A Phase 1a/1b Study of FPA150, an Anti-B7-H4 Antibody, in Patients with Advanced Solid Tumors

Protocol Number:	FPA150-001
Investigational Product:	FPA150
IND Number:	136997
EudraCT Number	Not applicable
Development Phase:	Phase 1a/1b
Indication Studied:	Advanced Solid Tumors
Protocol Version:	Amendment 2
Date of Protocol:	04 February 2019
Sponsor:	Five Prime Therapeutics, Inc. 111 Oyster Point Boulevard South San Francisco, CA 94080-7047 Phone: 415-365-5600
Responsible Medical Officer:	[redacted], MD, MS Director, Clinical Development Five Prime Therapeutics, Inc.

Confidential

Protocol Approval Signature Page

Declaration of Sponsor

A Phase 1a/1b Study of FPA150, an Anti-B7-H4 Antibody, in Patients with Advanced Solid Tumors

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements. Essential study documents will be archived in accordance with applicable regulations.

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 1989, and the International Conference on Harmonization (ICH) guidelines on GCP.

[redacted] MD
Chief Medical Officer
Five Prime Therapeutics, Inc.

[redacted] Date

Declaration of the Investigator

A Phase 1a/1b Study of FPA150, an Anti-B7-H4 Antibody, in Patients with Advanced Solid Tumors

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure (IB), electronic case report forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except as necessary to eliminate an immediate hazard to the patients.

I confirm that I have read the above-mentioned protocol/protocol amendments and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, applicable laws, regulations and ICH E6 Guideline for GCP.

Principal Investigator's Signature	Date
Name (printed)	
Institution or Company Name	

Document History

Document	Date
Amendment 2	04 February 2019
Amendment 1	23 January 2018
Original Protocol	31 October 2017

1 Protocol Synopsis

Title: A Phase 1a/1b Study of FPA150, an Anti-B7-H4 Antibody, in Patients with Advanced Solid Tumors

Protocol Number: FPA150-001

Clinical Phase: 1a/1b

Study Centers: There will be approximately 6 to 10 study centers participating in Phase 1a and approximately 35 study centers participating in Phase 1b. Phase 1a (including the pembrolizumb combination cohort) and the combination cohorts in Phase 1b will be conducted in the United States only. Phase 1b monotherapy will be conducted globally.

Objectives and Endpoints:

Phase 1a Objectives and Endpoints:

OBJECTIVES	ENDPOINTS
PRIMARY - SAFETY	
FPA150 Monotherapy • To evaluate the safety and tolerability of FPA150 as monotherapy in patients with advanced solid tumors treated at the Maximum Tolerated Dose (MTD) and/or Recommended Dose (RD) • To determine the MTD and/or RD of FPA150	**FPA150 Monotherapy** • The incidence of Grade 3 and Grade 4 AEs and clinical laboratory abnormalities defined as DLTs • The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
FPA150 in Combination with Pembrolizumab • To evaluate the safety and tolerability of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer • To determine the MTD and/or RD of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer	**FPA150 in Combination with Pembrolizumab** • The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities • The incidence of Grade 3 and Grade 4 AEs and clinical laboratory abnormalities defined as DLTs
SECONDARY - PHARMACOKINETIC	
FPA150 Monotherapy • To characterize the PK profile of FPA150 as monotherapy in patients with advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • Area under serum concentration time curve (AUC) • Maximum serum concentration (C_{max}) • trough serum concentration at the end of a dose interval (C_{trough}) • Terminal Half-life ($t_{1/2}$) • Volume of distribution at steady state (V_{ss}) • Other parameters, such as dose proportionality, accumulation ratio, attainment of steady state, will also be calculated if the data are available

OBJECTIVES	ENDPOINTS
SECONDARY - IMMUNOGENICITY	
FPA150 Monotherapy • To characterize the immunogenicity of FPA150 as monotherapy in patients with advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • Immune response (ADAs) to FPA150
EXPLORATORY - EFFICACY	
FPA150 Monotherapy • To evaluate the clinical benefit of FPA150 as monotherapy	**FPA150 Monotherapy** • Objective response rate (ORR), defined as the total number of patients with confirmed responses of either complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) divided by the total number of patients who are evaluable for a response • Duration of response (DOR), defined as the time from onset of response (CR or PR) that is subsequently confirmed to the first observation of progressive disease or death due to any cause • Progression free-survival (PFS), defined as the time from the patient's first dose to the first observation of progressive disease or death due to any cause
FPA150 in Combination with Pembrolizumab • To evaluate the clinical benefit of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer	**FPA150 in Combination with Pembrolizumab** • ORR, defined as the total number of patients with confirmed responses of either CR or PR per RECIST v1.1 divided by the total number of patients who are evaluable for a response • DOR, defined as the time from onset of response (CR or PR) that is subsequently confirmed to the first observation of progressive disease or death due to any cause • PFS, defined as the time from a patient's first dose to the first observation of progressive disease or death due to any cause.
EXPLORATORY - PHARMACOKINETICS	
FPA150 in Combination with Pembrolizumab • To characterize the pharmacokinetic (PK) profile of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer	**FPA150 in Combination with Pembrolizumab** The following PK parameters will be derived from concentration-time data for FPA150 in combination with pembrolizumab when appropriate and applicable: • AUC • C_{max} • C_{trough} • Clearance (CL) • $t_{1/2}$ • V_{ss} • Other parameters, such as dose proportionality, accumulation ratio, attainment of steady state, will also be calculated if the data are available for FPA150 C_{max} and C_{trough} as well as accumulation

OBJECTIVES	ENDPOINTS
	ratio of C_{max} and C_{trough} for pembrolizumab may be calculated if the data are available
EXPLORATORY - IMMUNOGENICITY	
FPA150 in Combination with Pembrolizumab • To characterize the immunogenicity of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer	**FPA150 in Combination with Pembrolizumab** • Immune response (ADAs) to FPA150 • Immune response (ADAs) to pembrolizumab
EXPLORATORY – PHARMACODYNAMIC BIOMARKERS	
FPA150 Monotherapy • To characterize the pharmacodynamic profile of FPA150 through an analysis of the immune cell infiltrate in pre-treatment and on-treatment tumor biopsies • To characterize the pharmacodynamic profile of FPA150 through evaluation of exploratory biomarkers in peripheral blood samples	**FPA150 Monotherapy** • Changes in markers of tumor immune infiltrate • [redacted] • Changes in selected pharmacodynamic biomarkers in peripheral blood samples
FPA150 in Combination with Pembrolizumab • To characterize the pharmacodynamic profile of FPA150 in combination with pembrolizumab through an analysis of the immune cell infiltrate in pre-treatment and on-treatment tumor biopsies • To characterize the pharmacodynamic profile of FPA150 in combination with pembrolizumab through evaluation of exploratory biomarkers in peripheral blood samples	**FPA150 in Combination with Pembrolizumab** • Changes in markers of tumor immune infiltrate • [redacted] • Changes in selected additional pharmacodynamic markers in peripheral blood in patients treated with FPA150 in combination with pembrolizumab

Phase 1b Objectives and Endpoints:

OBJECTIVES	ENDPOINTS
PRIMARY - SAFETY	
FPA150 Monotherapy • To evaluate the safety and tolerability of FPA150 as monotherapy in patients with B7-H4+ advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
FPA150 in Combination with Pembrolizumab • To evaluate the safety and tolerability of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer treated at the MTD and/or RD	**FPA150 in Combination with Pembrolizumab** • The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities in patients treated with FPA150 in combination with pembrolizumab

OBJECTIVES	ENDPOINTS
SECONDARY - EFFICACY	
FPA150 Monotherapy • To evaluate the clinical benefit of FPA150 as monotherapy in patients with B7-H4+ advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • ORR, defined as the total number of patients with confirmed responses of either CR or PR per RECIST v1.1 divided by the total number of patients who are evaluable for a response • DOR, defined as the time from onset of response (CR or PR) that is subsequently confirmed to the first observation of progressive disease or death due to any cause • PFS, defined as the time from the patient's first dose to the first observation of progressive disease or death due to any cause
FPA150 in Combination with Pembrolizumab • To evaluate the clinical benefit of FPA150 in combination with pembrolizumab in patients with B7-H4 + ovarian cancer treated at the MTD and/or RD	**FPA150 in Combination with Pembrolizumab** • ORR, defined as the total number of patients with confirmed responses of either CR or PR per (RECIST) v1.1 divided by the total number of patients who are evaluable for a response to FPA 150 combined with pembrolizumab • DOR, defined as the time from onset of response (CR or PR) that is subsequently confirmed to the first observation of progressive disease or death due to any cause to FPA150 combined with pembrolizumab • PFS, defined as the time from the patient's first dose to the first observation of progressive disease or death due to any cause
SECONDARY - PHARMACOKINETICS	
FPA150 Monotherapy • To characterize the PK profile of FPA150 as monotherapy in patients with B7-H4+ advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • AUC • C_{max} • C_{trough} • CL • $t_{1/2}$ • V_{ss} • Other parameters, such as accumulation ratio, attainment of steady state, will also be calculated if the data are available
SECONDARY - IMMUNOGENICITY	
FPA150 Monotherapy • To characterize the immunogenicity of FPA150 as monotherapy in patients with B7-H4+ advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • Immune response (ADAs) to FPA150

OBJECTIVES	ENDPOINTS
EXPLORATORY - PHARMACOKINETICS	
FPA150 in Combination with Pembrolizumab • To characterize the PK profile of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer treated at the MTD and/or RD • To characterize the PK profile of pembrolizimab in combination with FPA150 in patients with B7-H4+ ovarian cancer	**FPA150 in Combination with Pembrolizumab** • The following PK parameters will be derived from concentration-time data for FPA150 in combination with pembrolizumab when appropriate and applicable: • AUC • C_{max} • C_{trough} • CL • $t_{1/2}$ • V_{ss} • Other parameters, such as accumulation ratio, attainment of steady state, will also be calculated if the data are available for patients treated with FPA150 combined with pembrolizumab • C_{max} and C_{trough} as well as the accumulation ratio of C_{max} and C_{trough} for pembrolizumab may be calculated if the data are available
EXPLORATORY - IMMUNOGENICITY	
FPA150 in Combination with Pembrolizumab • To characterize the immunogenicity of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer treated at the MTD and/or RD • To characterize the immunogenicity of pembrolizumab in combination with FPA150 patients with with B7-H4+ ovarian cancer treated at the MTD and/or RD	**FPA150 in Combination with Pembrolizumab** • Immune response (ADAs) to FPA150 • Immune response (ADAs) to pembrolizumab
EXPLORATORY – PHARMACODYNAMIC BIOMARKERS	
FPA150 Monotherapy • To characterize the pharmacodynamic profile of FPA150 through an analysis of the immune cell infiltrate in pre-treatment and on-treatment tumor biopsies • To characterize the pharmacodynamic profile of FPA150 through evaluation of exploratory biomarkers in peripheral blood samples	**FPA150 Monotherapy** • Changes in markers of tumor immune infiltrate • [redacted] • Changes in selected pharmacodynamic biomarkers in peripheral blood samples
FPA150 in Combination with Pembrolizumab • To characterize the pharmacodynamic profile of FPA150 in combination with pembrolizumab through an analysis of the immune cell infiltrate in pre-treatment and on-treatment tumor biopsies • To characterize the pharmacodynamic profile of FPA150 in combination with pembroliumab	**FPA150 in Combination with Pembrolizumab** • Changes in markers of tumor immune infiltrate, • [redacted]

OBJECTIVES	ENDPOINTS
through evaluation of exploratory biomarkers in peripheral blood samples	[redacted] • Changes in selected additional pharmacodynamic biomarkers in peripheral blood samples for patients treated with FPA150 in combination with pembrolizumab
EXPLORATORY - EFFICACY	
FPA150 Monotherapy • To evaluate the clinical benefit of FPA150 as monotherapy in patients with B7-H4+ advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • OS, defined as time from patient's first dose to death due to any cause
FPA150 in Combination with Pembrolizumab • To evaluate the clinical benefit of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer treated at the MTD and/or RD	**FPA150 in Combination with Pembrolizumab** • OS, defined as time from patient's first dose to death due to any cause

Investigational Product:

FPA150 drug product is supplied for IV administration as a sterile, aqueous, colorless to slightly yellowish, pyrogen-free solution supplied in single-use glass vials (5 mL). The composition of the drug product contains 20 mg/mL active ingredient, 20 mM sodium acetate, 270 mM sucrose, 0.05% (w/v) polysorbate 20 at pH 5.0.

A 20 mL preparation will be available for use in the second half of 2019. The 20 mL vial is also supplied for IV administration as a sterile, aqueous, colorless to slightly yellowish, pyrogen-free solution supplied in single-use glass vials. The composition of the drug product contains 20 mg/mL active ingredient, 20 mM sodium acetate, 270 mM sucrose, 0.05% (w/v) polysorbate 20 at pH 5.0.

Pembrolizumab is available for injection as a 50 mg lyophilized powder in single-use vial for reconstition and in 100 mg/4 mL (25 mg/mL) solution in single use vial.

The lyophilized powder is reconstituted by adding 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL). Slowly swirl the vial and allow up to 5 minutes for the bubbles to cear. Do not shake the vial.

The injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg) and water for Injection. Refer to the pembrolizumab package insert for additional information.

Study Design:

This is a Phase 1a/1b open-label, multicenter, study to evaluate the dosing, safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of FPA150 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors.

This study includes a Phase 1a FPA150 Monotherapy Dose Escalation, Phase 1a FPA150 Monotherapy Dose Exploration,a Phase 1a Combination Safety Lead-in (FPA150 in combination with pembrolizumab), a Phase 1b FPA150 Monotherapy Dose Expansion, and a Phase 1b FPA150 Combination Dose Expansion (FPA150 in combination with pembrolizumab).

Pre-screening of archival tumor tissue (or fresh biopsy if archival tissue is not available) is required to test for B7-H4 (transmembrane protein of the B7 family also known as B7S1, B7x, or VTCN1) expression levels by immunohistochemistry (IHC) at a central laboratory for all patients in the Phase 1a Monotherapy Dose Exploration, Phase 1a Combination Safety Lead-in, Phase 1b Dose Expansion, and Phase 1b Combination Dose Expansion.

Phase 1a Monotherapy and Combination Safety Lead-in and Phase 1b Combination Dose Expansion, will be conducted in the US only. Phase 1b Monotherapy Dose Expansion will be conducted globally.

Requirements for Archival Tumor Tissue, Fresh Biopsies:

Required for <u>all patients in Phase 1a FPA150 Monotherapy Dose Escalation:</u>

- Provision of archival tumor tissue (or fresh biopsy if archival tissue is not available) for retrospective biomarker analysis for all patients.

Required for <u>all patients in Phase 1a Combination Safety Lead-in:</u>

- Archival tumor tissue (or fresh biopsy required if archival tissue is not available) for pre-screening to evaluate for B7-H4 expression levels through IHC testing performed at a central laboratory and for retrospective biomarker analysis at screening.

