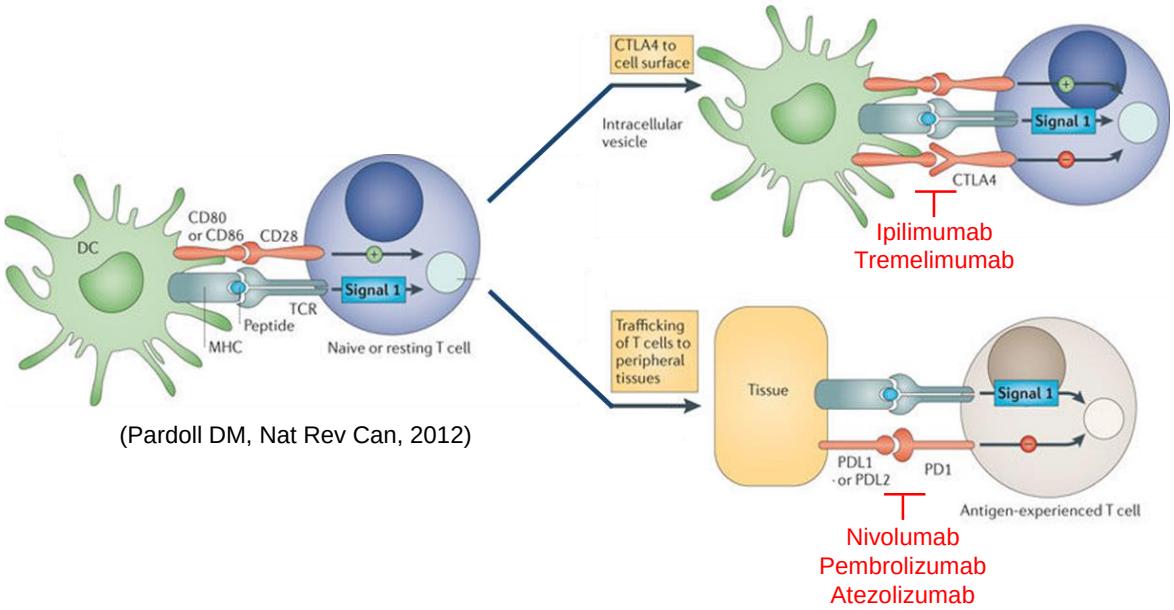
FPA150: A First-In-Class T Cell Checkpoint Blocking Antibody with ADCC Activity for the Treatment of Malignancies that Express High Levels of B7-H4

Charles D. Kaplan, Ph.D.

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



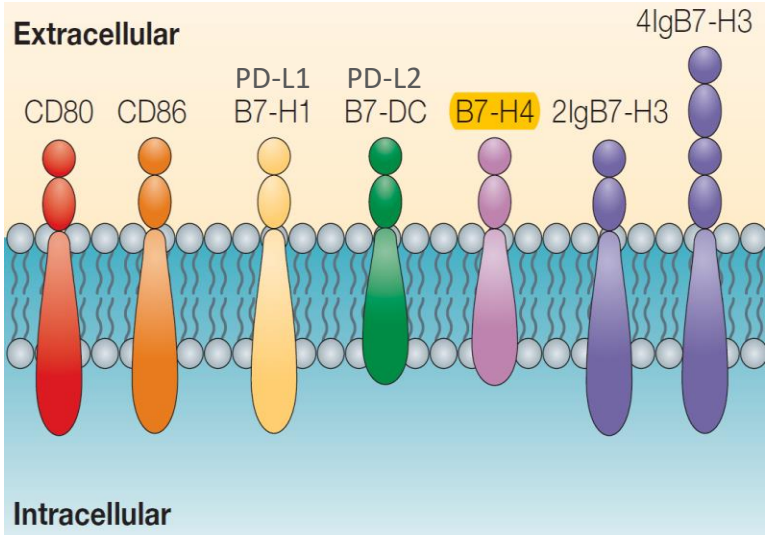
(Pardoll DM, Nat Rev Can, 2012)

- 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)

