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

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Abstract

FGFR2 gene amplification and FGFR2b overexpression occur in approximately 5% of gastric cancers and are associated with a poor prognosis in gastric cancer. Five Prime Therapeutics, Inc. has developed an FGFR2b-specific humanized monoclonal antibody, FPA144, to treat patients with cancer bearing overexpression of the FGFR2b receptor, and is currently in clinical trials as a single agent for gastric cancer (NCT02318329). In addition to blocking ligand binding and inducing FGFR2b internalization, FPA144 is glycoengineered for enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). We have shown previously that FPA144 can produce complete and durable tumor growth inhibition in FGFR2b-over-expressing and *FGFR2*-amplified gastric cancer xenografts in immune-compromised mice (Gemo et al., Poster 5446, AACR 2014). In order to understand the contribution of the immune system to the mechanisms of action of FPA144, we evaluated the anti-tumor effects and immune cell recruitment of FPA144 in the 4T1 model of breast cancer in immune-competent mice. Although this model expresses FGFR2b, it is not *FGFR2* amplified.

Therapeutic treatment with FPA144 in the orthotopic 4T1 model resulted in a reduction in tumor burden (33%, $P<0.001$) and concomitant recruitment of NK cells to the site of tumor implantation, while a modified antibody lacking Fc effector function neither inhibited tumor growth nor lead to the recruitment of NK cells. Together these data support a potential role for ADCC as a mechanism of FPA144 tumor growth inhibition. In addition, treatment with FPA144 increased PD-L1 expressing cells within the tumor microenvironment, providing a strong rationale that FPA144 may combine effectively with PD-1 blockade for additional tumor growth inhibition. PD-1 blockade by the RPM1-14 antibody did not inhibit tumor growth as a single agent in the 4T1 model. Treatment with RPM1-14 in combination with FPA144, however, inhibited tumor growth by 49% ($P<0.001$), demonstrating an additive benefit of combination therapy. Overall, these data suggest that the enhanced ADCC activity of FPA144 may be critical for anti-tumor efficacy in tumors that have modest expression of FGFR2b. In addition, FPA144 may reprogram the tumor micro-environment in a way that primes the tumor for additional anti-tumor activity when combined with PD-1 blockade.