FPA150: A First-In-Class T Cell Checkpoint Blocking Antibody with ADCC Activity for the Treatment of Malignancies that Express High Levels of B7-H4

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Disclosure Information

- I have the following financial relationships to disclose:
  - I am an employee of Five Prime Therapeutics
  - I am a stockholder in Five Prime Therapeutics
- I will not discuss off label use and/or investigational use in my presentation
Modulating T Cell Responses Using Immune Checkpoint Inhibitors: A Balance Between Efficacy and Safety

- Long-term, durable responses only observed in a subset of patients
- Targeting primary regulators of immune responses is associated with the development of immune related adverse events (irAE)
- irAEs include grade III/IV diarrhea, lupus nephritis, myocarditis, and pancreatitis

Opportunities remain to develop novel therapies to treat patients who do not respond to, or possibly cannot tolerate, such regimens
B7-H4 is a Member of the B7 Family of T Cell Checkpoint Ligands

- B7-H4 shares significant homology with other B7-family members, including PD-L1.
- B7-H4 is expressed in multiple human tumor types and its expression tends to correlate with poor prognosis (He C, Clin Dev Immunol, 2011).
- Similar to PD-L1, B7-H4 is a documented T cell checkpoint ligand that can suppress T cell responses (Sica GL, Immunity, 2003; Dangaj D, Can Res, 2013).
- Unlike CTLA4 and PD-1, B7-H4 does not appear to be a primary regulator of immune responses, as B7-H4-deficient mice do not develop spontaneous autoimmune disease (Zhu G, Blood, 2009).

A B7-H4 antibody represents an opportunity for a first-in-class T cell checkpoint inhibitor.
Overexpression of B7-H4 in tumors relative to healthy tissues is predicted to provide a favorable therapeutic index for a B7-H4 antibody that possesses ADCC activity.

B7-H4 Expression In TMA/Whole Section Samples

- Normal Breast Tissue
- Ductal Adenocarcinoma
- Invasive Ductal Carcinoma


(Five Prime Therapeutics)

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B7-H4 is a T Cell Checkpoint Ligand that Directly Suppresses T Cell Activity Through an Unidentified Counter-Receptor

B7-H4 Antibodies Isolated From Full-length Human IgG1 Naïve Antibody Libraries (Adimab)

- B7-H4 T cell immune checkpoint blocking antibodies bind a distinct epitope in the B7-H4 ectodomain
Five Prime’s B7-H4 Antibody FPA150 is Engineered to Possess Both T Cell Checkpoint Blockade and ADCC Activities

- Fully human IgG1κ monoclonal antibody
- Binds to the B7-H4 ectodomain
- T cell checkpoint blockade activity
  - FPA150 selected for its ability to prevent B7-H4 from delivering an inhibitory signal into T cells
- ADCC activity
  - FPA150 redirects FcγRIIIα⁺ effector cells (NK cells and Macrophages) to eliminate B7-H4 expressing tumor cells
  - FPA150 is afucosylated (i.e., produced in the FUT8 deficient Potelligent® CHO cell line) and demonstrates higher affinity binding to FcγRIIIα and potent ADCC activity
FPA150 is a High Affinity mAb that Binds the B7-H4 IgV Ectodomain and is Species Cross-reactive

FPA150 B7-H4 Recombinant Protein Binding (SPR)

<table>
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<tr>
<th>Species</th>
<th>Target</th>
<th>$ka$ (1/Ms)</th>
<th>$kd$ (1/s)</th>
<th>$K_D$ (nM)</th>
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<tbody>
<tr>
<td>Human</td>
<td>B7-H4 IgV</td>
<td>1.78E+05</td>
<td>3.61E-04</td>
<td>2.0</td>
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<tr>
<td>Human</td>
<td>B7-H4 ECD</td>
<td>7.16E+05</td>
<td>1.70E-03</td>
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<tr>
<td>Cynomolgus Monkey</td>
<td>B7-H4 ECD</td>
<td>9.62E+05</td>
<td>1.12E-03</td>
<td>1.2</td>
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<tr>
<td>Rat</td>
<td>B7-H4 ECD</td>
<td>7.84E+05</td>
<td>2.35E-03</td>
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<tr>
<td>Mouse</td>
<td>B7-H4 ECD</td>
<td>6.32E+05</td>
<td>2.13E-03</td>
<td>3.4</td>
</tr>
</tbody>
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FPA150 B7-H4 Cell Binding (FACS)

- SK-BR-3 (Endogenous Human B7-H4)
  - EC50 = 0.49nM

- Cynomolgus B7-H4-HEK293
  - EC50 = 1.77nM

- Rat B7-H4-HEK293
  - EC50 = 3.34nM

- Mouse B7-H4-HEK293
  - EC50 = 1.75nM

- FPA150 binds to and blocks an evolutionarily conserved functional epitope within the B7-H4 IgV ectodomain
FPA150 Provides Both T Cell Checkpoint Blockade and ADCC Activity *In Vitro*

- The afucosylated HuIgG1 domain improves FcγRIIIa binding and ADCC activity, but does not impact B7-H4 binding and blockade activity.
Challenges and Solutions to Targeting B7-H4 in Mice

- Challenges associated with targeting B7-H4 in mice
  - Five Prime has yet to detect endogenous cell surface B7-H4 protein expression in mouse syngeneic tumor models or tumor cell lines
  - Human B7-H4 is a Type I transmembrane protein whereas mouse B7-H4 is a GPI-linked protein
  - Syngeneic mouse tumor cell lines were engineered to express a Type I transmembrane version of mouse B7-H4
FPA150 Demonstrates Dose-Dependent Antitumor Activity *In Vivo* as a Monotherapy In Multiple Engineered Mouse Tumor Models

- cmFPA150F is FPA150 engineered onto a mslG2a Fc and is fucosylated
  - A “mouse” version of FPA150 is predicted to be less immunogenic
Complete tumor regressions (CTRs) observed in 50% of mice following treatment with cmFPA150F and anti-PD-1 blockade.

- Mice remained tumor free up to the end of the study (120 days post inoculation).
- Similar combinatorial activity also observed in the B16-moB7-H4/H3 model (65% CTRs).
FPA150 Phase 1 Clinical Trial Testing Monotherapy in Multiple Tumor Settings

PHASE 1a
*Dose escalation in any solid tumor*

- Evaluate safety, PK/PD and activity
- Demonstrate proof of mechanism by PD analysis

PHASE 1b
*Expansion in selected tumors ~30 patients/cohorts*

- Breast Cancer
- Ovarian Cancer
- Endometrial Cancer
- Urothelial (Bladder) Cancer
- Additional cohorts TBD based on emerging data

Study Objectives
- Safety
- Objective response rate and duration
- Survival
- Baseline and on-treatment biopsies
FPA150 is a first-in-class B7-H4 antibody that possesses both T cell immune checkpoint blockade and ADCC activities \textit{in vitro}.

FPA150 demonstrates dose-dependent anti-tumor activity \textit{in vivo} as a monotherapy and elicits complete tumor regressions in combination with anti-PD-1 blockade.

In rat and cynomolgus monkey PK and toxicity studies, FPA150 demonstrates a suitable antibody PK profile and was generally well tolerated.

Based on the therapeutic properties of FPA150, we believe that this agent has the potential to improve anti-tumor immune responses in cancer patients.

A B7-H4 IHC assay is in development for clinical use as a companion diagnostic.

Phase 1 Trial with dose escalation in any solid tumor has been initiated, with planned expansion cohorts in breast, gynecologic and bladder cancers with high B7-H4 expression levels.
THANK YOU!

Five Prime Therapeutics

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