

TUNING THE TUMOR MICROENVIRONMENT BY REPROGRAMMING TREM1+ MYELOID CELLS TO UNLEASH ANTI-TUMOR IMMUNITY IN SOLID TUMORS

Nadine Jahchan*, Hanna Ramoth, Vladi Juric, Erin Mayes, Shilpa Mankikar, Ranna Mehta, Mikhail Binnewies, Subhadra Dash, Rachael Palmer, Joshua Pollack, Joshua Rudolph, Pamela Canaday, Linnea Haegglom, Carlos Santamaria, Xiaoyan Du, Leonard Reyno, Kevin Baker, Linda Liang. *Pionyr Immunotherapeutics, San Carlos, CA, USA*

Background The tumor microenvironment (TME) often contains high levels of suppressive myeloid cells that contribute to innate checkpoint inhibitor (CPI) resistance. Pionyr's Myeloid Tuning approach involves altering the composition and/or the function of myeloid cells in the TME. Myeloid reprogramming alters the function of immunosuppressive myeloid cells to acquire an immunostimulatory phenotype. Triggering receptor expressed on myeloid cells-1 (TREM1) is an immunoglobulin superfamily cell surface receptor enriched on tumor-associated myeloid cells. To investigate the potential of TREM1 modulation as an anti-cancer therapeutic strategy, Pionyr developed an afucosylated humanized anti-TREM1 monoclonal antibody termed PY159 and characterized it in pre-clinical and translational biomarker assays described below.

Methods PY159 responses in human whole blood and dissociated primary tumor cells in vitro were evaluated by flow cytometry and measurement of secreted cytokines and chemokines by MSD. TREM1 expression in human tumors was validated by scRNAseq, flow cytometry, and immunohistochemistry (IHC). In vivo efficacy and pharmacodynamic studies of a surrogate anti-mouse TREM1 antibody, termed PY159m, were evaluated using syngeneic mouse tumor models, either as a single-agent or in combination with anti-PD-1. To select tumor types and patients most likely to benefit from PY159 therapy, Pionyr developed qualitative and quantitative monoplex and multiplex IHC assays that detect TREM1 expression levels in human tumor tissues.

Results PY159 treatment in vitro induced signaling, upregulated monocyte activation markers, and induced proinflammatory cytokines. In human tumors, TREM1 was detected on tumor-associated neutrophils, tumor-associated macrophages, and monocytic myeloid-derived suppressive cells. The surrogate PY159m anti-mouse TREM1 antibody exhibited anti-tumor efficacy in several syngeneic mouse tumor models, both as single-agent and in combination with anti-PD-1. Screening for TREM1 expression in tumor tissues demonstrated that TREM1+ tumor associated myeloid cells were highly enriched in the TME of multiple solid tumor indications. The monoplex and multiplex IHC assays offered insights into the localization of TREM1+ myeloid cells and their spatial relationship with other immune cells present in the TME to determine what immune composition will be more favorable for response to PY159 therapy.

Conclusions Collectively, the available nonclinical data support PY159 as a TREM1 agonist that reprograms myeloid cells and unleashes anti-tumor immunity. PY159 safety and efficacy are currently being evaluated in first-in-human clinical trial (NCT04682431) involving select advanced solid tumors patients resistant and refractory to standard of care therapies alone and in combination with a CPI. The TREM1 IHC assay is successfully being used on FFPE archival tumor tissues from enrolled patients to determine TREM1 expression levels.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.859>