Required for <u>all patients in Phase 1a Monotherapy Dose Exploration:</u>

- Archival tumor tissue (or fresh biopsy required if archival tissue is not available) for prescreening to evaluate for B7-H4 expression levels through IHC testing performed at a central laboratory and for retrospective biomarker analysis at screening.
- Fresh biopsies mandatory during screening and on-treatment (prior to C3D1) for expanded pharmacodynamic analysis. (please refer to Appendix 2 for additional information).

Required for <u>all patients in Phase 1b Dose Expansion:</u>

- Archival tumor tissue (or fresh biopsy required if archival tissue is not available) for prescreening to evaluate for B7-H4 expresion levels through IHC testing and retrospective biomarker analysis at screening will be performed at a central laboratory. Archival tissue for patients enrolled in Cohort 1b1 (Breast Cancer) must be within 24 months prior to pre-screening.
- Fresh biopsies mandatory for a **subset of patients** (at least 15 patients per 30-patient cohort) during screening and on-treatment (prior to C3D1), for expanded pharmacodynamic analysis.

Study Design (Continued): Additional details are provided below for each study phase under Phase 1a Monotherapy Dose Escalation, Phase 1a Monotherapy Dose Exploration, Phase 1b Monotherapy Dose Expansion, Phase 1a Combination Safety Lead-In, and Phase 1b Combination Dose Expansion sections of this Synopsis. All study assessments are outlined in Appendix 1: Schedule of Assessments – Phase 1a and Phase 1b (monotherapy and combination).

Phase 1a Monotherapy Dose Escalation:

In Phase 1a Dose Escalation, cohorts are planned at doses from 0.01 to 20 mg/kg, and enrollment will depend on safety and tolerability. Phase 1a Dose Escalation will include an initial accelerated titration design followed by a standard 3+3 dose escalation design at dose levels ≥ 1 mg/kg until the maximum tolerated dose (MTD) and/or recommended dose (RD) for Phase 1b is determined. The proposed FPA150 dose levels for escalation are as follows: 0.01 mg/kg once every 3 weeks (Q3W)

- 0.03 mg/kg Q3W
- 0.1 mg/kg Q3W
- 0.3 mg/kg Q3W
- 1 mg/kg Q3W
- 3 mg/kg Q3W
- 10 mg/kg Q3W
- 20 mg/kg Q3W

Review of safety, PK and pharmacodynamic profiles may inform decisions to add cohorts with alternative dose levels or dose regimens (eg, different dosing frequency, higher dose levels) in order to reach an optimal target exposure.

All dose escalation decisions will be based on the assessment of dose-limiting toxicities (DLTs) and overall safety and tolerability. Dose escalation decisions will be made after the last patient enrolled in each cohort has completed the first treatment cycle (ie, 21 days). Dose escalation decisions will be agreed upon by the Cohort Review Committee (CRC), consisting of at least the Sponsor's Medical Monitor and defined quorum of Study Investigators.

Dose-Limiting Toxicity Definitions:

DLTs during Phase 1a Dose Escalation are defined as any of the following events regardless of attribution (except for those events clearly due to the underlying disease or extraneous causes):

- Any Grade 3 or higher non-hematologic toxicity (except Grade 3 nausea, vomiting and diarrhea) occurring within the 21 days of treatment
- Grade 3 nausea, vomiting, diarrhea lasting > 72 hours, despite optimal supportive care, occurring within first 21 days of treatment
- Febrile neutropenia and/or documented infection with absolute neutrophil count (ANC) $< 1.0 \times 10^9$ per L, Grade 4 neutropenia lasting for more than 7 days, Grade 4 thrombocytopenia ($< 25.0 \times 10^9$ per L), or Grade 3 thrombocytopenia ($< 50.0–25.0 \times 10^9$ per L) accompanied by bleeding within first 21 days of treatment
- Aspartate aminotransferase/ alanine transaminase (AST/ALT) > 3 × upper limit of normal (ULN) and concurrent total bilirubin > 2 × ULN not related to liver involvement with cancer
- Any Grade 4 laboratory value regardless of clinical sequelae
- Other Grade 3 laboratory values that are not of clinical significance according to Investigator and Sponsor agreement that do not resolve within 72 hours

The DLT evaluation interval begins on the first day of treatment upon start of infusion and continues for 21 days. In Phase 1a Monotherapy Dose Escalation, patients' second dose must be at least 21 days after the first dose. Patients who receive at least one dose of study drug during the 21-day evaluation interval, or patients who discontinue study treatment for drug-related AEs before the DLT evaluation interval is complete, will be considered evaluable for DLT determination. In consultation with Investigators, the Sponsor may open cohorts at dose levels between the dose levels proposed in the protocol.

An accelerated titration design enrolling at least 1 patient at each dose level is planned for dose levels 0.01, 0.03, 0.1 and 0.3 mg/kg. Dose escalation to the next dose level may proceed after at least 1 patient completes the 21-day evaluation interval. If a single patient experiences a DLT or at least 2 patients experience moderate AEs (at any dose level) during the 21-day evaluation interval, additional patients will be enrolled at the current dose level and standard 3+3 dose escalation criteria will apply for that cohort as well as all subsequent dosing cohorts.

Moderate AEs are defined as ≥ Grade 2 AEs regardless of attribution (except for those events clearly due to the underlying disease or extraneous causes). Grade 2 laboratory values will not be considered as moderate AEs for this purpose unless accompanied by clinical sequelae.

The algorithm outlined in the table below will be used for all standard 3+3 dose escalation decisions in Phase 1a Monotherapy Dose Escalation. If not already applied at a lower dose level according to the criteria stated above, enrollment at all dose levels ≥ 1 mg/kg will follow a standard 3+3 dose escalation design.

Algorithm for 3+3 Dose Escalation Decisions in Phase 1a Monotherapy Dose Escalation:

Number of Patients with DLT at a Given Dose Level	Dose Escalation Decision Rule
0/3	Enroll 3 patients at next dose level (next/higher cohort)
1/3	Enroll 3 additional patients at current dose level (current cohort)
≥ 2/3	Stop enrollment. Enter 3 more patients at the previous dose level (previous/lower cohort), if only 3 were previously entered, or at an intermediate dose level
1/6	Enroll 3 patients at next dose level (next/higher cohort)
≥ 2/6	Stop enrollment. Enter 3 more patients at the lower dose level (previous/lower cohort), if only 3 were previously entered, or at an intermediate dose level

Abbreviations: DLT = dose-limiting toxicity.

The MTD and/or RD of FPA150 for Phase 1a monotherapy will be identified based on an evaluation of the overall safety, tolerability, PK, pharmacodynamics, and preliminary efficacy. The RD will take into account toxicities observed both during and beyond the DLT evaluation period as well as dose reductions and discontinuations due to toxicity that do not meet the DLT criteria. The RD, therefore, may or may not be the same as the identified MTD. For example, if the MTD is not reached, or if data from subsequent cycles of treatment from Phase 1a provide additional insight on the safety profile, then the RD may be a different, though not higher, dose than the MTD.

The MTD will be at a dose level where ≤ 1/3-6 patients reported a DLT. The RD will be a dose where ≤ 1/3-6 patients reported a DLT, but may be lower than the MTD.

In the event that no MTD is identified and drug exposure exceeds what is deemed necessary based on nonclinical pharmacology data or the clinical PK and pharmacodynamic data (if available), the Sponsor and the Investigators may make a decision to discontinue dose escalation.

Phase 1a Monotherapy Dose Exploration:

Phase 1a FPA150 monotherapy Dose Exploration may include cohorts that may enroll beyond 3 patients whose tumors express high levels of B7-H4 protein and/or have varying levels of B7-H4 expression [redacted] to further evaluate safety, PK, pharmacodynamics, and clinical activity at that dose (to be conditional upon the dose level clearing DLT criteria). Toxicities observed in these patients will contribute to the overall assessment of safety and tolerability, but will not be included in the formal DLT calculations per Protocol Table 5.

The proposed cohorts are:

Proposed Dose Cohort/Level for Phase 1a Monotheraphy Dose Exploration

Cohort	Dose	Regimen	B7-H4 Status
1aE1	FPA150 3 mg/kg	Q3W	High
1aE2	FPA150 10 mg/kg	Q3W	High
1aE3	FPA150 monotherapy MTD/RD	Q3W	[redacted]

Abbreviations: MTD = maximum tolerated dose; Q3W = once every 3 weeks; RD = recommended dose.

Phase 1a Combination Safety Lead-in (Ovarian B7-H4+ Patients Only):

Once the MTD and/or RD of FPA150 monotherapy is identified, the Sponsor will open a Safety Lead-in for the combination of FPA150 and pembrolizumab. At least 3 patients will be enrolled at the MTD and/or RD of FPA150 monotherapy combined with 200 mg pembrolizumab Q3W and evaluated for DLTs by the CRC. Once the RD for the combination is identified, the Sponsor may treat additional patients for a total of up to 10 patients treated at the RD of FPA150 + pembrolizumab. If required, the dose of FPA150 may be reduced in accordance with the algorithm for de-escalation described below. The proposed dose levels are:

Proposed Dose Cohort/Levels for Phase 1a Combination Safety Lead-in (FPA150 in Combination with Pembrolizumab)

Cohort	Dose	Regimen
1aC1	FPA150 (RD) + pembrolizumab 200 mg IV infusion	Q3W
1aC2	FPA150 (dose level -1) + pembrolizumab 200 mg IV infusion	Q3W
1aC3	FPA150 (dose level -2) + pembrolizumab 200 mg IV infusion	Q3W

Abbreviations: IV = intravenous; Q3W = once every 3 weeks; RD = recommended dose.

The de-escalation scheme will follow the same dose levels used in Phase 1a dose escalation. The Sponsor may evaluate lower or intermediate dose levels of FPA150 based on emerging safety data and in consultation CRC . The DLT criteria for the combination of FPA150 and pembrolizumab will be the same as those for FPA150 monotherapy, with the following additional considerations:

Additional DLT Considerations for FPA150 in combination with Pembrolizumab

Because pembrolizumab is a known immune checkpoint inhibitor and one of the proposed mechanisms of action of FPA150 is immune checkpoint blockade, immune-related adverse events (irAEs) are anticipated with this combination. An irAE is defined as a clinically significant AE that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Based on that background, the first occurrence of the following irAEs will not be considered a DLT because they are expected with immune therapy:

- Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
- Grade 3 rash
- Grade 3 immune-related adverse event (irAE) that resolved to a Grade 1 or less within 14 days
- Transient (resolving within 6 hours of onset) Grade 3 infusion-related AE

A second occurrence of these events (except Grade 3 tumor flare) either in the same or different patient during the DLT window will be considered a DLT

The DLT evaluation interval begins on the first day of treatment upon start of infusion and continues for 21 days. The algorithm outlined in the table below will apply for dosing decisions. The dose of FPA150 may be lowered as needed in response to DLTs. The MTD and/or RD of FPA150 in combination with pembrolizumab will be a dose where ≤ 1/3-6 patients encounter a DLT.

Algorithm for Dose De-Escalation Decisions for Phase 1a Combination Safety Lead-In

Number of Patients with DLT at a Given Dose Level	Dosing Decision Rule
0/3	Proceed with enrollment of up to 10 total patients at that dose level for additional safety assessment
1/3	Enroll 3 additional patients at current dose level (current cohort)
≥ 2/3	Stop enrollment at current cohort and de-escalate FPA150 to one dose level below current dose
1/6	Proceed with enrollment of up to 10 total patients at that dose level
≥ 2/6	Stop enrollment at current cohort and de-escalate FPA150 to one dose level below current dose.

Phase 1b FPA150 Monotherapy and Phase 1b Combination Dose Expansion:

Enrollment in Phase 1b will begin when the MTD and/or RD has been identified by the CRC. The MTD and/or RD determination will be based on overall safety, tolerability, objective response, PK, and pharmacodynamics from the Phase 1a Monotherapy Dose Escalation and Phase 1a Combination Safety Lead-In portions of the study and estimates of efficacious exposures extrapolated from nonclinical data.

Phase 1b will initially consist of cohorts of up to 30 patients each in the following 3 tumor types with B7-H4 expression levels determined by IHC. There will be three FPA150 monotherapy cohorts and one FPA150 combination cohort at the MTD and/or RD:

Phase 1b Expansion Cohorts, Tumor Types, and Therapy

Cohort	Tumor Type	Therapy Type (Monotherapy or Combination)
1b1	Breast cancer	Monotherapy: FPA150
1b2	Ovarian cancer	Monotherapy: FPA150
1b3	Endometrial cancer	Monotherapy: FPA150
1bC1	Ovarian cancer	Combination: FPA150 with pembrolizumab

Based on emerging clinical and translational data from the study, cohorts for additional tumor types with FPA150 as monotherapy or in combination may be opened during the trial (not to exceed 30 patients in any individual cohort and not exceed 7 cohorts).

Dosing: FPA150 will be administered as a single agent in a 60-minute (± 5 minutes) IV infusion Q3W, on Day 1 of each 21-day cycle. The dose of FPA150 will be based on body weight at Cycle 1 Day 1 (C1D1). After Cycle 1, the FPA150 dose will be recalculated at each infusion visit only if the patient's weight has changed > 10% from Cycle 1, Day 1. There is no pre-specified maximum number of doses of FPA150 for patients receiving monotherapy.

Patients may continue receiving FPA150 monotherapy according to their study specified cohort/dose until Investigator-assessed clinical progressive disease, unacceptable toxicity, or the patient meets any of the other protocol-specified withdrawal criteria (refer to Section 7).

For combination cohorts, pembrolizumab will be administered at a dose of 200 mg IV over 30 minutes (± 5 minutes) starting on C1D1 after the completion of FPA150 infusion. Dosing for combination cohorts will be repeated on Day 1 of each 21-day cycle. Patients in the combination cohort may receive one or both drugs in combination according to their study specified cohort/dose until Investigator-assessed clinical progressive disease, unacceptable toxicity, or the patient meets any of the other protocol-specified withdrawal criteria (refer to Section 7). Patients treated with the combination would be able to receive pembrolizumab treatment for up to 24 months. If one of the two drugs has to be discontinued, patients may continue to receive the other drug alone.

Treatment beyond disease progression may be allowed in patients with progressive disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) if the benefit/risk assessment favors continued administration of study treatment (eg, if patients are continuing to experience clinical benefit as assessed by the Investigator, and tolerating treatment).

Study Duration: The duration of study for an individual patient includes screening (up to 28 days), treatment and an End of Treatment (EOT) follow-up period which will include visits at approximately 28 (±7) days and 100 (±7) days after the last dose. Since all patients are eligible to be treated until disease progression, the actual treatment duration for each individual patient will vary depending on the anticipated time to progression for their respective tumor type. Treatment beyond disease progression may be allowed in patients with initial RECIST v1.1 defined progressive disease if the benefit/risk assessment favors continued administration of study treatment (eg, patients are continuing to experience clinical benefit as assessed by the Investigator, and tolerating treatment).

In addition, patients enrolled in either the Phase 1b Monotherapy Dose Expansion or Phase 1b Combination Dose Expansion will be followed for survival for up to 2 years.

Number of Patients:

The total number of patients planned for this study is estimated to be up to 278.

