 32-00059

Challenge

Diffuse large B-cell lymphomas (DLBCL) exhibit high degree of genetic heterogeneity. MyD88^{L265P} is a prominent genetic aberration responsible for fostering tumor growth in this heterogenous lymphoma entity. In particular 17% of DLBCL and 42% in primary central nervous system lymphoma (PCNSL) patients carry the oncogenic mutation. The resulting aberrant scaffold protein would theoretically provide a suitable target for therapeutic intervention but is almost not addressable by conventional pharmacological means.



Therapeutic efficacy of TCR-T-cells in a OCI-Ly3 xenograft mouse model (Çınar Ö, et al. J Immunother Cancer 2021;9:e002410).

Technology

Novel human TCRs for targeting the mutant epitope of MyD88^{L265P} have been developed for an adoptive TCR cell therapy approach in HLA-B7 positive patients. This cell therapy approach offers a novel therapeutic option for patients with relapsed and/or refractory DLBCL and primary CNS lymphoma in a personalized fashion (stratification by presence of somatic mutation). TCR redirected T-cells are able to selectively recognize and kill only those target cells presenting the MyD88^{L265P} mutant epitope in an HLA-B7 restricted manner. This technology provides an opportunity for a straightforward development path towards clinical application in a defined patient population.

Commercial Opportunity

This opportunity is available for in-licensing or (pre)clinical (co-)development towards First-in-Human with retrovirally or non-virally modified TCR-T-cells.

Developmental Status

Extensive analysis regarding specificity, reactivity, cytotoxicity and safety for various TCRs has been carried out *in vitro* in multiple Non-Hodgkin lymphoma cells as well as in suitable *in vivo* experiments. A lead TCR has been identified.
A single-arm, multicenter phase I study in patients with r/r MyD88^{L265P}-mutated DLBCL including PCNSL is planned (First Patient In Q3 2024). Patients will receive increasing doses of retrovirally transduced TCR-T-cells. The primary endpoints of this first-in-human study are safety and determination of the maximum tolerable dose of a single infusion of TCR-T-cells.

Patent Situation

Patent applications pending in CA, CN, EP, US (based on WO2020/152161, priority January 2019).

Further Reading

Çinar, Ö., *et al.*, «High-affinity T-cell receptor specific for MyD88 L265P mutation for adoptive T-cell therapy of B-cell malignancies», J Immunother Cancer. 2021 Jul;9(7):e002410. doi: 10.1136/jitc-2021-002410.
Weber, A.N.R., *et al.*, «Oncogenic MYD88 mutations in lymphoma: novel insights and therapeutic possibilities». Cancer Immunol Immunother. 2018 Nov;67(11):1797-1807.

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