Gene Therapy: Nonclinical and Regulatory Strategy

Module 4, Part 2 Abstract: Approved Gene Therapy Products: Case Studies
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Nonclinical Development of Kymriah: A CAR T cell-based Therapy for ALL and DLBCL

Tisagenlecleucel (CTL019, Kymriah) is an autologous immunocellular cancer therapy representing the first immune gene therapy drug approved by the FDA in 2017 for therapy of acute lymphoblastic leukmia (ALL) in patients up to the age of 25 years. In May 2018, FDA approved tisagenlecleucel for treatment of diffuse large B cell lymphoma (DLBCL). Patient's T cells are reprogrammed with a transgene encoding a chimeric antigen receptor (CAR) that allows these T cells to precisely identify and eliminate CD19 expressing malignant and normal B cells in an antigen-dependent but MHC-independent manner. The gene transfer is accomplished via *ex vivo* transduction with a replication-deficient human lentiviral vector. Under the control of an EF1α promoter, the expressed transgene is comprised of a CD8α leader sequence, a murine single-chain antibody fragment (anti-CD19scFv), a CD8 hinge and transmembrane region and a 4-1BB (CD137) and CD3ζ (TCRζ) signalling domain. The expression of the transgene confers the transduced T cells with specificity for cells that express CD19.

This presentation focusses on the non-clinical development of tisagenlecleucel and explains the strategy how to support first-in-man clinical trials for a product-based ex vivo genetically modified human autologous T cells. Furthermore, the value of nonclinical models for the prediction of CAR T cell related toxicities, the impact of insertional mutagenesis and potentially resulting oncogenicity as well as the assessment of target and tumor specificity of CAR T cells will be discussed. Back-translation of clinical safety outcomes into the nonclinical area and how this drives the development of improved non-clinical models will be touched as well.