Phase 1a will enroll up to 68 patients depending on incidence of DLTs; this includes 23 to 26 patients enrolled in the Phase 1a Monotherapy dose escalation portion, 6 to 22 patients enrolled in the Phase 1a Combination Safety Lead-in portion, and up to 20 patients that may receive FPA150 in the Phase 1a Monotherapy Dose Exploration portion.

Phase 1b will enroll up to 210 patients. Initially 3 tumor-type specific cohorts of up to 30 patients each will be enrolled to receive FPA150 Monotherapy in Phase 1b. One additional tumor-type specific cohort evaluating FPA150 in combination with pembrolizumab will be enrolled. No individual Phase 1b Dose Expansion cohort will exceed 30 patients and the total number of Phase 1b cohorts will not exceed 7. Up to 3 additional Phase 1b cohorts (up to 30 patients each) may be determined at a later time upon emerging data.

Eligibility Criteria

Inclusion Criteria: Phase 1a Inclusion Criteria (Monotherapy and Combination Safety Lead-in Therapy)

Patients enrolling into **Phase 1a** must meet ***all*** of the following inclusion criteria:

1) Histologically confirmed solid tumors except primary central nervous system (CNS) tumors.
2) Disease that is unresectable, locally advanced, or metastatic.
3) Able to understand and sign an Institutional Review Board / Independent Ethics Committee (IRB/IEC) approved Informed Consent Form (ICF) prior to any study-specific evaluation.
4) Patients should be refractory to or intolerant of existing therapy(ies) known to provide clinical benefit for their condition.
5) All patients must have at least one measurable lesion at baseline according to RECIST v1.1; tumor sites situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.
6) Adequate washout for prior anti-cancer therapy (ie, ≥ 5 half-lives or 4 weeks since the last dose, whichever is shorter).
7) Availability of archival tumor tissue and consent to providing archival tumor for retrospective biomarker analysis, or patient must undergo a fresh tumor biopsy during screening if archival tissue is not available (a biopsy is required for patients in the Phase 1a Dose Exploration portion).
8) Age ≥ 18 years at the time the ICF is signed.
9) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10) Life expectancy of at least 3 months in the opinion of the Investigator.
11) Willing and able to comply with all study procedures.
12) Prior radiotherapy must be completed at least 2 weeks before the first dose of study drug.

13) Prior radiopharmaceuticals (eg, strontium, samarium) must be completed at least 8 weeks before the first dose of study drug.

14) Prior surgery that requires general anesthesia must be completed at least 1 week before first dose of study drug administration. Surgery requiring local/ epidural anesthesia must be completed at least 72 hours before first dose of study drug administration. Patients must have recovered from any surgery.

15) Screening laboratory values must meet the following criteria:

    Hematologic:

    a. Neutrophils ≥ 1200 cells/ μL
    b. Platelets ≥ 75×10^3/ μL
    c. Hemoglobin (Hb) ≥ 9.0 g/dL

    Renal:

    d. Serum creatinine < 1.5 × ULN or creatinine clearance (CrCl) of ≥ 40 mL/ minute (using Cockcroft/Gault Formula)

$$\text{Female CrCl} \quad \frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})}$$

$$\text{Male CrCl} \quad \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

    Hepatic:

    e. AST and ALT ≤ 3× ULN (AST and ALT < 5× ULN in patients with liver metastases is permitted)
    f. Bilirubin < 1.5× ULN (except patients with Gilbert's syndrome, who must have total bilirubin < 3 mg/dL)

16) Negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test ≤ 96 hours prior to treatment on Cycle 1, Day 1 (women of childbearing potential only).

17) In sexually active patients (women of child bearing potential and males), willingness to use 2 effective methods of contraception, of which 1 must be a physical barrier method (eg condom, diaphragm, or cervical/vault cap) until 6 months after the last dose of FPA150. Other effective forms of contraception include:

    - Permanent sterilization (hysterectomy and/or bilateral oophorectomy, or bilateral tubal ligation with surgery, or vasectomy) at least 6 months prior to Screening
    - Women of childbearing potential who are on stable oral contraceptive therapy or intrauterine or implant device for at least 90 days prior to the study, or abstain from sexual intercourse as a way of living

50) For Phase 1a Combination Safety Lead-in Patients ONLY:

50.01) B7-H4 positive ovarian cancer

50.02) Histologically or cytologically confirmed diagnosis of recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma that is refractory to existing therapy(ies) known to provide clinical benefit

50.03) Progressive disease on or after at least two prior regimens of treatment including at least one platinum-containing regimen, *or* unable to tolerate additional chemotherapy

50.04) No prior therapy with an anti-PD1 or PD-L1-directed agent

Phase 1b (Monotherapy and Combination) Inclusion criteria:

Patients enrolling into **Phase 1b** must meet ***all*** of the following inclusion criteria:

18) All Inclusion Criteria for Phase 1a (Exception: Inclusion Criterion #1).

19) Positive for B7-H4 expression in an archival or fresh tumor sample as evaluated by an accompanying validated central laboratory IHC assay.

20) History of other malignancy is permitted provided it has been definitively treated with no evidence of recurrence within the past 2 years (Exception: Definitively treated non-melanoma skin cancer, lobular cancer in situ, and cervical cancer in situ within 2 years are permitted).

Additional Cohort-Specific Inclusion Criteria For Phase 1b (Monotherapy and Combination)

Cohort 1b1 Breast Cancer:

Triple Negative Breast Cancer (TNBC)

21.01) Histologically or cytologically confirmed metastatic TNBC

21.02) At least two prior lines of systemic chemotherapy with at least one being administered in the metastatic setting

HR+ Breast Cancer

21.03) Histologically or cytologically confirmed metastatic HR+ breast carcinoma

21.04) Patients must have received at least two prior lines of hormonal therapy

21.05) Patients must have received at least one prior line of systemic chemotherapy (in the adjuvant or metastatic setting)

Cohort 1b2 Ovarian Cancer:

22.01) Histologically or cytologically confirmed diagnosis of recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma that is refractory to existing therapy(ies) known to provide clinical benefit

22.02) Progressive disease on or after at least two prior regimens of treatment including at least one platinum-containing regimen, or unable to tolerate additional chemotherapy

Cohort 1b3 Endometrial Cancer:

23.01) Histologically or cytologically confirmed recurrent or persistent endometrial carcinoma that is refractory to curative or established treatments

23.02) Progressive disease on or after at least one prior regimen of systemic chemotherapy, or unable to tolerate systemic chemotherapy

Cohort 1bC1 Ovarian Cancer:

24.01) Histologically or cytologically confirmed diagnosis of recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma that is refractory to existing therapy(ies) known to provide clinical benefit

24.02) Progressive disease on or after at least two prior regimens of treatment including at least one platinum-containing regimen, *or* unable to tolerate additional chemotherapy

24.03) No prior therapy with an anti-PD1 or PD-L1-directed agent

No waivers will be granted for any of these inclusion criteria.

Eligibility Criteria

Exclusion Criteria (Phase 1a And Phase 1b)

Patients who meet ANY of the following criteria will be excluded from study entry:

1) Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent daily) must be discontinued at least 2 weeks before the first dose of study drug. Short courses of high dose steroids, continuous low dose (prednisone < 10 mg/day), inhaled, intranasal, intraocular, and joint injections of steroids are allowed.
2) Decreased cardiac function with New York Heart Association (NYHA) > Class 2 at screening.
3) Uncontrolled or significant heart disorder such as unstable angina

4) QT interval corrected for heart rate (QTc) per institutional guidelines > 450 msec for males or > 470 msec for females at screening.

5) History of anti-drug antibodies (ADAs), severe allergic, anaphylactic, or other infusion-related reaction to a previous biologic agent.

6) Known hypersensitivity to any component of FPA150 investigational product (IP) formulation and/or pembrolizumab.

7) Vaccines (eg, human papilloma virus [HPV] vaccine) within 4 weeks before the first dose of study drug. The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (ie, pneumovax, varicella, etc.) may be permitted, but must be discussed with the Sponsor's Medical Monitor and may require a study drug washout period prior to and after administration of the vaccine.

8) Current unresolved infection or history of chronic, active, clinically significant infection (viral, bacterial, fungal, or other) which, in the opinion of the Investigator, would preclude the patient from exposure to a biologic agent or may pose a risk to patient safety.

9) Patients with abnormal serum chemistry values that in the opinion of the Investigator are considered to be clinically significant. This includes patients who show clinical signs and symptoms related to their abnormal serum chemistry values, as well as patients whose serum chemistry values are asymptomatic, but clinically significant according to the Investigator (eg, hypokalemia or hyponatremia).

10) Any uncontrolled medical condition or psychiatric disorder which, in the opinion of the Investigator, would pose a risk to patient safety or interfere with study participation or interpretation of individual patient results.

11) Pregnant or breastfeeding.

12) Active, known, or suspected autoimmune disease. Patients with Type I diabetes mellitus, hypothyroidism requiring only hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger, are permitted to enroll.

13) Known history of testing positive for human immunodeficiency virus (HIV) 1 or 2 or known acquired immunodeficiency syndrome (AIDS).

14) Positive test for hepatitis B virus surface antigen (HBsAg) or detectable hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection.

15) Ongoing adverse effects from prior treatment > Grade 1 (with the exception of Grade 2 alopecia or peripheral neuropathy) based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

16) Symptomatic interstitial lung disease or inflammatory pneumonitis.
17) Untreated or active CNS or leptomeningeal metastases. Patients are eligible if metastases have been treated and patients are neurologically returned to baseline or neurologically stable (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks before the first dose of study drug.
18) Evidence of coagulopathy or bleeding diathesis. Patients receiving stable therapeutic doses of anti-coagulants will be permitted.
19) Transfusion of blood or platelets completed within 72 hours before the first dose of study drug.
20) Any uncontrolled inflammatory GI disease including Crohn's Disease and ulcerative colitis
21) For Cohort 1b1 only: Patients with HER2 positive disease

No waivers will be granted for any of these exclusion criteria.

Tests and Observations: Safety assessments include vital signs, body weight, physical exam, ECOG score, laboratory tests (hematology, serum chemistries, and urinalysis), electrocardiograms (ECGs), and monitoring of adverse events (AEs) and concomitant medications.

Archival tumor tissue (or a fresh tumor biopsy required during screening) will be collected for biomarker analysis to explore the relationship between baseline target levels, tumor immune phenotype and pharmacodynamic response, and is mandatory for all patients.

Pre- and on-treatment tumor tissue will be mandatory for all patients in Phase 1a Monotherapy Dose Exploration, Phase 1a Combination Safety Lead-in and a subset of patients (at least 15 patients per cohort of 30 patients) in Phase 1b Dose Expansion (monotherapy and in combination with pembrolizumab) for expanded pharmacodynamic analysis.

Efficacy assessments will consist of radiographic imaging that is performed every 6 weeks. Responses will be assessed according to RECIST v1.1.

Statistical Methods:

Sample Size Determination:

This study is designed as a dose escalation, dose exploration, and dose expansion study with objectives that include determination of an MTD and/or RD and assessments of the safety and tolerability of FPA150 alone and in combination with pembrolizumab. The sample size of this study was not determined by statistical considerations. The total number of patients planned for this study is estimated to be up to 278.

Phase 1a will enroll up to 68 patients. The 68 patients include 23 to 26 patients in the Phase 1a Monotherapy Dose Escalation cohorts, 6 to 22 patients in the Phase 1a Combination Safety Lead-in and up to 20 additional patients in the Phase 1a Dose Exploration (10 patients with B7-H4 high and 10 patients with low/no B7-H4 expression; refer to Section 4.1.3) to further evaluate safety, PK, pharmacodynamics, and clinical activity at one or more dose levels (to be conditional upon the dose level clearing DLT criteria).

For the objective of estimating the overall response rate (ORR) of FPA150 in Phase 1b Dose Expansion, it is estimated that up to 30 patients will be enrolled to ensure 25 evaluable patients in each cohort. The following table displays the corresponding 2-sided 90% confidence interval (CI) and the precision for the various observed response rates based on 25 evaluable patients. The sample size of 25 is chosen to ensure that it will allow to exclude 10% when the observed ORR is 24% or higher.

Phase 1b will enroll up to 210 patients with specific tumor types. Up to 30 patients are planned for each of three FPA150 Monotherapy expansion cohorts and the one FPA150 in combination with pembrolizumab cohort. Additional cohorts of up to 30 patients each may be enrolled (not to exceed 7 cohorts), based on emerging clinical and translational data.

Two-Sided 90% Confidence Intervals of the Observed Response Rates

Sample Size	Observed Response Rate	90% CI	Precision (longest one-sided CI length*)
25	5/25 (20%)	(8%, 38%)	18%
	6/25 (24%)	(11%, 42%)	18%
	7/25 (28%)	(14%, 46%)	18%
	8/25 (32%)	(17%, 50%)	18%
	9/25 (36%)	(20%, 54%)	18%
	10/25 (40%)	(24%, 58%)	18%

Abbreviations: CI = confidence interval.
*Distance from the observed response rate to the lower or upper CI boundary.

Safety Analysis:

Safety analyses will be performed separately within both phases of the study and for all patients combined. Data from all patients that receive at least one dose of FPA150 monotherapy or part of one dose of either pembrolizumab or FPA150 in the combination cohort will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, weight, ECGs, and concomitant medications/procedures will be tabulated and summarized. In addition, the incidence of DLTs in Phase 1a will be summarized.

Efficacy Analysis:

The ORR will be summarized with frequencies and percentages with 90% confidence interval (CI). The duration of response (DOR) for complete response (CR) and partial response (PR) patients for all treated patients will be summarized with descriptive statistics (N, arithmetic mean, standard deviation (SD), median, minimum, and maximum). The ORR, DOR, and PFS will be determined using RECIST v1.1. Kaplan-Meier methodology will be used to estimate median DOR and PFS and corresponding 95% CI. A 2-stage design will be used to determine the actual enrolled subjects. Sponsor will evaluate efficacy in phase 1b on an ongoing basis and may suspend or terminate enrollment in specific cohorts if <=1 response (CR or PR per RECIST 1.1) is observed in the first 16 patients enrolled in each cohort. . In this case, the probability of early termination is 0.81 with 0.05 responder rate for futility and 0.2 responder rate for efficacy.

Pharmacokinetic Analysis:

Individual and mean (±SD) serum FPA150 concentration-time data from monotherapy will be tabulated and plotted by dose level/cohort. PK parameters will be tabulated and summarized by dose level/cohort when appropriate and applicable. The impact of immunogenicity on FPA150 exposure will be assessed, tabulated, and summarized by dose level as data allow.

For cohorts of FPA150 in combination with pembrolizumab samples for PK analysis will be collected and held. Individual and mean (±SD) serum concentration-time data for FPA150 and pembrolizumab may be tabulated and plotted by dose level/cohort. PK parameters for the combination may be tabulated and summarized by dose level/cohort when appropriate and applicable.

Immunogenicity Analysis:

A baseline ADA-positive subject is defined as a subject who has an ADA positive sample at baseline. An ADA-positive subject is a subject with at least one ADA-positive sample relative to baseline after initiation of the treatment. The frequency distribution of baseline ADA-positive subjects and ADA-positive subjects after initiation of the treatment will be summarized for FPA150 and FPA150 in combination with pembrolizumab, respectively.