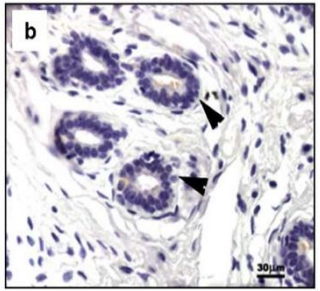


(Chen L, Nat Rev Imm, 2004)

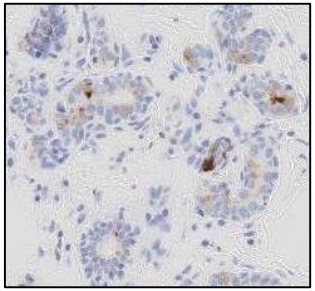
A B7-H4 antibody represents an opportunity for a first-in-class T cell checkpoint inhibitor

B7-H4 is Over-Expressed in a Subset of Cancers

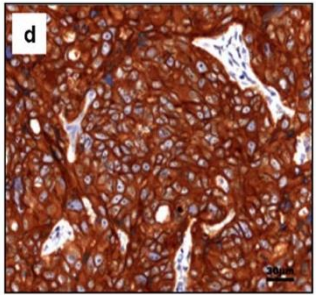
Normal Breast Tissue



Normal Breast Tissue

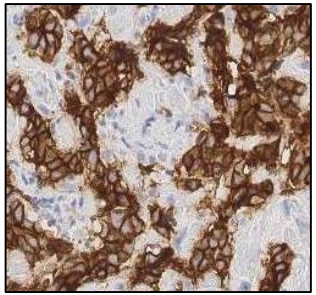


Ductal Adenocarcinoma



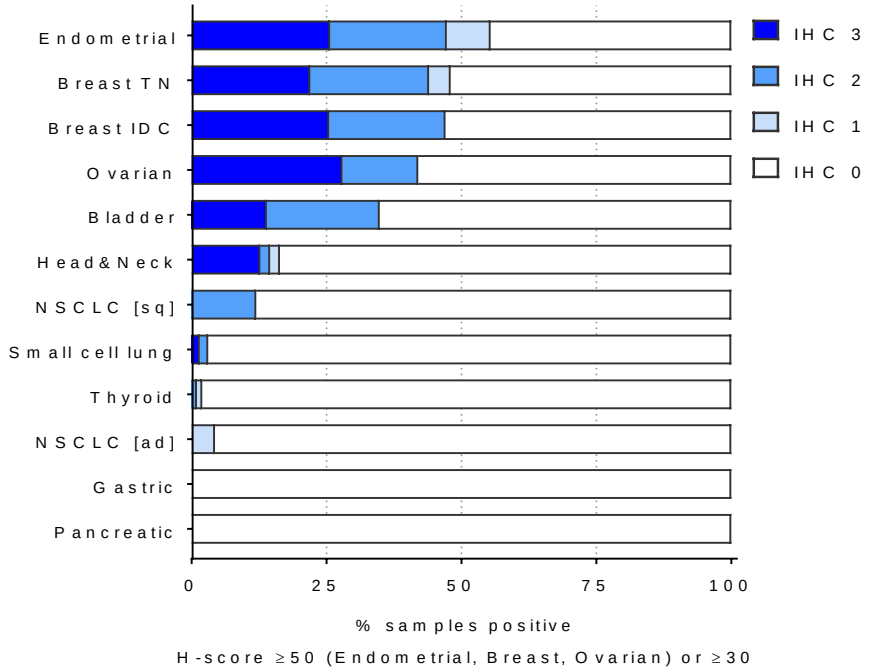
(Salceda S, Exp Cell Res, 2005)

Invasive Ductal Carcinoma



(Five Prime Therapeutics)

