6PD - FPA150, a novel B7-H4 therapeutic antibody with checkpoint blockade and ADCC activities

Background

B7-H4, a member of the B7 family of immune modulators, negatively regulates both T cell immune responses and anti-tumor immunity. While B7-H4 is highly expressed in a range of solid tumors, expression in heathy tissues is limited. Hence, we sought to generate a therapeutic antibody that both blocks the T cell inhibitory checkpoint activity of B7-H4 and mediates potent antibody-dependent cell-mediated cytotoxicity (ADCC) against B7-H4-expressing tumor cells.

Methods

Fully human B7-H4 antibodies raised by screening Adimab's yeast-based platform were evaluated for protein and cell binding, epitope specificity, and species cross-reactivity. We assessed these B7-H4 antibodies for checkpoint blockade activity using our proprietary in vitro assay, comprised of primary human T cells and B7-H4-expressing artificial antigen presenting cells. We used primary human cell-based and reporter cell line-based assays to assess the in vitro ADCC activity of B7-H4 antibodies against B7-H4-expressing target cell lines. We assessed the in vivo anti-tumor efficacy of our lead B7-H4 antibody in mice bearing syngeneic tumor cell lines engineered to display mouse B7-H4.

Results

After generating a panel of B7-H4 antibodies, we found that 12 out of 41 antibodies reverse B7-H4-mediated inhibition of T cell proliferation and IFNg production in vitro. Importantly, 11 of these antibodies with checkpoint blockade activity belong to the same epitope bin, recognize the B7-H4 IgV domain, and fully cross-react with cynomolgus monkey and rodent B7-H4, suggesting that these antibodies bind and block an evolutionarily conserved functional domain. When glycoengineered for enhanced FcgRIIIa binding, selected checkpoint blockade antibodies also mediate potent ADCC activity against cells exhibiting a range of B7-H4 expression. In a murine tumor model expressing B7-H4, our selected therapeutic candidate FPA150 significantly impairs tumor growth in a dose-dependent manner.

Conclusions

We generated a therapeutic candidate B7-H4 antibody, FPA150, which possesses both T cell immune checkpoint blockade and ADCC activity. We initiated IND-enabling studies and plan to file an IND application by the end of 2017.

Legal entity responsible for the study

Five Prime Therapeutics

Funding

Five Prime Therapeutics

Disclosure

C.D. Kaplan: Currently employed by and own stock in Five Prime Therapeutics. D. Houser, A. Hsu, K. Legris, G. Brattich, H. Xiang, A. Ahene, U. Jeffry, D. Bellovin, L. Borges, F. Kemp: Currently employed by Five Prime Therapeutics N. Nielson: Currently employed by Adimab.