Pharmacodynamic Analysis:

A list of potential pharmacodynamic analyses is provided in Appendix 3. Selected pharmacodynamic biomarkers will be assessed for meaningful changes between pretreatment and on-treatment tumor and peripheral blood samples.

Schedule of Assessments:

The Schedule of Assessments – Phase 1a and Phase 1b is provided in Appendix 1.

The Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collection is provided in Appendix 2.

The List of Pharmacodynamic Analyses is provided in Appendix 3.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations and Definitions

Abbreviation	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine transaminase
ANC	absolute neutrophil count
APCs	antigen presenting cells
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under serum concentration-time curve
$AUC_{0\text{-}7days}$	AUC weekly exposure
β-hCG	β-human chorionic gonadotropin
B7-H4	transmembrane protein of the B7 family, also known as VTCN1
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	complete blood count
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatinine kinase
CL	clearance
C_{max}	maximum observed serum concentration/ maximum concentration
CNS	central nervous system
Combo	combination
CR	complete response
CRC	Cohort Review Committee
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTA	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	trough serum concentration at the end of a dose interval
DILI	Drug-induced Liver Injury
DLT	dose-limiting toxicity
[redacted]	
DOR	duration of response

Abbreviation	Definition
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme linked immunosorbent assay
EOT	End of Treatment
ER	estrogen receptor
eSAE Form	Electronic Serious Adverse Event Form
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded;
FcγIIIa	Fcγ receptor IIIa
GCP	Good Clinical Practices
GI	gastrointestinal
GLP	Good Laboratory Practices
GTT	Gamma-glutamyl transferase
Hb	Hemoglobin
HbcAb	hepatitis B core antibody
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HEK293	human embryonic 293 cells
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HPV	human papilloma virus
HR+	hormone receptor positive
HU IgG	human immunoglobulin G
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
[redacted]	
IgG	immunoglobulin G
IND	investigational new drug (application)
IFNγ	interferon gamma
IL	interleukin
INR	international normalized ratio
IP	investigational product (FPA150 or placebo)
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous

Abbreviation	Definition
LDH	lactate dehydrogenase
LTFU	long-term follow-up
MDSC	myeloid derived suppressor cells
MRI	magnetic resonance imaging
msIgG	mouse IgG
MTD	maximum tolerated dose
NCA	non-compartment(al) analysis
NCI	National Cancer Institute
NK	natural killer cells
NFAT-Res	Nuclear Factor Activated T cells responsive elements (RBL2H3-NFAT-Re cell line)
NOAEL	no-observed-adverse-effect level
NCA	non-compartmental analysis
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBMC(s)	peripheral blood mononuclear cell(s)
PD	progressive disease
PD1	programmed death 1
PD-L1	programmed death ligand 1
PD-L2	program death ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	once every 3 weeks
Q12W	once every 12 weeks
QTc	QT interval corrected for heart rate
RBC	red blood cell
RD	recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RNAseq	ribonucleic acid sequencing
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	terminal half-life
TB	tuberculosis

Abbreviation	Definition
TEAE	treatment-emergent adverse event
TK	toxicokinetics
TNBC	triple negative breast cancer/triple negative breast carcinoma
[redacted]	
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
V_{ss}	volume of distribution at steady state

2 Introduction

B7-H4 (a transmembrane protein of the B7 family also known as B7S1, B7x, or VTCN1) is a negative regulator of T cell function. It is expressed on antigen presenting cells (APCs) and binds to an unknown receptor on activated T cells. While there is limited expression in normal tissues, there is high level of aberrant expression on the cell surface of a number of tumor types, particularly breast and gynecological cancers. This high expression is correlated with poor outcomes in several tumors, including breast, ovarian, and endometrial carcinoma (He 2011, Fan 2014, Liu 2014, Miyatake 2007, Simon 2007, Kryczek 2007). FPA150 is a fully human Immunoglobulin G1 (IgG1) kappa monoclonal antibody targeting B7-H4 that is being developed for the treatment of malignancies that express high levels of B7-H4 protein.

Recent immuno-oncology approaches have focused on reprogramming the immune system to mount an effective response against tumors that have evaded the initial immune response. Specifically, blocking antibodies against both the programmed death 1/ programmed death ligand 1 (PD1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) axes have been effective in re-invigorating anti-tumor immunity, resulting in improved progression-free survival (PFS) and overall survival (OS) in some patients. However, responses have only been observed in select tumor types, and even in these tumor types only a subset of patients show durable responses to checkpoint inhibitors. Breast and gynecological tumors are examples of tumor types where checkpoint inhibitors have demonstrated limited activity thus far (Hamanishi 2015).

Similar to other checkpoint molecules, when tumor cells expressing B7-H4 encounter activated T cells expressing the B7-H4 counter receptor, anti-tumor immunity is dampened. One therapeutic strategy for increasing anti-tumor immunity is to inhibit the interaction between B7-H4 on tumor cells with its counter receptor expressed on activated T cells, thus restoring anti-tumor immunity. This strategy could be effective in tumor types in which PD-L1 is not expressed or expressed alongside B7-H4, and it could thus provide efficacy on its own or in combination with PD1 pathway inhibitors, respectively.

In addition to checkpoint inhibition, a potential therapeutic strategy for targeting tumors with high B7-H4 expression is to promote direct tumor cell killing via antibody-dependent cell-mediated cytotoxicity (ADCC). FPA150 is an IgG1 antibody that has been engineered with an Fc domain with high affinity for the Fcγ receptor IIIa (FcγIIIa) present on natural killer (NK) cells and macrophages. Antibody recognition of B7-H4 on tumor cells would lead to enhanced recruitment of NK cells and macrophages and enhanced ADCC.

FPA150 is a fully human IgG1 kappa monoclonal antibody specific for B7-H4 that has been designed to comprise both T cell immune checkpoint blockade and ADCC activity. FPA150 is being developed for the treatment of patients with solid tumors that express high levels of B7-H4.

2.1 Study Rationale

B7-H4 is highly expressed in a variety of solid tumors including breast carcinoma, ovarian carcinoma, endometrial carcinoma, and bladder carcinoma (He 2011, Fan 2014, Liu 2014, Miyatake 2007, Simon 2007, Kryczek 2007). [redacted] B7-H4 appears to be an ideal target for the development of a therapeutic antibody given its high expression pattern in solid tumors compared to normal tissue, negative correlation with patient outcomes, and its role as a T cell checkpoint. FPA150, a fully human IgG1 antibody targeting B7-H4 is being developed for testing in patients with advanced solid tumors types that express high levels of B7-H4. To the best of our knowledge, this is the first human trial of any molecule targeting this pathway. In vitro studies indicated that FPA150 may inhibit tumor growth through ADCC and T cell immune checkpoint inhibition. FPA150 demonstrated, dose-dependent anti-tumor activity in syngeneic mouse cancer models that were engineered to express the B7-H4 protein, both as monotherapy and in combination with an anti-PD1 antibody.

This study (Study Title: A Phase 1a/1b Study of FPA150, an Anti-B7-H4 Antibody, in Patients with Advanced Solid Tumors) is a Phase 1a/1b open-label, multicenter, study to evaluate the dosing, safety, tolerability, pharmacokinetic (PK), pharmacodynamics, and preliminary efficacy of FPA150 as a monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors. The study includes Phase 1a Dose Escalation, Phase 1a combination safety lead-in, Phase 1a Dose Exploration, and Phase 1b Dose Expansion for FPA150 monotherapy and in combination with pembrolizumab in patients with specific tumor types whose tumors overexpress B7-H4. After identification of the maximum tolerated dose (MTD) and/or recommended dose (RD), preliminary efficacy will be evaluated in planned expansion cohorts in specific tumor types based on the known levels of B7-H4 over-expression. The planned Phase 1b tumor types include advanced/ metastatic breast cancer, ovarian cancer, and endometrial cancer. Despite recent advances in immunotherapy, significant unmet need remains for these recurrent or metastatic tumor types that express B7-H4. Sequential single agent chemotherapy is common in metastatic breast carcinoma, particularly after failure of endocrine therapy (in hormone-receptor positive patients) and human epidermal growth factor receptor 2 (HER2)-directed therapy (in HER2-positive patients). Patients with triple negative breast cancer (TNBC) and patients that have failed targeted therapy have a particularly poor prognosis. Metastatic breast cancer patients that had failed at least one prior chemotherapy and subsequently received capecitabine had a median time to progression of 4.9 months and a median OS of 15.2 months (Fumoleau 2004). The median PFS and OS is generally consistent across multiple trials with other chemotherapeutic agents in heavily pretreated patients (Cortes 2011, Martin 2007). TNBC patients who had received at least one prior chemotherapy and treated with pembrolizumab, a PD1 immunotherapy, had a median PFS of 1.9 months and overall response rate (ORR) of less than

5% irrespective of PD-L1 status (Adams 2017). The combination of atezolizumab and nab-paclitaxel in frontline metastatic TNBC patients showed improvement in median OS compared to nab-paclitaxel alone. However the benefit was predominatly observed in PD-L1 positive patients (HR 0.62) compared to all patients (HR 0.84) suggesting low efficacy in PD-L1 negative patients (Schmid 2018). Patients with recurrent or metastatic endometrial carcinoma who experience progressive disease on frontline chemotherapy have a poor prognosis with median OS of less than 1 year. For example, patients treated with the anti-vascular endothelial growth factor (VEGF)-A monoclonal antibody bevacizumab after failure of 1 or 2 lines of chemotherapy reported a median PFS of 4.2 months and median OS of 10.5 months (Aghajanian 2011). Patients with early platinum-refractory, recurrent or metastatic ovarian cancer have a median OS of 13 to 16 months and median PFS of 3 to 6 months with single agent chemotherapy with or without bevacizumab (Pujade-Lauraine 2014). Median PFS and OS significantly diminish in patients with multiply relapsed disease (Hanker 2012). Immunotherapy has demonstrated limited activity to date in this tumor type (Hamanishi 2015). Therefore, significant unmet need still exists in these tumor types particularly in the metastatic setting after failure of standard frontline therapy.

2.2 Background

2.2.1 50, an Anti-B7-H4 Antibody

FPA150 is a fully human IgG1 kappa monoclonal antibody targeting B7-H4 that is being developed for the treatment of malignancies that express high levels of B7-H4. FPA150 is an antibody designed to recognize B7-H4 when expressed on surface membrane of tumors. B7-H4 can be highly expressed in certain types of tumor without known genetic aberrations. FPA150 has been glycoengineered for high affinity binding to the FcγRIIIa receptor and can potentially induce ADCC against tumor cells with high B7-H4 expression. FPA150 may also block B7-H4-mediated inhibition of T cell proliferation and interferon gamma (IFNγ) production. Therefore, FPA150 has the potential to demonstrate anti-tumor immune responses in patients with B7-H4-high tumors by providing both ADCC and T cell immune checkpoint blockade activities.

2.2.2 Nonclinical Pharmacology Studies with FPA150

FPA150 has 2 potential mechanisms of action: It acts as a T cell checkpoint inhibitor by blocking B7-H4 inhibition of T cell proliferation and IFNγ production, and it induces ADCC against tumor cells. Both of these mechanisms were explored in vitro and in vivo.

2.2.2.1 In Vitro Biology

Both T cell immune checkpoint blockade activity and ADCC of FPA150 were determined by in vitro assays as summarized below.

The ability of FPA150 to overcome B7-H4-mediated inhibition of IFNγ production was determined using a co-culture system. There were 2 cell types employed in the co-culture system: 1) human embryonic 293 cells (HEK293) cells (which were engineered to be artificial antigen presenting cells, by expressing both a single chain version of the CD3 activator antibody OKT3 and B7-H4), and 2) primary human T cells. In the co-culture system, the HEK293 cells were incubated with the primary human T cells and treated with FPA150. Upon co-culture, IFNγ was significantly increased in the presence of FPA150 in comparison to human IgG1 isotype-treated cells, suggesting that FPA150 functionally blocks B7-H4-mediated suppression of IFNγ production from primary human T cells and that FPA150 may act as a T cell checkpoint inhibitor in patients.

In vitro, ADCC was demonstrated using IL-2 activated peripheral blood mononuclear cells (PBMCs) as the effector cells and SKBR-3 human breast cancer cells, which endogenously express B7-H4, as the target cells. FPA150 treatment led to a dose-dependent increase in ADCC, and this effect was > 61 fold more potent than ADCC performed with a non-glycoengineered version of FPA150. To determine the relationship between B7-H4 receptor cell surface density and FPA150-mediated ADCC activity, Jurkat cells transduced to expresses human FcγRIIIA and an Nuclear Factor Activated T cells responsive elements (NFAT-Res) luciferase-reporter, were co-cultured with target cells endogenously expressing varying levels B7-H4 on the cell surface (~15,000 to ~340,000 molecules/ cell). Maximal ADCC activity correlated with the number of receptors, increasing almost 5-fold from the lowest expressing cells to the highest expressing cells, suggesting that the strongest ADCC activity may be seen in patients whose tumors express the highest levels of B7-H4.

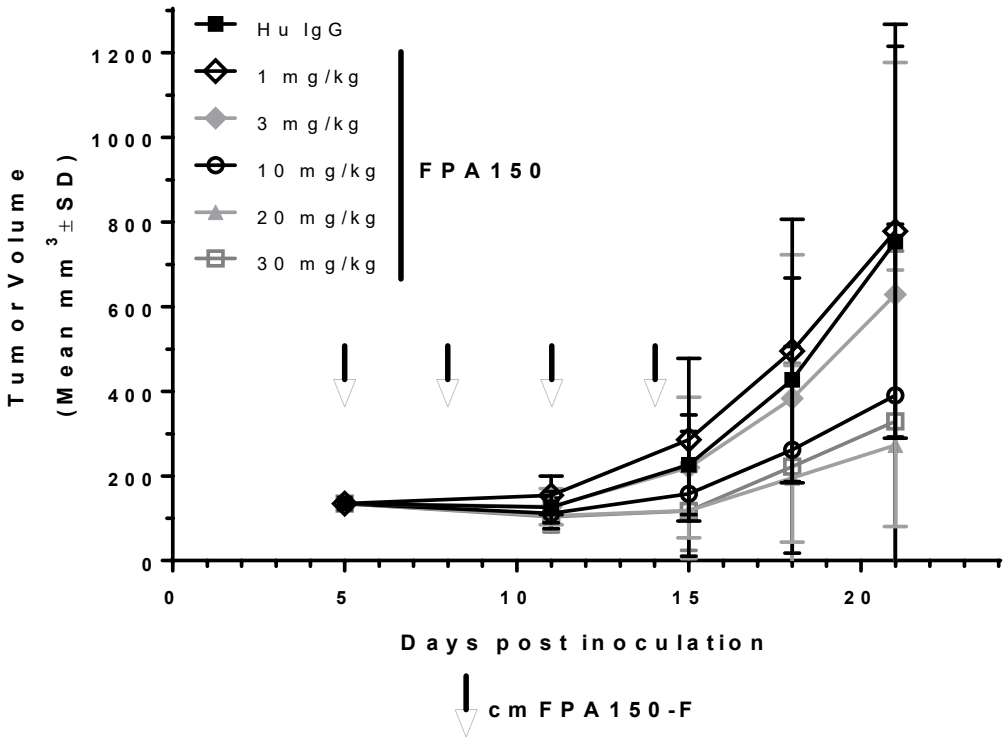
2.2.2.2 In Vivo Pharmacology

Unlike human tumors, mouse models do not endogenously express high levels of B7-H4 protein. To test FPA150 in mice, syngeneic mouse cancer models using murine tumor cell lines engineered to express B7-H4 protein were used. These cancer models express moderate to high levels of the B7-H4 protein on their cell surface and demonstrate significant tumor growth suppression upon treatment with FPA150, though because they are engineered models they may not be as sensitive to FPA150 as humans. A dose response study (twice weekly dosing) was performed with a sensitive model, a mouse colon cancer cell line, CT26, which grows in immune competent mice. Propagating this model in a wild-type mouse allows for the presence of intact tumor-immune interactions, thereby allowing the assessment of FPA150 against the tumor cells directly and in modulating the host immune system to more potently suppress tumor growth.