B7-H4 Expression In TMA/Whole Section Samples

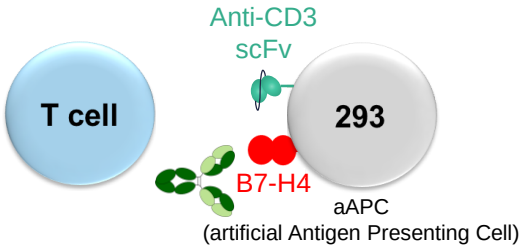


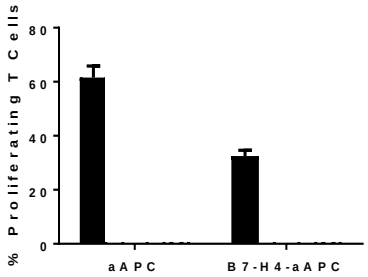
H-score ≥50 (Endometrial, Breast, Ovarian) or ≥30

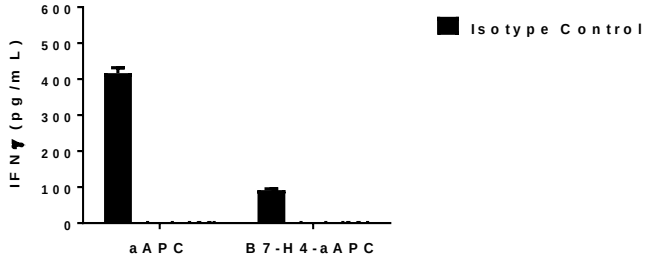
- Overexpression of B7-H4 in tumors relative to healthy tissues is predicted to provide a favorable therapeutic index for a B7-H4 antibody that possesses ADCC activity

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

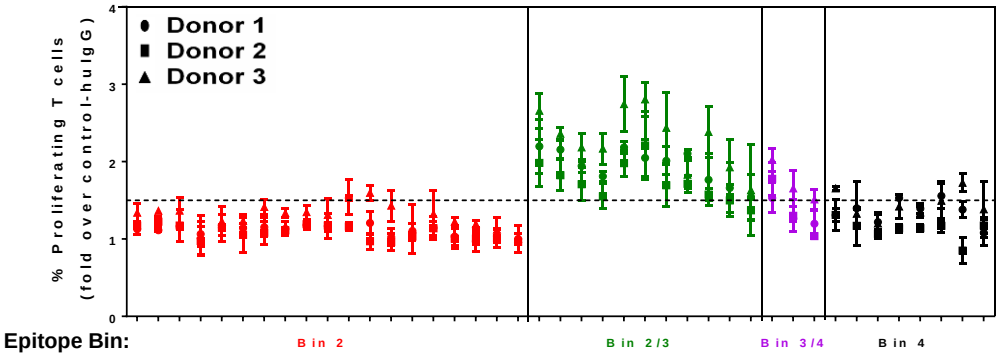
T Cell Checkpoint Blockade Assay

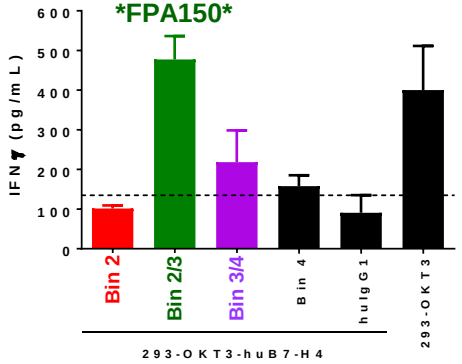






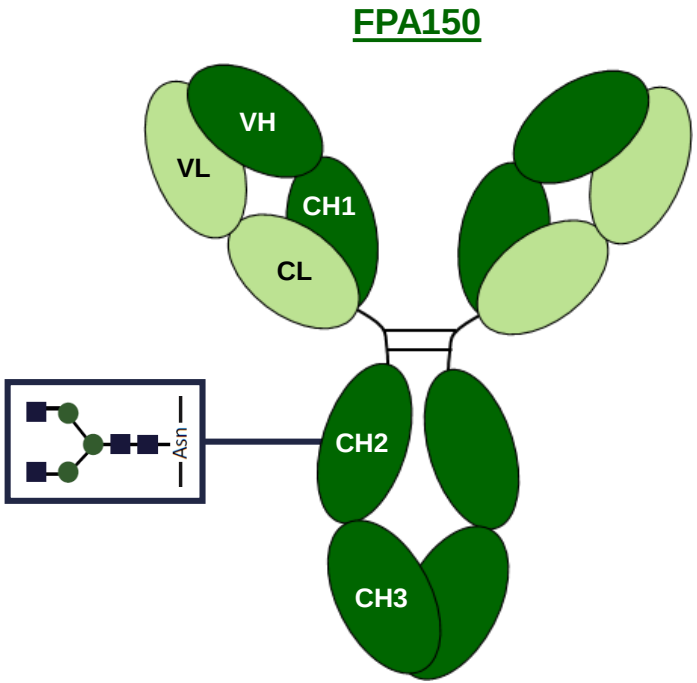
B7-H4 Antibodies Isolated From Full-length Human IgG1 Naïve Antibody Libraries (Adimab)





