Development of PY314, a monoclonal antibody that selectively depletes tumor-associated macrophages, for solid tumors

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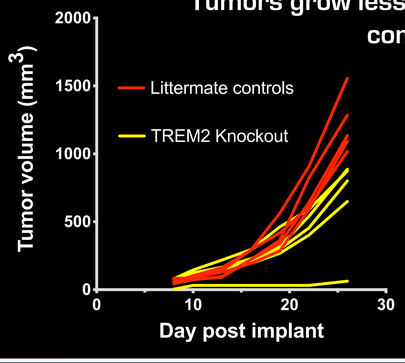
Background

The proportion of patients who benefit from checkpoint inhibitor (CPI) therapy is modest, and additional immune pathways need to be targeted to improve overall patient outcomes. The abundance of immune-suppressive, tumor-associated macrophages (TAMs) is thought to be a key CPI resistance mechanism. To target TAMs, we developed monoclonal antibodies (mAbs) that specifically bind the cell surface protein Triggering Receptor Expressed on Myeloid Cells 2 (TREM2).

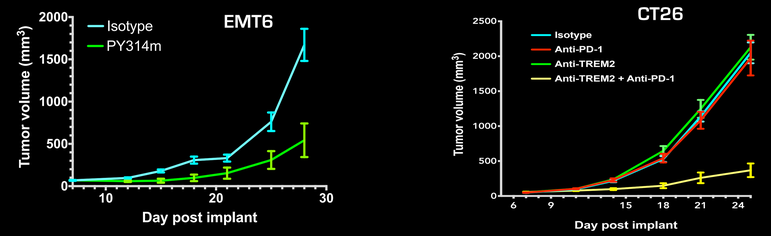
The available preclinical and nonclinical data support PY314 immunotherapy, alone or in combination with a CPI, in cancer patients who are resistant or refractory to CPI therapies, to improve both the overall response rates as well as the durability of responses. First in human clinical testing will start in 2020.

Tumors grow less well in TREM2 knockout mice compared to control mice



TREM2 knockout and littermate control C57BL/6J mice were implanted with MC38 tumor cells subcutaneously in the ventral right flank. Tumor volumes were monitored over the study period.

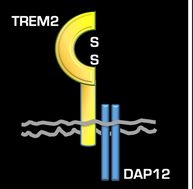
PY314m treatment as a single-agent or in combination with anti-PD-1 effectively controls syngeneic tumors



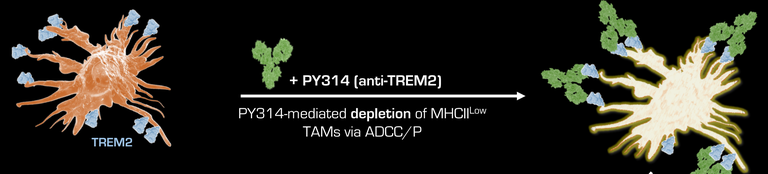
Eight to ten week old female C57BL/6 or BALB/c were implanted with 1x10e6 EMT6 (BALB/c; **A**), 1x10e6 CT26 (BALB/c; **B**). Indicated antibodies in the legend were administered intraperitoneally every 5 days

Triggering Receptor Expressed on Myeloid cells 2 (TREM2)

- Inhibitory receptor for macrophages
- Ig-like V-type domain in ECD; small ICD without signaling motifs but signals through DAP12
- Expressed on macrophages, immature myeloid DCs, and osteoclasts
- ApoE, polyanionic lipids, and Aβ oligomers are known ligands of TREM2
- KO mice exhibit mild osteopenia, less severe IBD. In-vitro KO macrophages display increased responsiveness to TLR ligands
- Human LOF mutations linked to Nasu-Hakola disease (dementia)



PY314, PIONYR's anti-TREM2 mAb "surgically" depletes M2-like TAMs



$TREM2^{High}$, $MHCII^{Low}$ TAMs ("M2-like")

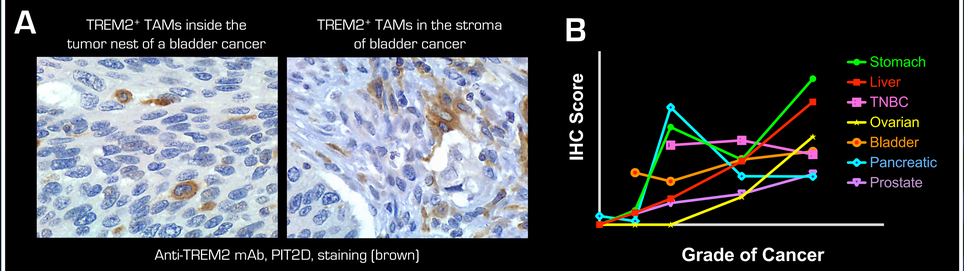
- Promote immunosuppression
  - Block infiltration of $CD8^+$ T cells
  - Generate immunosuppressive factors (eg, NO, IL-10, and TGFβ)
- Support tumor cell proliferation
- Facilitate metastasis and angiogenesis