The engineered CT26 model expressing B7-H4 protein demonstrated significant dose-dependent tumor growth inhibition in 5 dose levels in the dose range from 1 to 30 mg/kg (Figure 1). The most common impact in individual animals was tumor growth inhibition. However, FPA150 treatment did result in complete tumor regression in 7 of 15 mice in the 30 mg/kg group, 6 of 15 mice in the 20 mg/kg group, and 5 of 15 mice in the 10 mg/kg group.

FPA150 dosed at 3 mg/kg or lower elicited minimal anti-tumor activity compared to the negative control treatment group (human IgG).

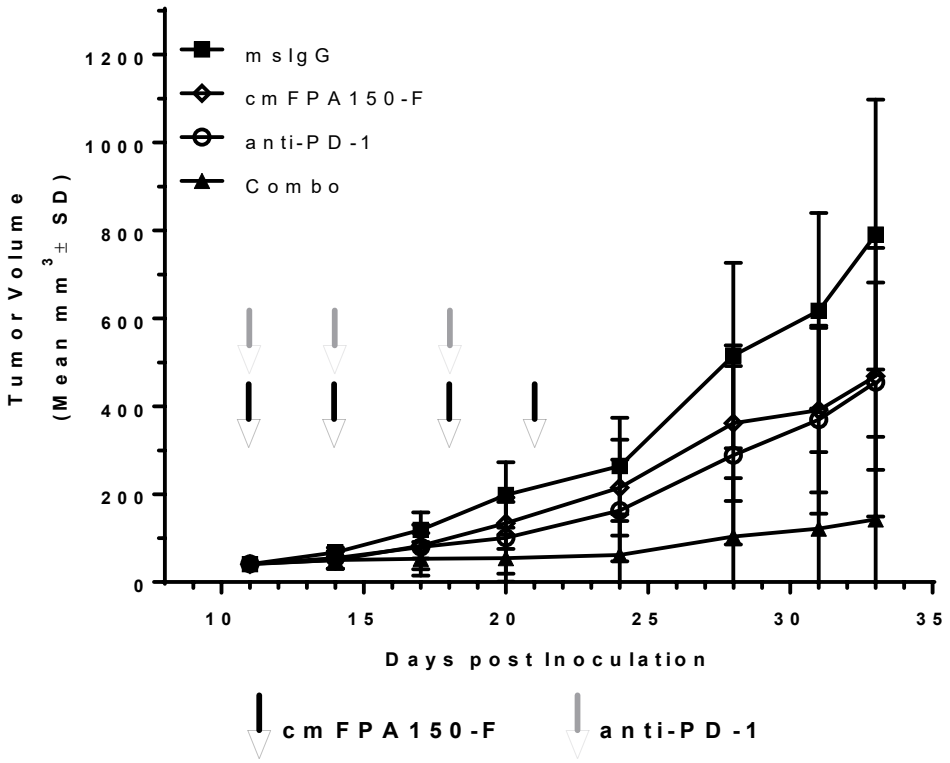
Figure 1: Tumor Growth Inhibition in CT26 Engineered to Express B7-H4 Protein



Abbreviations: B7-H4 = transmembrane protein of the B7 family; Hu IgG = human immunoglobulin G; SD = standard deviation.

In addition, the efficacy of cmFPA150-F (anti-B7-H4 mouse IgG [msIgG]2a, fucosylated) and anti-PD1 antibody was examined as single agent and in combination (Figure 2). In the tumor model that was utilized, human B7-H4 was engineered to be expressed on the tumor cell surface of the mouse breast cancer cell line, 4T1. The 4T1 cell line, which arose from and is propagated in immune competent mice, is known to be less sensitive to immune modulatory therapeutics. This study examined the anti-tumor efficacy of cmFPA150-F, of mouse anti-PD1 antibody, or of the combination (cmFPA150-F + anti-PD1). Monotherapy with either anti-B7-H4 antibody or anti-PD1 demonstrated similar, significant tumor growth reduction. Importantly, the combination of cmFPA150-F and anti-PD1 was significantly more potent than either monotherapy, with a significantly greater reduction in mean tumor volume as well as 6 of 12 mice demonstrating complete tumor regression, compared to 1 of 12 mice for anti-PD1, and 0 of 12 for cmFPA150-F.

Figure 2: Combination of anti-B7-H4 and anti-Programmed Death 1 in 4T1 Engineered to Express B7-H4 Protein



Abbreviations: B7-H4 = transmembrane protein of the B7 family; Combo = combination; IgG = immunoglobulin G; msIgG = mouse IgG; PD1 = programmed death 1; SD = standard deviation.

Mechanistically, FPA150 was developed to bind to B7-H4 on the tumor cell surface and elicit anti-tumor efficacy via ADCC and T cell checkpoint blockade. Although these tumor models are engrafted in immune competent mice, the mouse Fcγ receptors (the receptors on immune cells required for ADCC) have lower affinity for human antibodies than the human Fcγ receptors.

2.2.3 Nonclinical Pharmacokinetics

The PK/ toxicokinetics (TK) of FPA150 were evaluated following a single and/or repeat weekly intravenous (IV) administration in mice, rats, and cynomolgus monkeys. PK characteristics observed were consistent across all studies and similar to other mAbs in general. In all species, FPA150 demonstrated linear PK and a dose proportional increase in exposure (area under serum concentration-time curve [AUC]) with increasing dose. There was an approximate 2-fold increase in weekly exposure ($AUC_{0\text{-}7days}$) following 4 weekly administrations of FPA150 between first and last dose, however, steady state was not achieved. No substantial gender differences were apparent in the serum FPA150

concentration-time profiles. In the cynomolgus monkey (across 2 different studies), half-life estimated from recovery animals only ranged from approximately 8.8 days to 12 days with doses levels ranging from 1 to 100 mg/kg. The estimated half-life in rat following a single IV infusion administration at 40 mg/kg was approximately 13.2 days. The PK characteristics of FPA150 in animals support IV infusion in humans with a once every 3 week (Q3W) dose regimen.

2.2.4 Toxicology

Toxicology studies with FPA150 have been performed in rat and cynomolgus monkey. The studies performed have included a pilot single dose PK/tolerability study in rats, a pilot repeat-dose toxicity study in cynomolgus monkeys and investigational new drug (IND)-enabling Good Laboratory Practices (GLP) repeat-dose toxicity studies in rats and cynomolgus monkeys, as well as a GLP tissue cross-reactivity study with human, rat, and cynomolgus monkey tissues.

In the single dose pilot tolerability study in rats, the animals received doses up to 40 mg/kg as a 30-minute IV infusion. FPA150 had no effect on clinical observations, body weights, food consumption, clinical pathology (serum chemistry or hematology) assessments, gross observations, organ weights, or histopathology assessment.

In the pilot repeat-dose toxicology study cynomolgus monkeys received 4 weekly IV doses of FPA150 up to 100 mg/kg as a 30-minute IV infusion. All doses were well tolerated by cynomolgus monkeys. There were no test article-related unscheduled mortalities or changes attributed to administration of FPA150 during assessment of clinical observations, body weights, clinical pathology, necropsy, organ weight, or histopathology parameters.

In the repeat-dose GLP toxicology studies, FPA150 was administered by IV at dose levels of 1, 10, or 100 mg/kg/dose to both rats and cynomolgus monkeys for 4 weekly doses. Reversibility of toxicity was evaluated during a 6-week recovery period following the final administration. Parameters for evaluation included ophthalmic examinations, clinical observations, body temperatures, body weights, food consumption, hematology, coagulation, clinical chemistry, urinalysis, organ weights, macroscopic, and microscopic evaluation. In the cynomolgus monkey study, electrocardiograms (ECGs) were also assessed to evaluate potential cardiac toxicities.

During the evaluation of the GLP rat study, FPA150 was generally well tolerated and there were no toxic effects attributed to FPA150. The no-observed-adverse-effect level (NOAEL) in Sprague Dawley rats was considered to be 100 mg/kg/dose.

In the GLP cynomolgus monkey study, FPA150 was generally well tolerated and there were no adverse events (AEs) attributed to FPA150 observed in any of the parameters evaluated. During the study, a higher incidence of diarrhea was observed at the end of the dosing phase in the higher dose groups. Due to the higher incidence of affected animals in the mid and high

dose, as well as onset in the later phase of the dosing period, a relationship with FPA150 exposure is possible. There were no microscopic changes in the intestinal tract in animals treated with FPA150, including animals with diarrhea; therefore, this finding was considered non-adverse but possibly related to the test article. There was a single mortality in the study. One animal in the mid dose recovery group was found dead on Study Day 35, 14 days post the last dose. Clinical observations, macroscopic and microscopic evaluation were consistent with the diagnosis of intestinal torsion. Intestinal torsions occasionally occur in cynomolgus monkeys, and this was considered a spontaneous condition in this animal and not test article-related. The NOAEL in cynomolgus monkey was considered to be 100 mg/kg/dose.

In addition to in vivo toxicology studies, a GLP-compliant tissue cross reactivity study has been performed to compare the binding of FPA150 to a panel of 36 tissues from rat, cynomolgus monkey, and human. The result showed that the binding pattern of FPA150 was similar among the 3 species and limited to the mammary gland epithelium.

In summary FPA150 was well tolerated in cynomolgus monkey and rat. The NOAEL in both species was considered to be 100 mg/kg/dose, the highest dose tested when given as 4 weekly IV doses.

2.2.5 Clinical Experience with FPA150

This is a first-in-human clinical study and there is limited clinical experience with FPA150.

2.2.5.1 Study Population:

25 patients with a variety of solid tumors have been enrolled in clinical trial FPA150-001 as of the data cut off date December 31, 2018: 19 patients unselected for B7-H4 expression in Phase 1a Dose Escalation; 6 patients with B7-H4+ solid tumors in Phase 1a Dose Exploration. One patient in dose escalation was dosed but not included in the safety summary, so the safety data is based on 24 patients.

2.2.5.2 Patient Characteristics

The 24 patients had a median age of 67.5 years (range 40, 84), 18 of 24 patients were female and 23 were white. Most patients enrolled on the study had Stage III or IV cancer (n=22) with ovarian carcinoma being the most common tumor type (n=9). Other common tumors included gallbladder/cholangiocarcinoma (n=4) and leiomyosarcoma (n=3).

2.2.5.3 Study Drug Exposure

During Dose Escalation 18 patients received FPA150 across a range of dose levels from 0.01 mg/kg to 20 mg/kg. Two patients received FPA150 at the highest 20 mg/kg dose level prior to the data cutoff date while 2 additional patients have subsequently received FPA150 at that dose level and have completed their dose-limiting toxicity (DLT)) review period. Dose Exploration patients received FPA150 at 3 mg/kg (n=5) and 10 mg/kg (n=1). Median number of doses in phase 1a (dose escalation and exploration) was 3 (range 1,11) and median

exposure was 63 days (range 21,233). No dose reductions were required, and the median dose intensity was 100%.

2.2.5.4 Dose Limiting Toxicities:

No dose limiting toxicities (DLTs) have been identified in patients enrolled in the dose escalation cohorts in FPA150-001 at any dose level up to 20 mg/kg..

2.2.5.5 Adverse Events:

As of 31 Dec 2018, 20 of 24 patients enrolled on FPA150-001 have experienced at least one treatment emergent adverse event (TEAE). The most frequently reported TEAEs include fatigue (n=6) followed by nausea, diarrhea, abdominal pain, decreased appetite, and decreased albumin (n=4 patients):

Eight of 24 patients enrolled on FPA150-001 experienced at least one Grade 3-4 TEAEs with abdominal pain reported in 2 patients being the most common. . One patient with cholangiocarcinoma had a Grade 5 AE of acute kidney injury, which was assessed by the investigator as unrelated to study drug and occurred in the setting t of disease progression.

Treatment related AEs (TRAEs) as determined by the investigator were reported in 14 of 24 patients, most of which were grades 1 and 2. Diarrhea and fatigue were the most common TRAEs reported in 4 patients each. One Grade 3 TRAE of hypertension was reported among 24 patients.

2.2.5.6 Serious Adverse Events

Three of 24 patients enrolled on FPA150-001 have experienced at least 1 serious adverse event (SAE). These events included a grade 3 intestinal obstruction, a grade 3 hypokalemia and a grade 5 acute kidney injury.

None of the SAEs in patients treated with FPA150-001 were assessed as related to treatment. One of the 3 patients with SAEs was treated at a dose of 0.01 mg/kg, one at 1 mg/kg and one at 10 mg/kg.

2.2.5.7 Deaths

Study FPA150-001 accrued a patient population with advanced solid tumors for which standard curative or palliative measures did not exist or were no longer effective. As of 31 December 2018, one on study death was reported in study FPA150-001. The patient treated at 10 mg/kg died of acute kidney injury (not related to FPA150) in the setting of underlying disease progression.

2.2.6 Pembrolizumab Background

The PD-1 ligand-receptor interaction is one of the most signficant immune checkpoint pathways sequestered by tumor cells to escape T-cell mediated immune surveillance.

Pembrolizumab is a humanized IgG4 mAb with specificity of binding to the programmed cell death 1 (PD1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Keytruda® (pembrolizumab) is indicated for the treatment of patients with non-small cell lung cancer, melanoma, urothelial carcinoma, and head and neck cancer. Refer to the Keytruda® (pembrolizumab) Prescribing Information (Keytruda® USPI) for additional information.