- 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



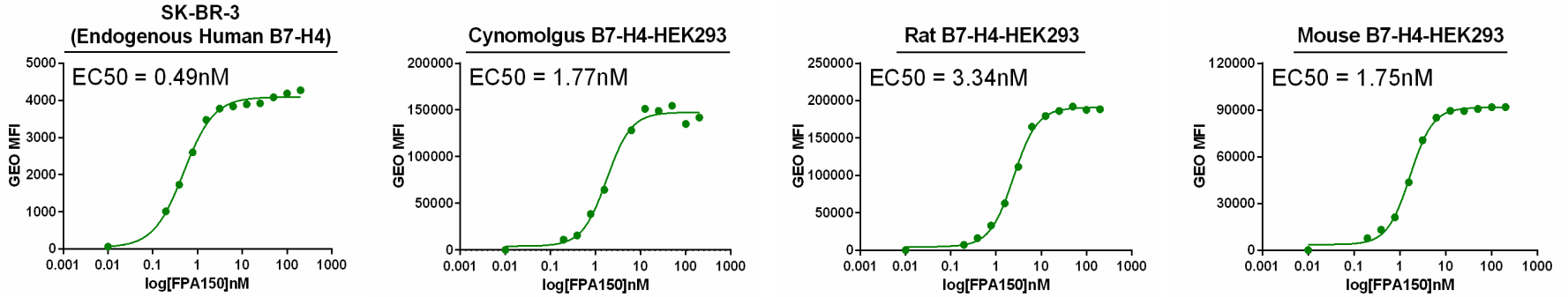
- Fully human IgG1κ monoclonal antibody
- Binds to the B7-H4 ectodomain
- T cell checkpoint blockade activity
  - FPA150 selected for its ability to prevent B7-H4 from delivering an inhibitory signal into T cells
- ADCC activity
  - FPA150 redirects FcγRIIIa^{+} effector cells (NK cells and Macrophages) 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 FcγRIIIa 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)

Species	Target	ka (1/Ms)	kd (1/s)	K_D (nM)
Human	B7-H4 IgV	1.78E+05	3.61E-04	2.0
Human	B7-H4 ECD	7.16E+05	1.70E-03	2.4
Cynomolgus Monkey	B7-H4 ECD	9.62E+05	1.12E-03	1.2
Rat	B7-H4 ECD	7.84E+05	2.35E-03	3.0
Mouse	B7-H4 ECD	6.32E+05	2.13E-03	3.4

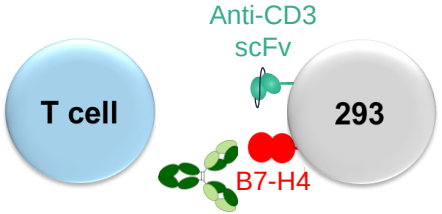
FPA150 B7-H4 Cell Binding (FACS)

