Therapeutic targeting of TREM2+ tumor-associated macrophages as a means of overcoming checkpoint inhibitor resistance


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Abstract # C104

Introduction

Discussion of healthy vs. cancer tissue immune cells

Tumor-associated macrophages (TAMs) are a major source of checkpoint inhibitor (CPI) resistance, as they subvert anti-tumor immunity through immunosuppression and support of tumor growth. In patients, high levels of TAMs predict poor prognosis across multiple solid tumor indications. Therefore, therapeutic targeting of TAMs by impacting their survival and/or modulating their suppressive function is a promising strategy to augment response rates in solid tumor indications, as well as overcome resistance to CPI therapies. We and others have identified the transmembrane protein triggering receptor expressed on myeloid cells 2 (TREM2) as a highly enriched TAM target.

Triggering Receptor Expressed on Myeloid Cells 2 (TREM2)

PY314m Therapy Enhances the TME Immune Landscape

Increased Expression of TREM2 with Higher Grade in Multiple Solid Tumors

PY314m Treatment Reduced Tumor Growth as Single Agent or in Combination with anti-PD-1

PY314m Combined with anti-PD-1 Induces T Cell Expansion and Reactivation in anti-PD-1 Resistant Tumor Models

Summary

(1) Pionyr developed anti TREM2 mAb, termed PY314 (humanized IgG1 framework) and PY314m (mouse IgG2a framework) that cross-reacts with human, mouse, and cynomolgus TREM2. TREM2 is expressed on many different solid tumors, and high TREM2 expression is inversely correlated with poor patient survival probability.

(2) PY314m significantly reduced M2-like, MHC-IIlow M1-like TAMs, expanded MHC-IIhigh M1-like TAMs, and was associated with the release of pro-inflammatory cytokines.

(3) PY314m treatment resulted in an increase in the absolute number of intra-tumor immune cells that are known to drive anti-tumor responses, including cytotoxic CD8+ T cells.

(4) PY314m demonstrated compelling anti-tumor activity in combination with anti-PD-1 mAb in a number of preclinical, anti-PD-1 resistant mouse syngeneic tumor models. Furthermore, PY314m also exhibited strong single-agent activity in a subset of these tumor models. PY314m plus anti-PD-1 mAb combination treatment produced long-term immunological memory as evidenced by the lack of tumor growth upon rechallenge in mice cured of their tumors.

(5) Based on these preclinical findings, we are developing PY314m as a therapeutic agent for monotherapy and/or CPI combination therapy for solid tumors.

Tumor microarrays (TMAs) of multiple histological types were obtained from Reveal Biosciences. Immunohistochemical analysis of TREM2 expression was evaluated in TMAs using 5 ug per ml PIT2D, an anti-TREM2 mAb developed at Pionyr. (A) Semi-quantitative scoring by two investigators took into account both the cells positive for the stain as well as stain intensity. (B) Depicts representative staining of TREM2 within tumor nests (left) and in the stroma (right).

PY314, PIONYR’s Anti-TREM2 mAb “Surgically” Depletes M2-like TAMs in the TME

PY314 and anti-PD-1 mAb treatment resulted in a decrease in the number of M2-like TAMs and an increase in M1-like TAMs. Additionally, there was an increase in CD8+ T cells and activated NK cells within the TME.

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Increased TREM2 Expression in Multiple Solid Tumors Inversely Correlates with Patient Survival

PY314m combined with anti-PD1 induces T cell expansion and reactivation in anti-PD1 resistant tumor models.

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