2.2.7 Rationale for Combination with Pembrolizumab

FPA150 has two potential mechanisms of action: it acts as a T cell checkpoint inhibitor by blocking B7-H4 inhibition of T cell proliferation and IFNγ production, and it induces ADCC against tumor cells. As previously discussed, administration of FPA150 to patients whose tumors do not express PD1 may prove to be an effective strategy. Additionally, there is the possibility that the administration of two checkpoint inhibitors would be synergistic. This hypothesis was explored on an in vivo model examining the anti-tumor efficacy of cmFPA150-F (a mouse surrogate of FPA150), of mouse anti-PD1 antibody, or of the combination (cmFPA150-F + anti-PD1). Monotherapy with either anti-B7-H4 antibody or anti-PD1 demonstrated similar, significant tumor growth reduction. Importantly, the combination of cmFPA150-F and anti-PD1 was significantly more potent than either monotherapy, with a significantly greater reduction in mean tumor volume as well as 6 of 12 mice demonstrating complete tumor regression, compared to 1 of 12 mice for anti-PD1, and 0 of 12 for cmFPA150-F (Figure 2). These findings suggest that exploring the combination may be a viable strategy in a variety of tumors. In tumors where anti-PD1 agents have demonstrated efficacy and that co-express B7-H4 and PD1, administering the combination of FPA150 and an anti-PD1 antibody may further enhance the antitumor activity of anti-PD1 agents (e.g. TNBC; (Schmid 2018)). In addition, some of the tumors that are known to express B7-H4 at a high level [eg ovarian, ER+ breast and micro-satellite stable (MSS) endometrial cancer] have demonstrated limited responses to anti-PD1 agents so far and the combination may lead to a potential role for immune-oncology therapies in these tumors.

2.3 Benefit/ Risk Assessment

This overview is not intended to replace the complete information presented in the FPA150 IB. Please consult the IB for more detailed information.

This first in human study is currently ongoing to evaluate the dosing, safety, tolerability, PK and clinical activity of FPA150. The phase 1a dose escalation included an accelerated titration design followed by a standard 3+3 design across 8 dose levels. The starting dose of 0.01 mg/kg was selected based on MABEL calculations. While clinical experience with FPA150 is currently limited, data from 25 patients dosed to date show that FPA150 monotherapy is well tolerated at doses as high as 20 mg/kg with no DLTs. There have been no reports of FPA150-related grade 4 AEs or SAEs (including deaths).

FPA150 also demonstrated a favorable safety profile in animal studies with no toxic effects attributed to FPA150 being observed following 4 weekly doses. As noted in Section 2.2.4, in the GLP cynomolgus monkey study, a higher incidence of diarrhea was observed at the end of the dosing phase in the higher dose groups. Although the higher incidence of diarrhea in the cynomolgus monkey study was not considered adverse, and was without microscopic correlates, monitoring of patients in study FPA150-001 for diarrhea/enteritis will be conducted.

The proposed expansion cohorts in Phase 1b after determination of the MTD and/or RD have been rationally selected based on the presence of B7-H4 expression across various tumor types. Preclinical data support specific targeting of tumors with high B7-H4 expression. Despite recent advances in targeted and immunotherapy, significant unmet need remains for the tumor types being proposed for evaluation in Phase 1b such as advanced breast cancer, ovarian cancer, and endometrial cancer. Targeting B7-H4 with FPA150, which possesses dual T cell checkpoint blockade and ADCC activity, is a viable approach in these patients with limited treatment alternatives.

A strong mechanistic rationale supported by preclinical data exists for combining FPA150 with pembrolizumab (Section 2.2.7). Given the underlying mechanisms of action of both drugs (ie, immune checkpoint blockade) there is a potential to observe increased incidence of immune-mediated AEs with the combination. However, it should be noted that in the 25 patients treated with FPA150 monotherapy there have not been any reports of immune-mediated toxicities.

As this is the first clinical study of FPA150, the safety profile in humans has not yet been established, and unanticipated side effects may occur. Close monitoring of safety is planned in this study in order to limit the risk to patients.

3 Objectives and Endpoints

3.1 Phase 1a Objectives and Endpoints

The objectives and endpoints for Phase 1a of the study are summarized in Table 1. Additional information regarding study assessments and procedures is provided in Section 8; statistical analysis information is provided in Section 9.

Table 1: Objectives and Endpoints: Phase 1a

OBJECTIVES	ENDPOINTS
PRIMARY - SAFETY	
FPA150 Monotherapy • To evaluate the safety and tolerability of FPA150 as monotherapy in patients with advanced solid tumors treated at the MTD and/or RD • To determine the MTD and/or RD of FPA150	**FPA150 Monotherapy** • The incidence of Grade 3 and Grade 4 AEs and clinical laboratory abnormalities defined as DLTs • The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
FPA150 in Combination with Pembrolizumab • To evaluate the safety and tolerability of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer • To determine the MTD and/or RD of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer	**FPA150 in Combination with Pembrolizumab** • The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities • The incidence of Grade 3 and Grade 4 AEs and clinical laboratory abnormalities defined as DLTs
SECONDARY - PHARMACOKINETIC	
FPA150 Monotherapy • To characterize the PK profile of FPA150 as monotherapy in patients with advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • AUC • Maximum serum concentration (C_{max}) • Trough serum concentration at the end of a dose interval (C_{trough}) • Clearance (CL) • Termina half-life ($t_{1/2}$) • Volume of distribution at steady state (V_{ss}) • Other parameters, such as dose proportionality, accumulation ratio, attainment of steady state, will also be calculated if the data are available
SECONDARY - IMMUNOGENICITY	
FPA150 Monotherapy • To characterize the immunogenicity of FPA150 as monotherapy in patients with advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • Immune response (ADAs) to FPA150

OBJECTIVES	ENDPOINTS
EXPLORATORY - EFFICACY	
FPA150 Monotherapy • To evaluate the clinical benefit of FPA150 as monotherapy	**FPA150 Monotherapy** • ORR defined as the total number of patients with confirmed responses of either CR or PR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 divided by the total number of patients who are evaluable for a response • Duration of response (DOR), defined as the time from onset of response (CR or PR) that is subsequently confirmed to the first observation of progressive disease or death due to any cause • Progression free-survival (PFS), defined as the time from the patient's first dose to the first observation of progressive disease or death
FPA150 in Combination with Pembrolizumab • To evaluate the clinical benefit of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer	**FPA150 in Combination with Pembrolizumab** • ORR, defined as the total number of patients with confirmed responses of either CR or PR per RECIST v1.1 divided by the total number of patients who are evaluable for a response • DOR, defined as the time from onset of response (CR or PR) that is subsequently confirmed to the first observation of progressive disease or death due to any cause • PFS, defined as the time from a patient's first dose to the first observation of progressive disease or death due to any cause.
EXPLORATORY - Pharmacokinetics	
FPA150 in Combination with Pembrolizumab • To characterize the pharmacokinetic (PK) profile of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer	**FPA150 in Combination with Pembrolizumab** The following PK parameters will be derived from concentration-time data for FPA150 in combination with pembrolizumab when appropriate and applicable: • AUC • C_{max} • C_{trough} • Clearance (CL) • $t_{1/2}$ • V_{ss} • Other parameters, such as dose proportionality, accumulation ratio, attainment of steady state, will also be calculated if the data are available for FPA150 • C_{max} and C_{trough} as well as accumulation ratio of C_{max} and C_{trough} for pembrolizumab may be calculated if the data are available

OBJECTIVES	ENDPOINTS
EXPLORATORY - Immunogenicity	
FPA150 in Combination with Pembrolizumab • To characterize the immunogenicity of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer	**FPA150 in Combination with Pembrolizumab** • Immune response (ADAs) to FPA150 • Immune response (ADAs) to pembrolizumab
EXPLORATORY – Pharmacodynamic Biomarkers	
FPA150 Monotherapy • To characterize the pharmacodynamic profile of FPA150 through an analysis of the immune cell infiltrate in pre-treatment and on-treatment tumor biopsies • To characterize the pharmacodynamic profile of FPA150 through evaluation of exploratory biomarkers in peripheral blood samples	**FPA150 Monotherapy** • Changes in markers of tumor immune infiltrate • [redacted] • Changes in selected pharmacodynamic biomarkers in peripheral blood samples
FPA150 in Combination with Pembrolizumab • To characterize the pharmacodynamic profile of FPA150 in combination with pembrolizumab through an analysis of the immune cell infiltrate in pre-treatment and on-treatment tumor biopsies • To characterize the pharmacodynamic profile of FPA150 in combination with pembrolizumab through evaluation of exploratory biomarkers in peripheral blood samples	**FPA150 in Combination with Pembrolizumab** • Changes in markers of tumor immune infiltrate • [redacted] • Changes in selected additional pharmacodynamic markers in peripheral blood in patients treated with FPA150 in combination with pembrolizumab

3.2 Phase 1b Objectives and Endpoints

The objectives and endpoints for Phase 1b of the study are summarized in Table 2. Additional information regarding study assessments and procedures is provided in Section 8; statistical analysis information is provided in Section 9.

Table 2: Objectives and Endpoints: Phase 1b

OBJECTIVES	ENDPOINTS
PRIMARY - SAFETY	
FPA150 Monotherapy • To evaluate the safety and tolerability of FPA150 as monotherapy in patients with B7-H4+ advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities

OBJECTIVES	ENDPOINTS
FPA150 Combined with Pembrolizumab • To evaluate the safety and tolerability of FPA150 in combination with pembrolizumab in selected patients with B7-H4+ ovarian cancer treated at the MTD and/or RD	**FPA150 Combined with Pembrolizumab** • The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities in patients treated with FPA150 in combination with pembrolizumab
SECONDARY - EFFICACY	
FPA150 Monotherapy • To evaluate the clinical benefit of FPA150 as monotherapy in patients with B7-H4+ advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • ORR, defined as the total number of patients with confirmed responses of either CR or PR per RECIST v1.1 divided by the total number of patients who are evaluable for a response • DOR, defined as the time from onset of response (CR or PR) that is subsequently confirmed to the first observation of progressive disease or death due to any cause • PFS, defined as the time from the patient's first dose to the first observation of progressive disease or death due to any cause)
FPA150 in Combination with Pembrolizumab • To evaluate the clinical benefit of FPA150 in combination with pembrolizumab in patients with B7-H4 + ovarian cancer treated at the MTD and/or RD	**FPA150 in Combination with Pembrolizumab** • ORR, defined as the total number of patients with confirmed responses of either CR or PR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 divided by the total number of patients who are evaluable for a response to FPA 150 combined with pembrolizumab • DOR, defined as the time from onset of response (CR or PR) that is subsequently confirmed to the first observation of progressive disease or death due to any cause to FPA150 combined with pembrolizumab • PFS, defined as the time from the patient's first dose to the first observation of progressive disease or death due to any cause to FPA150 combined with pembrolizumab
SECONDARY - PHARMACOKINETICS	
FPA150 Monotherapy • To characterize the PK profile of FPA150 as monotherapy in patients with B7-H4+ advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • AUC • C_{max} • C_{trough} • CL • $t_{1/2}$ • V_{ss} • Other parameters, such as accumulation ratio, attainment of steady state, will also be calculated if the data are available

OBJECTIVES	ENDPOINTS
SECONDARY - IMMUNOGENICITY	
FPA150 Monotherapy • To characterize the immunogenicity of FPA150 as monotherapy in patients with B7-H4+ advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • Immune response (ADAs) to FPA150
EXPLORATORY - PHARMACOKINETICS	
FPA150 in Combination with Pembrolizumab • To characterize the PK profile of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer treated at the MTD and/or RD • To characterize the PK profile of pembrolizimab in combination with FPA150 in patients with ovarian cancer	**FPA150 in Combination with Pembrolizumab** The following PK parameters will be derived from concentration-time data for FPA150 in combination with pembrolizumab when appropriate and applicable: • AUC • C_{max} • C_{trough} • CL • $t_{1/2}$ • V_{ss} • Other parameters, such as accumulation ratio, attainment of steady state, will also be calculated if the data are available for patients treated with FPA150 combined with pembrolizumab • C_{max} and C_{trough} as well as accumulation ratio of C_{max} and C_{trough} for pembrolizumab may be calculated if the data are available
EXPLORATORY - IMMUNOGENICITY	
FPA150 in Combination with Pembrolizumab • To characterize the immunogenicity of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer treated at the MTD and/or RD • To characterize the immunogenicity of pembrolizumab in combination with FPT150 patients with with B7-H4+ ovarian cancer treated at the MTD and/or RD	**FPA150 in Combination with Pembrolizumab** • Immune response (ADAs) to FPA150 • Immune response (ADAs) to pembrolizumab
EXPLORATORY – PHARMACODYNAMIC BIOMARKERS	
FPA150 Monotherapy • To characterize the pharmacodynamic profile of FPA150 through an analysis of the immune cell infiltrate in pre-treatment and on-treatment tumor biopsies • To characterize the pharmacodynamic profile of FPA150 through evaluation of exploratory biomarkers in peripheral blood samples	**FPA150 Monotherapy** • Changes in markers of tumor immune infiltrate • [redacted] • Changes in selected pharmacodynamic biomarkers in peripheral blood samples

OBJECTIVES	ENDPOINTS
FPA150 in Combination with Pembrolizumab • To characterize the pharmacodynamic profile of FPA150 in combination with pembrolizumab through an analysis of the immune cell infiltrate in pre-treatment and on-treatment tumor biopsies • To characterize the pharmacodynamic profile of FP150 in combination with pembroliumab through evaluation of exploratory biomarkers in peripheral blood samples	**FPA150 in Combination with Pembrolizumab** • Changes in markers of tumor immune infiltrate, • [redacted] • Changes in selected additional pharmacodynamic biomarkers in peripheral blood samples for patients treated with FPA150 in combination with pembrolizumab
EXPLORATORY - EFFICACY	
FPA150 Monotherapy • To evaluate the clinical benefit of FPA150 as monotherapy in patients with B7-H4+ advanced solid tumors treated at the MTD and/or RD	**FPA150 Monotherapy** • OS, defined as time from patient's first dose to death due to any cause
FPA150 in Combination with Pembrolizumab • To evaluate the clinical benefit of FPA150 in combination with pembrolizumab in patients with B7-H4+ ovarian cancer treated at the MTD and/or RD	**FPA150 in Combination with Pembrolizumab** • OS, defined as time from patient's first dose to death due to any cause

4 Study Design

4.1 Overall Design

The Study Schema is provided below in Figure 3.

This is a Phase 1a/1b open-label, multicenter study to evaluate the dosing, safety, tolerability, PK, pharmacodynamics, and preliminary efficacy of FPA150 as monotherapy and in combination with pembrolizumab, an anti-PD1 antibody, in patients with advanced solid tumors.

There will be approximately 6 to 10 study centers participating in Phase 1a in the United States and approximately 35 study centers participating in Phase 1b. Phase 1a and the combination cohorts in Phase 1b will be conducted in the United States only. Phase 1b monotherapy will be conducted globally.

This study includes a Phase 1a FPA150 Monotherapy Dose Escalation, Phase 1a Monotherapy Dose Exploration, Phase 1a combination Safety Lead-in (FPA150 + pembrolizumab), a Phase 1b FPA150 Monotherapy Dose Expansion, and a Phase 1b combination Dose Expansion (FPA150 + pembrolizumab).

The Phase 1a Monotherapy Dose Escalation will include an initial accelerated titration design followed by a standard 3+3 dose escalation design until the MTD and/or RD for Phase 1b is determined. The Phase 1a combination Safety Lead-In will start enrolling once the FPA150 monotherapy RD is identified in Phase 1a monotherapy dose escalation and will continue until the FPA150 MTD/RD in combination is identified.

Phase 1a FPA150 monotherapy Dose Exploration may include cohorts that may enroll beyond 3 patients whose tumors express high levels of B7-H4 protein and/or have varying levels of B7H4 expression [redacted] to further evaluate safety, PK, pharmacodynamics, and clinical activity at that dose (to be conditional upon the dose level clearing DLT criteria)..