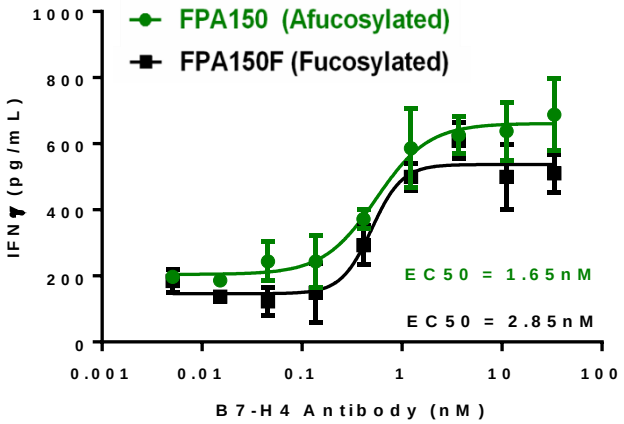


- FPA150 binds to and blocks an evolutionarily conserved functional epitope within the B7-H4 IgV ectodomain

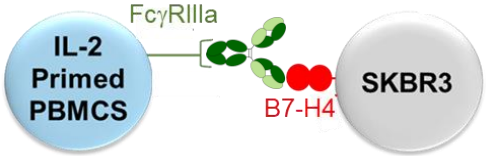
FPA150 Provides Both T Cell Checkpoint Blockade and ADCC Activity *In Vitro*

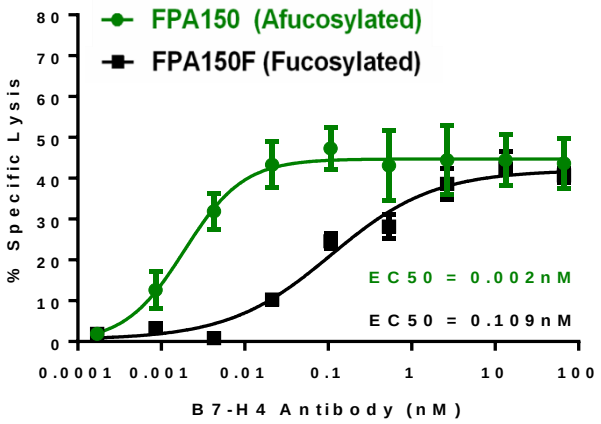
T Cell Checkpoint Blockade Assay





ADCC Assay

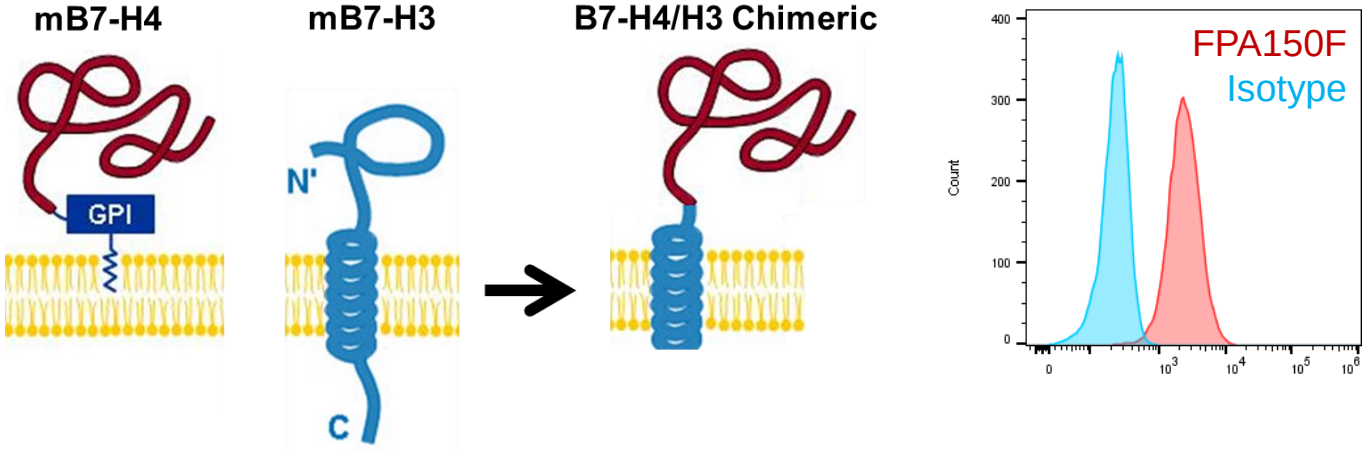




- The afucosylated HuIgG1 domain improves FcγRIIIa binding and ADCC activity, but does not impact B7-H4 binding and blockade activity

