ANTI-PD-1/IL-7V BISPECIFIC ANTIBODY PROMOTES TCF1 + STEM LIKE T CELLS EXPANSION AND LONG-LASTING IN VIVO EFFICACY

Aurore Morello*, Margaux Seite, Justine Durand, Isabelle Girault, Geraldine Teppaz, Virginie Thepenier, Vanessa Gauttier, Caroline Mary, Nicolas Poirier. OSE Immunotherapeutics, Nantes, France

Background Immunocytokines can strengthen anti-PD-(L)1 therapy by promoting T-cell survival, but their shortened half-life and systemic toxicity limit their clinical development. We propose to selectively deliver IL-7 to PD-1+ T-cells using a bispecific anti-PD1/IL-7v mutein fused to reinvigorate PD1+IL-7R+ tumor-specific T cells and sustain long-term response. RNAseq and TILs scRNAseq analyses illustrate that IL-7R and IL-7R pathway gene expression is significantly correlated with better long-term OS and/or PFS across several cancers. Higher IL-7R and IL-7R pathway expression by tumor-specific T-cell clonotype is significantly correlated with ICI response, higher stemness & proliferative signature, lower exhaustion and apoptosis markers, providing a strong rationale of co-targeting IL-7 to PD-1 to sustain durable tumor-specific T-cells response. Despite low IL-7R expression on tumor-specific T-cell clonotype a high concentration of IL-7 can rescue them. We propose with the anti-PD-1/IL-7v to cis-target and provide a survival/proliferative specific signal.

Methods Proliferation, IL-7R signaling assays were tested to determine the mechanism. For the suppressive assay, CD4 Treg and autologous CD8 Teff were co-cultured. In vivo experiments were performed in hPD-1KI immunocompetent mice.

Results A high-affinity antagonist anti-PD-1 mAb was fused to a single IL-7 mutein (IL7v) having lower affinity to IL-7R complex allowing a preferential and optimal cis-potentiation of PD-1+ T-cells. Anti-PD1/IL7v restores proliferation and maintains long-term survival of chronically stimulated human T-cells in vitro (over 5 stimulation). scRNAseq and FACs analyses demonstrated that anti-PD1/IL7v triggers the expansion of TCF1+ stem-like memory T-cells (CCR7+PD1+Ki67+), whereas IL-2 and IL-15 promote differentiation of T-cells into exhausted T-cells (TCF1-Tim3+Ki67+). Furthermore, anti-PD1/IL7v preferentially stimulated Teff over Treg as opposed to IL-2 & IL-15 and abrogated the Treg suppression by restoring IFN-γ secretion and proliferation of CD8 Teff.

In vivo, anti-PD1/IL-7v has impressive monotherapy efficacy in PD-1 sensitive model (orthotropic mesothelioma, >90%CR) and in a PD-1 resistant model (orthotropic HCC, >65% CR) in which anti-PD-1 or IL-7 has no effect. Further analyses in HCC model demonstrate that anti-PD1/IL7v enhanced quality and biodistribution of T-cells by promoting intratumoral TCF1+CD8+stem-like T-cells proliferation and favoring T-cell migration into the tumor nest whereas anti-PD-1 promotes T-cell exclusion. Combination with sorafenib chemotherapy in HCC model further enhances in vivo efficacy.

Conclusions Our data validate the rational of selective delivery of IL-7 to tumor-specific T-cells to sustain long-lasting response, proliferation, and survival of these key effectors upon ICI therapy. Anti-PD1/IL-7v preferentially cis-potentiates PD1+-tumor-specific-T-cells limiting the risk of I-O/I-O immunotoxicity and induces the expansion of stem-like T-cell capable to strengthen PD-1 therapy efficacy.