Anti-tumor immunity

- Increased $CD8^+$ T cells
- Increased $NKp46^+$ NK cells
- Increased $MHCII^{High}$, $TREM2^{Low}$ TAMs ("M1-like")

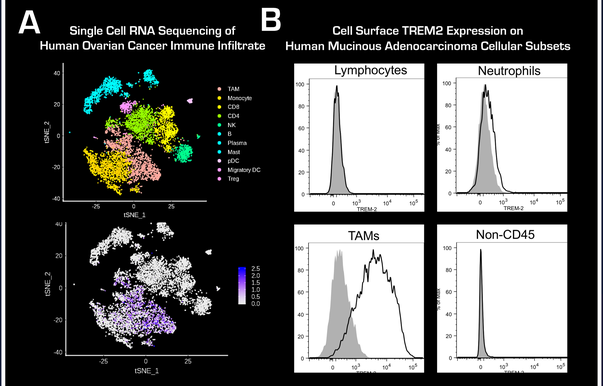
Model of the mechanism-of-action of PY314. PY314 binds to and depletes M2-like TAMs with low MHC class II expression and high TREM2 expression. Depletion of these immunosuppressive TAMs negates multiple immune suppressive pathways. Concomitant increase in pro-inflammatory M1-like macrophages results in productive anti-tumor immunity accompanied by functional augmentation of CD8 T cells and activated NK cells within the TME.

TREM2 expression increases with stage in multiple human tumors



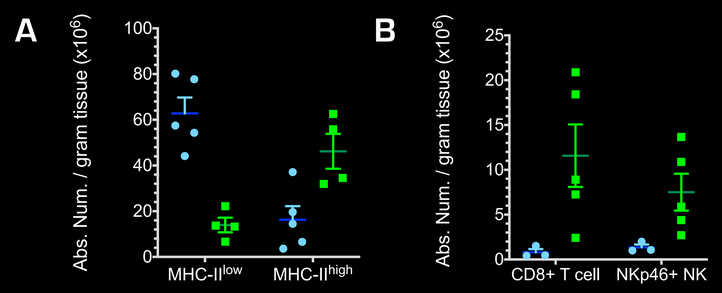
TREM2 expression was evaluated using tumor microarrays (TMAs) using PIT2D, an anti-TREM2 mAb developed at Pionyr. (**A**) Depicts representative staining of TREM2 within tumor nests (left) and in the stroma (right)(**B**) Semi-quantitative scoring by two investigators took into account both the cells positive for the stain as well as stain intensity.

TREM2 is Enriched on TAMs



Dissociated human tumor samples were used for single cell RNA sequencing (**A**) or flow cytometry to identify immune subsets (**B**). TREM2 RNA and protein expression is restricted to TAMs with minimal to no expression in most of the other immune cell types.

PY314m treatment regulates the tumor immune landscape



Treatment of EMT6 tumor bearing mice with PY314m (green) alters immune composition in the TME. (**A**) MHC-II-LOW TAMs are reduced and MHC-II-HIGH TAMs are increased following PY314m treatment. (**B**) CD8+ TILs and NKp46+ NK cells increase in the TME following PY314m therapy.

Summary of safety and PK assessment of PY314

NHP PK

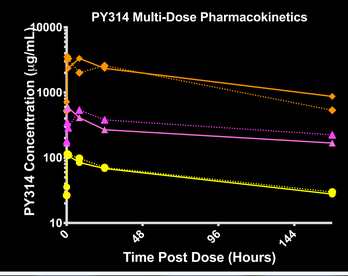
- Terminal half-life ($T_{1/2}$) of ~7 days
- No evidence of target-mediated drug disposition
- Volume of distribution (Vd) of ~84 mL/kg, suggesting distribution beyond the vasculature and into tissues

Single dose NHP pilot

- Well tolerated up to 100 mg/kg
- No changes in clinical pathology parameters

Repeat dose NHP pilot

- PY314 is generally well tolerated up to 100 mg/kg for 4 weekly doses
- Elevations in AST and ALT in high dose (100 mg/kg) male after last dose
- Mild increases in macrophage in kidney and liver at 100 mg/kg



Summary of PY314 manufacturing

PY314 has excellent development properties

GMP manufacturing yields to date are 3.9 g purified PY314 per liter

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