Phase 1b will be the Dose Expansion (monotherapy and combination) portion of the study. Enrollment into Phase 1b Dose Expansion will begin after identification of the MTD and/or RD in Phase 1a (monotherapy and Safety Lead-in). Preliminary efficacy will be evaluated in Phase 1b in planned expansion cohorts that include patients with specific tumor types that are B7-H4+ advanced solid tumors.

Archival tumor tissue or fresh biopsy requirements are as follows:

Required for all patients in Phase 1a Monotherapy Dose Escalation:

- Provision of archival tumor tissue (or fresh biopsy if archival tissue is not available) for retrospective biomarker analysis for all patients

Required for all patients in Phase 1a Combination Safety Lead-in:

- Pre-screening of archival tumor tissue (or fresh biopsy required if archival tissue is not available) to evaluate for B7-H4 expression levels through IHC testing performed at a central laboratory and for retrospective biomarker analysis.

Required for all patients in Phase 1a Monotherapy Dose Exploration:

- Pre-screening test for B7-H4 expression levels through IHC testing and retrospective biomarker analysis will be performed at a central laboratory; fresh biopsy tissue will be required for this test if archival tissue is not available.
- Fresh biopsies mandatory during screening and on-treatment (prior to C3D1, please refer to Appendix 2 for additional information).

Required for all patients in Phase 1b Monotherapy and Combinbination Dose Expansion:

- Pre-screening of archival tumor tissue to evaluate for B7-H4 expresion level through IHC testing and retrospective biomarker analysis will be performed at a central laboratory; fresh biopsy tissue will be required for this test if archival tissue is not available.
- Fresh biopsies mandatory for a **subset of patients (at least 15 patients per 30-patient cohort)** during screening and on-treatment (prior to C3D1), for expanded pharmacodynamic analysis

Figure 3: Study Schema- Monotherapy

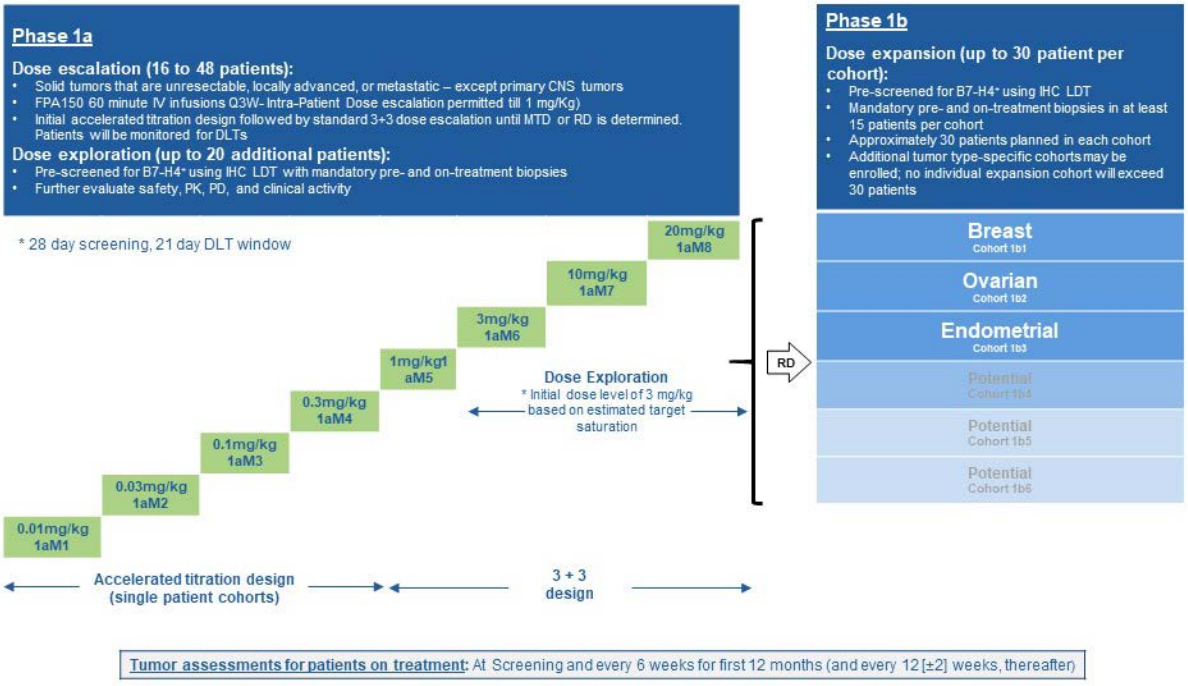
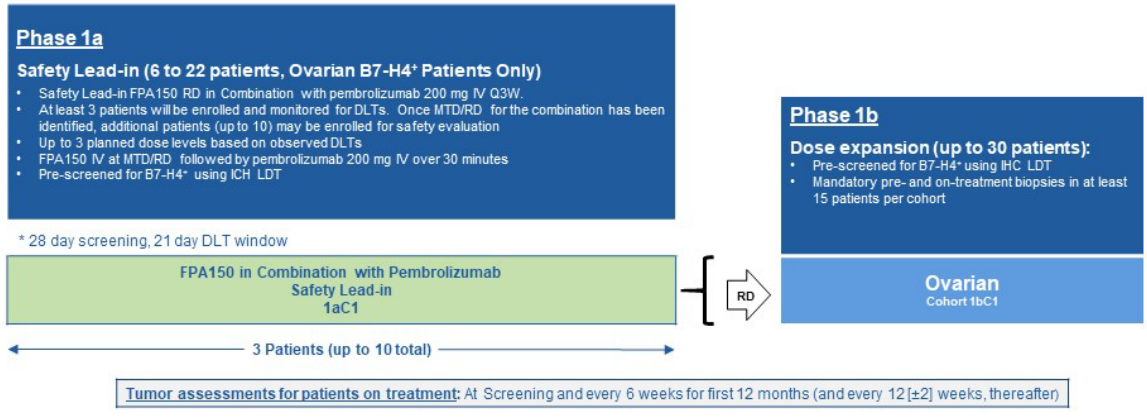


Figure 4: Study Schema - Combination



4.1.1 Cohort Review Committee

Safety will be monitored throughout the study by the Sponsor's Cohort Review Committee (CRC), consisting of at least the Sponsor's Medical Monitor, Safety Representative, and Study Investigators participating in Phase 1a. The CRC will meet routinely to review the emerging safety, PK, pharmacodynamics, and efficacy data, and to make dose escalation decisions. The CRC may recommend further evaluation of the safety at a given dose. The CRC will also review cumulative safety data in order to identify safety concerns that may emerge due to cumulative exposure beyond the DLT window. The process for dose escalation decisions and dose interval recommendations and the roles and responsibilities of the CRC will be detailed in the CRC Charter.

4.1.2 Study Design: Phase 1a Dose Escalation

Cohorts are planned at doses from 0.01 to 20 mg/kg, and enrollment will depend on safety and tolerability. Phase 1a Monotherapy Dose Escalation of the study will include an initial accelerated titration design followed by a standard 3+3 dose escalation design at dose levels ≥ 1 mg/kg until the MTD and/or RD for Phase 1b is determined. As of 28 January 2019, the RD for FPA150 monotherapy has been established as 20 mg/kg Q3W.

The proposed dosing cohorts are outlined in Table 3.

Table 3: Proposed Dose Levels for Phase 1a FPA150 Monotherapy

Dose Level	Cohort	Dose	Regimen
-1	-	FPA150 0.005 mg/kg	Q3W
1	1aM1	FPA150 0.01 mg/kg	Q3W
2	1aM2	FPA150 0.03 mg/kg	Q3W
3	1aM3	FPA150 0.1 mg/kg	Q3W
4	1aM4	FPA150 0.3 mg/kg	Q3W
5	1aM5	FPA150 1 mg/kg	Q3W
6	1aM6	FPA150 3 mg/kg	Q3W
7	1aM7	FPA150 10 mg/kg	Q3W
8	1aM8	FPA150 20 mg/kg	Q3W

Abbreviations: Q3W = once every 3 weeks.

4.1.2.1 Phase 1a Combination Safety Lead-in (Ovarian B7-H4$^+$ Patients Only)

Once the MTD and/or RD of FPA150 monotherapy in Phase 1a Dose Escalation is identified, the Sponsor will open a Safety Lead-in for the combination of FPA150 and pembrolizumab. At least 3 patients will be enrolled at the monotherapy RD of FPA150 in combination with pembrolizumab 200 mg IV Q3W and evaluated for DLTs by the CRC. If required due to the presence of DLTs, the dose of FPA150 will be reduced in accordance with the algorithm for

de-escalation described in Table 4. The same dose levels that were assessed during dose escalation for FPA150 monotherapy will be evaluated for the combination in reverse order (from highest to lowest). Once the RD for the combination of FPA150 and pembrolizumab is identified the Sponsor may treat additional patients at that dose for additional safety assessment (up to 10 patients total).

Table 4: Proposed Dose Cohort/Levels for Phase 1a Combination Safety Lead-in (FPA150 in Combination with Pembrolizumab)

Cohort	Dose	Regimen
1aC1	FPA150 (RD) + pembrolizumab 200 mg IV	Q3W
1aC2	FPA150 (dose level -1) + pembrolizumab 200 mg IV	Q3W
1aC3	FPA150 (dose level -2) + pembrolizumab 200 mg IV	Q3W

Abbreviations: IV = intravenous; Q3W = once every 3 weeks; RD = recommended dose.

4.1.2.2 Definition of a Dose-Limiting Toxicity

4.1.2.2.1 FPA150 Monotherapy

DLTs during Phase 1a Dose Escalation are defined as any of the following events regardless of attribution (except for those events clearly due to the underlying disease or extraneous causes):

- Any Grade 3 or higher non-hematologic toxicity (except Grade 3 nausea, vomiting and diarrhea) occurring with the first 21 days of treatment
- Grade 3 nausea, vomiting, diarrhea lasting > 72 hours, despite optimal supportive care, occurring within first 21 days of treatment
- Febrile neutropenia and/or documented infection with absolute neutrophil count (ANC) $< 1.0 \times 10^9$ per L, Grade 4 neutropenia lasting more than 7 days, Grade 4 thrombocytopenia ($< 25.0 \times 10^9$ per L), or Grade 3 thrombocytopenia ($< 50.0–25.0 \times 10^9$ per L) accompanied by bleeding within first 21 days of treatment
- Aspartate aminotransferase/alanine transaminase (AST/ALT) > 3 × upper limit of normal (ULN) and concurrent total bilirubin > 2 × ULN not related to liver involvement with cancer
- Other Grade 3 laboratory values that are not of clinical significance according to Investigator and Sponsor agreement that do not resolve within 72 hours
- Any Grade 4 laboratory value regardless of clinical sequelae

4.1.2.2.2 FPA150 Combined with Pembrolizumab (Safety Lead-in)

Additional DLT Considerations for the Combination of FPA150 and Pembrolizumab

Because pembrolizumab is a known immune checkpoint inhibitor and one of the proposed mechanisms of action of FPA150 is immune checkpoint blockade, immune-related adverse events (irAEs) are anticipated with this combination. An irAE is defined as a clinically significant AE that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Based on that background, the first occurrence of the following irAEs will not be considered a DLT because they are expected with immune therapy:

- Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
- Grade 3 rash
- Grade 3 immune-related adverse event (irAE) that resolved to a Grade 1 or less within 14 days
- Transient (resolving within 6 hours of onset) Grade 3 infusion-related AE

A second occurrence of these events (except Grade 3 tumor flare) either in the same or different patient during the DLT period will be considered a DLT

4.1.2.3 Dose-Limiting Toxicity Evaluation and Dose Escalation (FPA150 Monotherapy and Combination Safety Lead-in)

The DLT evaluation interval begins on the first day of treatment upon start of infusion and continues for 21 days. In Phase 1a Dose Escalation, patients' second dose must be at least 21 days after the first dose.

Review of safety, PK and pharmacodynamic profiles may inform decisions to add cohorts with alternative dose levels or dose regimens (eg, different dosing frequency, higher dose levels) in order to reach an optimal target exposure.

All dose escalation decisions will be based on the assessment of DLTs and overall safety and tolerability, and will be made after the last patient enrolled in each cohort has completed the first treatment cycle (ie, 21 days). Dose escalation decisions will be agreed upon by the CRC as outlined in Section 4.1.1.

Patients who receive at least one dose of study drug during the 21-day evaluation interval, or patients who discontinue study treatment for drug-related AEs before the DLT evaluation interval is complete, will be considered evaluable for DLT determination. Patients who discontinue study treatment for reasons other than drug-related AEs before the DLT evaluation interval is complete may be replaced. In consultation with Investigators, the Sponsor may open cohorts at dose levels between the dose levels proposed in the protocol.

For monotherapy dose escalation an accelerated titration design enrolling at least 1 patient at each dose level is planned for dose levels 0.01, 0.03, 0.1, and 0.3 mg/kg. Dose escalation to the next dose level may proceed after at least 1 patient completes the 21-day evaluation interval. If a single patient experiences a DLT or at least 2 patients experience moderate AEs (at any dose level) during the 21-day evaluation interval, additional patients will be enrolled at the current dose level and standard 3+3 dose escalation criteria will apply for that cohort as well as all subsequent dosing cohorts. Moderate AEs are defined as ≥ Grade 2 AEs regardless of attribution (except for those events clearly due to the underlying disease or extraneous causes). Grade 2 laboratory values will not be considered as moderate AEs for this purpose unless accompanied by clinical sequelae.

The algorithm outlined in Table 5 will be used for all standard 3+3 dose escalation decisions in Phase 1a monotherapy. If not already applied at a lower dose level for the reasons stated above, escalation for dose levels ≥ 1 mg/kg will follow standard 3+3 dose escalation criteria.

Table 5: Phase 1a Algorithm for FPA150 Monotherapy Dose-Escalation Decisions

Number of Patients with DLT at a Given Dose Level	Dose Escalation Decision Rule
0/3	Enroll 3 patients at next dose level (next/higher cohort)
1/3	Enroll 3 additional patients at current dose level (current cohort)
≥ 2/3	Stop enrollment. Enter 3 more patients at the previous dose level (previous/lower cohort), if only 3 were previously entered, or at an intermediate dose level
1/6	Enroll 3 patients at next dose level (next/higher cohort)
≥ 2/6	Stop enrollment. Enter 3 more patients at the lower dose level (previous/lower cohort), if only 3 were previously entered, or at an intermediate dose level

Abbreviations: DLT = dose-limiting toxicity.

The algorithm outlined in Table 6 will apply for dosing decisions for the FPA150 and pembrolizumab combination.

Table 6: Algorithm for Dose De-Escalation Decisions for FPA150 Safety Lead-In in Combination with Pembrolizumab in Phase 1a

Number of Patients with DLT at a Given Dose Level	Dosing Decision Rule
0/3	Proceed with enrolment of up to 10 total patients at that dose level for additional safety assessment
1/3	Enrol 3 additional patients at current dose level (current cohort)
≥ 2/3	Stop enrolment at current cohort and de-escalate FPA150 to one dose level below current dose
1/6	Proceed with enrolment of up to 10 total patients at that dose level
≥ 2/6	Stop enrolment at current cohort and de-escalate FPA150 to one dose level below current dose.