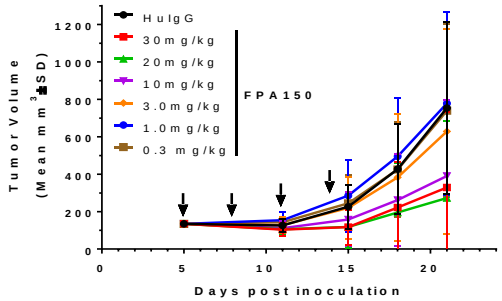
Challenges and Solutions to Targeting B7-H4 in Mice

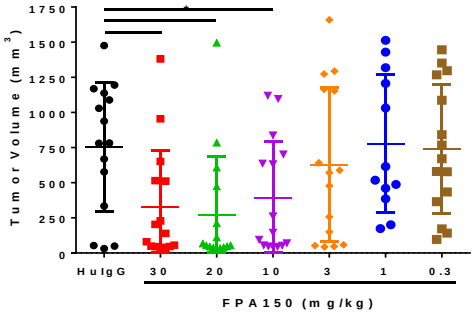
- Challenges associated with targeting B7-H4 in mice
  - Five Prime has yet to detect endogenous cell surface B7-H4 protein expression in mouse syngeneic tumor models or tumor cell lines
  - Human B7-H4 is a Type I transmembrane protein whereas mouse B7-H4 is a GPI-linked protein
- Syngeneic mouse tumor 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

