FPA144, a Therapeutic Monoclonal Antibody Targeting the FGFR2b Receptor, Promotes Antibody Dependent Cell-Mediated Cytotoxicity and Stimulates Sensitivity to PD-1 Blockade in the 4T1 Syngeneic Tumor Model in Mice

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ABSTRACT #1036

Background

FGFR2b expression is lower in 4T1 model than FGFR2 amplified xenografts

- Fibroblast growth factors (FGFs) and their receptors play important roles in cellular proliferation, differentiation, migration and survival
- There are 22 known human FGFs and 4 FGFR receptors (FGFR1-4). Alternative splicing of the first immunoglobulin-like domain of FGFR1-3 produces two splicing variants, designated IIb and IIc, with distinct ligand binding specificity and tissue distribution (Tumer, 2012)
- FGFR2b (also known as FGFR2IIIb, FGFR, or K-sam) binds to the KSP family of FGFs, with FG7 and FG10 being the most well-characterized binding partners
- FPA144 is a monoclonal antibody directed against FGFR2b
- FPA144 blocks FGFR2b activation by its ligands
- FPA144-driven regulates FGFR2b
- FPA144 is engineered for enhanced antibody-dependent cell-mediated cytotoxicity (ADCC)
- FPA144 N297Q mimics ligand blocking activity but cannot promote ADCC in vitro

Assessing Efficacy and Mechanism of Action for FPA144

- Study Design
- Engineering of FPA144 for ADCC Drives Innate and Adaptive Responses

- 24 hours post 1st dose:
  - Recruitment of NK cells to the tumor
  - Increase in PD1 positive cells within the tumor
  - T cells remain at the periphery of the tumor

- 24 hours post 2nd dose:
  - Persistence of NK cell recruitment
  - Persistence of PD1 positive cells
  - Infiltration of T cells within the tumor

Summary

- Engineering of FPA144 for enhanced ADCC drives both innate and adaptive immune responses.
- Treatment of mice bearing the orthotopic 4T1 tumor with FPA144 leads to:
  - Recruitment of Natural Killer (NK) cells to the tumor
  - Infiltration of T cells into the tumor
  - Regeneration of tumor growth
- FPA144 reprograms the tumor micro-environment, upregulates PD-1 expression, and shows additional anti-tumor activity when combined with PD-1 blockade
- These combined data suggest that the enhanced ADCC activity of FPA144 may be critical for anti-tumor efficacy in tumors that have modest expression of FGFR2b.
- These non-clinical observations suggest that the combination of FPA144 with PD-1/PD-L1 blockers should be further investigated in the clinic.

References


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