CT26-moB7-H4/H3 Model

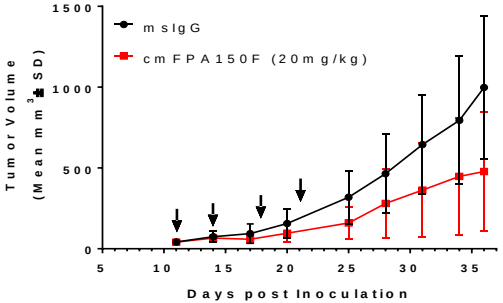


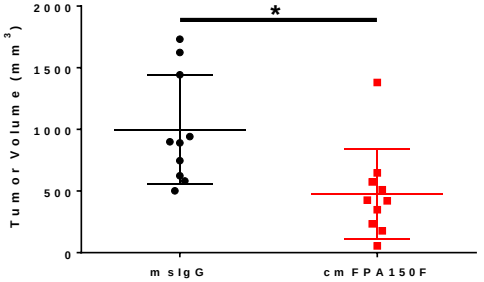


Day 21

* = $P < 0.05$

4T1-moB7-H4/H3 Model

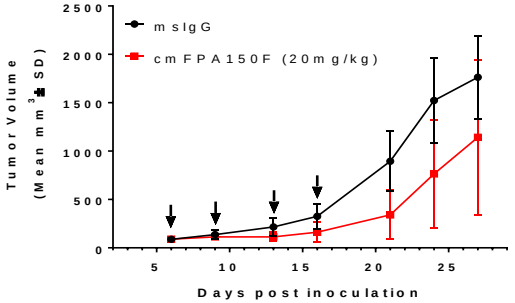


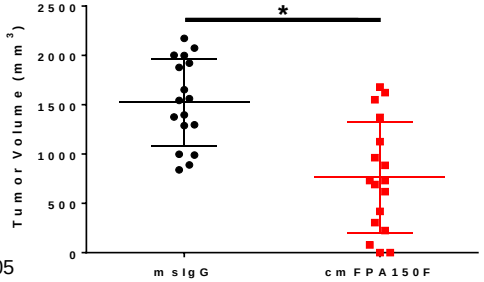


Day 36

* = $P < 0.05$

B16-moB7-H4/H3 Model





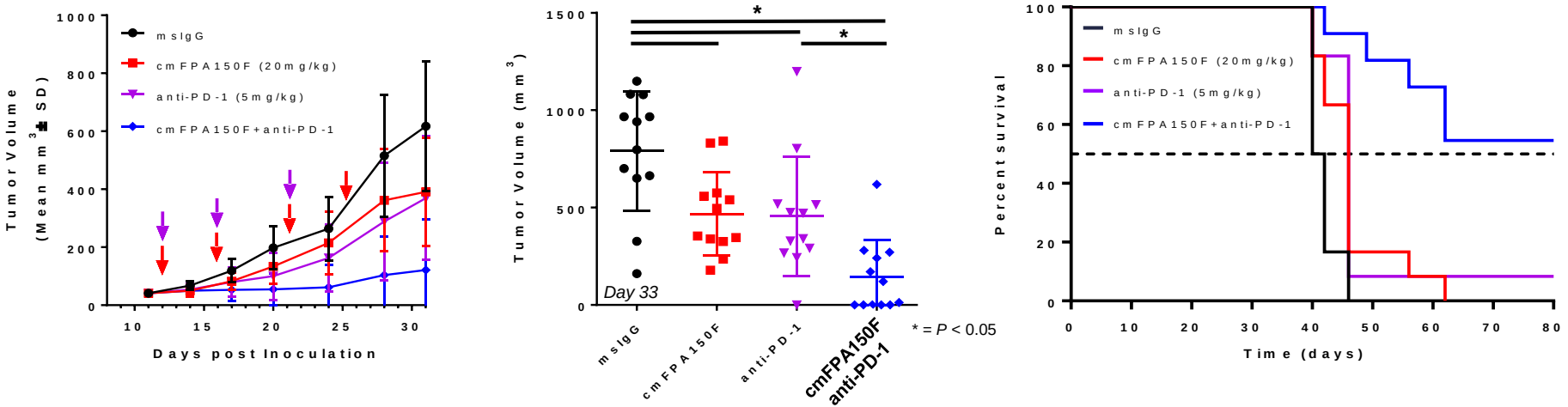
Day 24

* = $P < 0.05$

- cmFPA150F is FPA150 engineered onto a msIgG2a Fc and is fucosylated
  - A “mouse” version of FPA150 is predicted to be less immunogenic

Complete Tumor Regressions Observed When FPA150 is Combined with Anti-PD-1 Blockade

4T1-moB7-H4/H3 Model



- Complete tumor regressions (CTRs) observed in 50% of mice following treatment with cmFPA150F and anti-PD-1
  - 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

FPA150

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

PHASE 1b

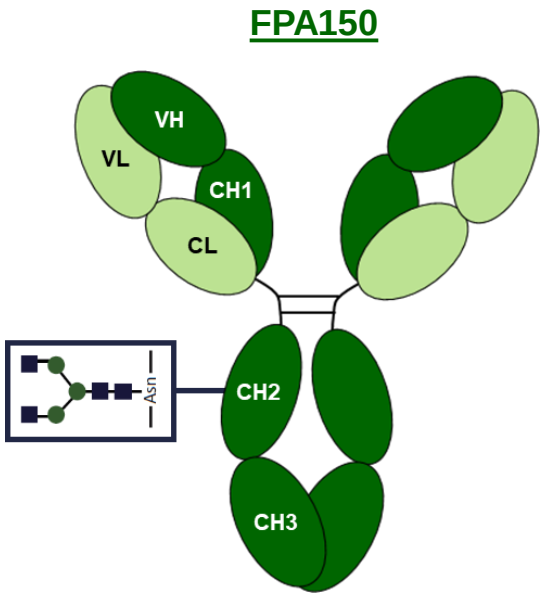
Expansion in selected tumors
~30 patients/cohort

- **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

Summary



- FPA150 is a first-in-class B7-H4 antibody that possesses both T cell immune checkpoint blockade and ADCC activities *in vitro*
- FPA150 demonstrates dose-dependent anti-tumor activity *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

- FPA150 Core Team
  - Sandeep Inamdar
  - Kristen Pierce
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  - Shawn Russell
  - Lisa Shamon
  - Leslie Fok
  - Marc Lopez
  - Maike Schmidt
  - Kathy Miller
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  - Francis Sarena
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  - Kristin Rookey
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  - Ross Connor