4.1.2.4 Determination of the Recommended Dose or Maximum Tolerated Dose

The MTD and/or RD of FPA150 monotherapy and FPA150 combined with pembrolizumab for Phase 1a will be identified based on an evaluation of the overall safety, tolerability, pharmacodynamics, PK, and preliminary efficacy. The RD will take into account toxicities observed both during and beyond the DLT evaluation period as well as dose reductions and discontinuations due to toxicity that do not meet the DLT criteria. The RD, therefore, may or may not be the same as the identified MTD. For example, if the MTD is not reached, or if data from subsequent cycles of treatment from Phase 1a provide additional insight on the safety profile, then the RD may be a different, though not higher, dose than the MTD.

The MTD will be at a dose level where ≤ 1/3-6 patients reported a DLT. The RD will be a dose where ≤ 1/6 patients reported a DLT, but may be lower than the MTD.

In the event that no MTD is identified and drug exposure exceeds what is deemed necessary based on nonclinical pharmacology data or the clinical PK and pharmacodynamic data (if available), the Sponsor and the Investigators may make a decision to discontinue dose escalation.

4.1.3 Study Design: Phase 1a Dose Exploration

Phase 1a includes a dose exploration cohort that may enroll beyond 3 patients (up to 20 additional patients across all dose levels). This 20 patients include 10 patients whose tumors express high levels of B7-H4 protein (3 mg and 10 mg), to further evaluate safety, PK, pharmacodynamics, and clinical activity at that dose (to be conditional upon the dose level clearing DLT criteria) of FPA150 monotherapy. It also includes up to 10 patients selected to have varying levels of B7-H4 expression [redacted] dosed at the FPA150 monotherapy MTD/RD.

Table 7: Proposed Dose Cohort/Level for Phase 1a Dose Exploration

Cohort	Dose/Regimen	B7-H4 Status
1aE1	FPA150 3 mg/kg	High
1aE2	FPA150 10mg/kg	High
1aE3	FPA150 monotherapy MTD/RD	[redacted]

Abbreviations: MTD = maximum tolerated dose; Q3W = once every 3 weeks; RD = recommended dose

Toxicities observed in these patients will contribute to the overall assessment of safety and tolerability, but will not be included in the formal DLT calculations per Protocol Table 5.

4.1.4 Study Design: Phase 1b Dose Expansion

Enrollment in Phase 1b monotherapy and in combination with pembrolizumab will begin when the MTD and/or RD has been identified by the CRC (refer to Section 4.1.1), based on overall safety, tolerability, objective response, PK, pharmacodynamics from the Phase 1a part of the study.

Phase 1b will consist of tumor-specific cohorts of up to 30 patients each.

Requirements for archival tumor tissue and fresh biopsies by study phase are listed in Section 4.1. Separate ICFs for patients will be required regarding provision of fresh biopsies.

During the Screening Period, the patient will undergo protocol-specified screening procedures to ensure all eligibility criteria are met. Enrollment in Phase 1b will initially occur in 3 monotherapy cohorts and one cohort with FPA150 in combination with pembrolizumab (once the Safety Lead-in is completed and the MTD/RD for the combination is identified) as outlined in Table 8.

Table 8: Phase 1b Expansion Cohorts and Tumor Types

Cohort	Tumor Type	Therapy Type (Monotherapy or Combination)
1b1	Breast cancer	Monotherapy: FPA150
1b2	Ovarian cancer	Monotherapy: FPA150
1b3	Endometrial cancer	Monotherapy: FPA150
1bC1	Ovarian cancer	Combination: FPA150 with pembrolizumab

4.2 Number of Patients

The total number of patients planned for this study is estimated to be approximately 278.

Phase 1a will enroll approximately 68 patients depending on incidence of DLTs; this number of 68 patients includes:

- Up to 23 to 26 patients in the Phase 1a Dose Escalation and
- Up to 6 to 22 patients in the FPA150 and pembrolizumab combination Safety Lead-in and
- Allows for up to 20 additional patients in 2 cohorts in Phase 1a Dose Exploration.

Phase 1b will enroll up to 210 patients with specific tumor types with B7-H4 expression levels determined by IHC; this number of 210 patients includes:

- Up to 30 patients planned for each of three monotherapy expansion cohorts (refer to Table 8) and one FPA150 in combination with pembrolizumab cohort.
- Additional tumor type-specific cohorts may be enrolled based on emerging data. No individual expansion cohort will exceed 30 patients.

4.3 Patient and Study Completion

The duration of study for an individual patient includes screening (up to 28 days), treatment and an End of Treatment (EOT) follow-up period which will include visits at approximately 28 (±7) days and 100 (±7) days after the last dose. Since all patients are eligible to be treated until disease progression, the actual treatment duration for each individual patient will vary depending on the anticipated time to progression for their respective tumor type. Treatment beyond disease progression may be allowed in patients with initial Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) defined progressive disease if the benefit/risk assessment favors continued administration of study treatment (eg, patients are continuing to experience clinical benefit as assessed by the Investigator, and tolerating treatment).

In addition, patients enrolled in Phase 1b Dose Expansion will be followed for survival (including scans and survival status every 12 weeks [Q12W]) for up to 2 years).

4.4 End of Study Definition

The study will end when the last patient enrolled completes the EOT follow-up period. The EOT follow-up period will include visits at approximately 28 (±7) days and 100 (±7) days after the last dose.

4.5 Scientific Rationale for Study Design

This is a Phase 1a/1b study. Phase 1a includes an accelerated titration design followed by standard 3+3 dose escalation design in unselected solid tumor patients. Once MTD/RD of FPA150 monotherapy is identified a cohort of patients will be enrolled on a Phase 1a Safety Lead-in with FPA150 + pembrolizumab to determine the RD of FPA150 in the combination.

Phase 1a will also include the option of enrolling up to 20 additional patients at 1 or more dose levels with varying levels of B7-H4 expression. Fresh biopsies will be mandatory in these additional patients. This will enable a more robust exploration of safety, PK and pharmacodynamics at any dose level.

Phase 1b is a dose expansion portion in patients with advanced breast, ovarian, and endometrial cancer that will be selected based on B7-H4 expression. These tumor types have been identified based on their known high prevalence of B7-H4 expression (Section 2.1) and limited availability of effective therapies in the unresectable and metastatic setting. Based on the preclinical activity of FPA150 and PD-L1 inhibitors (see Section 2.2.2.2) Phase 1b will also include a cohort of the combination of FPA150 and pembrolizumab to evaluate safety, tolerability and preliminary efficacy. The initial tumor type to be evaluated with the combination will be ovarian cancer based on the high unmet need in this population, high expression of B7-H4 and the limited clinical benefit observed with anti-PD1 agents alone. Additional cohorts with different tumor types or combinations may be enrolled based on emerging clinical and translational data for this pathway and molecule. Phase 1b Dose Expansion will enable a more thorough investigation of the clinical and biological activity of FPA150 monotherapy and in combination with pembrolizumab in more homogenous patient groups (by tumor type and biomarker expression) and will help define further clinical development of this molecule.

Fresh pre-treatment and on treatment study biopsies are mandatory in at least 15 of 30 patients enrolled in each Phase 1b cohort which may provide insight into the mechanism of action of FPA150 and help further refine potential tumor tissue-based biomarkers The primary endpoints for both the Phase 1a and Phase 1b portions are related to safety and tolerability and the statistical analyses will be descriptive. Additional details regarding the statistical assumptions for secondary endpoints related to evaluating preliminary efficacy in the 30-patient expansion cohort are described in Section 9.1.

4.6 Justification for Dose and Dosing Regimen

FPA150 is a glycoengineered IgG1 anti-B7-H4 monoclonal antibody with enhanced ADCC and checkpoint blockade activities, developed to be administered to patients with advanced solid tumors. The International Conference on Harmonization (ICH) S9 guidance ("Nonclinical Evaluation for Anticancer Pharmaceuticals") is applied to select FPA150 starting dose in human. The proposed starting dose in this study is 0.01 mg/kg IV Q3W. This was calculated using the established dose selection guidelines for the MABEL approach

(Saber 2016). The design is an accelerated titration followed by standard 3+3 dose escalation with approximately half log dose escalations.

FPA150 will be administered via IV infusion Q3W, which is consistent with a schedule commonly used for humanized monoclonal antibodies with an expected half-life of approximately 10 to 20 days. The dose of FPA150 will be based on body weight at Cycle 1 Day 1. After Cycle 1, the FPA150 dose will be recalculated at each infusion visit only if the patient's weight has changed > 10% from Cycle 1, Day 1.

The proposed dose of pembrolizumab of 200 mg Q3W is consistent with the current approved US Prescribing Information. The initial starting dose of FPA150 in combination with pembrolizumab will be the RD identified during monotherapy dose escalation. This is an acceptable approach given the preliminary safety data of FPA150 monotherapy and the well characterized safety profile of pembrolizumab. Step down dosing of FPA150 in response to emerging safety data is planned.

4.7 Patient Selection

FPA150 is an antibody designed to recognize B7-H4 which is expressed highly on tumors, such as on breast cancer, ovarian cancer, and endometrial cancer. Because it is predicted that patients whose tumors have higher expression of the target B7-H4 protein are more likely to respond to FPA150, patients will undergo pre-screening to allow selection based on B7-H4 expression in the Phase 1a Combination Safety Lead-in, Phase 1a Monotherapy Dose Exploration and in Phase 1b Dose Expansion (Monotherapy and in combination with pembrolizumab).

Tumor samples (fresh or archival) from all patients will be assessed by IHC to determine the expression of B7-H4 protein, and patients in Phase 1b and a subset of patients in Phase 1a will be selected based on being positive for B7-H4.

5 Study Population

5.1 Inclusion Criteria

5.1.1 Phase 1a Inclusion Criteria (Monotherapy and Combination Therapy)

Patients enrolling into **Phase 1a** must meet ***all*** of the following inclusion criteria:

1) Histologically confirmed solid tumors except primary central nervous system (CNS) tumors.
2) Disease that is unresectable, locally advanced, or metastatic.
3) Able to understand and sign an IRB/IEC)approved ICF prior to any study-specific evaluation.
4) Patients should be refractory to or intolerant of existing therapy(ies) known to provide clinical benefit for their condition.
5) All patients must have at least one measurable lesion at baseline according to RECIST v1.1; tumor sites situated in a previously irradiated area, or in an area subjected to other loco-reginal therapy, are not considered measurable unless there has been demonstrated progression in the lesion.
6) Adequate washout for prior anti-cancer therapy (ie, ≥ 5 half-lives or 4 weeks since the last dose, whichever is shorter).
7) Availability of archival tumor tissue for retrospective biomarker analysis, or patient must undergo a fresh tumor biopsy during screening if archival tissue is not available (a biopsy is required for patients in the Phase 1a Dose Exploration portion). Archival tissue for patients enrolled in Cohort 1b1 (Breast Cancer) must be within 24 months prior to pre-screening.
8) Age ≥ 18 years at the time the ICF is signed.
9) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10) Life expectancy of at least 3 months in the opinion of the Investigator.
11) Willing and able to comply with all study procedures.
12) Prior radiotherapy must be completed at least 2 weeks before the first dose of study drug.
13) Prior radiopharmaceuticals (eg, strontium, samarium) must be completed at least 8 weeks before the first dose of study drug.
14) Prior surgery that requires general anesthesia must be completed at least one week before first dose of study drug administration. Surgery requiring local/ epidural anesthesia must be completed at least 72 hours before first dose of study drug administration. Patients must have recovered from any surgery.

15) Screening laboratory values must meet the following criteria:

Hematologic:

a. Neutrophils ≥ 1200 cells/μL
b. Platelets ≥ 75×10^3/μL
c. Hemoglobin (Hb) ≥ 9.0 g/dL

Renal:

d. Serum creatinine < 1.5 × ULN or creatinine clearance (CrCl) of ≥ 40 mL/minute (using Cockcroft/Gault Formula)

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

Hepatic:

e. AST and ALT ≤ 3× ULN (AST and ALT <5× ULN in patients with liver metastases is permitted)

f. Bilirubin < 1.5× ULN (except patients with Gilbert's syndrome, who must have total bilirubin < 3 mg/dL)

16) Negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test ≤ 96 hours prior to treatment on Cycle 1, Day 1 (women of childbearing potential only).

17) In sexually active patients (women of child bearing potential and males), willingness to use 2 effective methods of contraception, of which 1 must be a physical barrier method (condom, diaphragm, or cervical/vault cap) until 6 months after the last dose of FPA150. Other effective forms of contraception include:

- Permanent sterilization (hysterectomy and/or bilateral oophorectomy, or bilateral tubal ligation with surgery, or vasectomy) at least 6 months prior to Screening
- Women of childbearing potential who are on stable oral contraceptive therapy or intrauterine or implant device for at least 90 days prior to the study, or abstain from sexual intercourse as a way of living

50) For Phase 1a Combination Safety Lead-in Patients ONLY:

50.01 B7-H4 positive ovarian cancer

50.02 Histologically or cytologically confirmed diagnosis of recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma that is refractory to existing therapy(ies) known to provide clinical benefit

50.03) Progressive disease on or after at least two prior regimens of treatment including at least one platinum-containing regimen, *or* unable to tolerate additional chemotherapy

50.04) No prior therapy with an anti-PD1 or PD-L1-directed agent

5.1.2 Phase 1b Inclusion Criteria (Monotherapy and Combination Therapy)

Patients enrolling into **Phase 1b** must meet ***all*** of the following inclusion criteria:

18) All Inclusion Criteria for Phase 1a (Exception: Phase 1a Inclusion Criterion #1).

19) Positive for B7-H4 expression in an archival or fresh tumor sample as evaluated by an accompanying validated central laboratory IHC assay. Archival tissue for patients enrolled in Cohort 1b1 (Breast Cancer) must be within 24 months prior to pre-screening.

20) History of other malignancy is permitted provided it has been definitively treated with no evidence of recurrence within the past 2 years (Exception: Definitively treated non-melanoma skin cancer, lobular cancer in situ, and cervical cancer in situ within 2 years are permitted).

5.1.3 Additional Cohort-Specific Inclusion Criteria for Phase 1b (Monotherapy and Combination Therapy)

Cohort 1b1 Breast Cancer

Triple Negative Breast Cancer (TNBC)

21.01) Histologically or cytologically confirmed metastatic TNBC

21.02) At leat two prior lines of systemic chemotherapy with at least one being administered in the metastatic setting

HR+ Breast Cancer

21.03) Histologically or cytologically confirmed metastatic HR+ breast carcinoma

21.04) Patients must have received at least two prior lines of hormonal therapy

21.05) Patients must have received at least one prior line of systemic chemotherapy (in the adjuvant or metastatic setting)

Cohort 1b2 Ovarian Cancer

22.01) Histologically or cytologically confirmed diagnosis of recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma that is refractory to existing therapy(ies) known to provide clinical benefit

22.02) Progressive disease on or after at least two prior regimens of treatment including at least one platinum-containing regimen, or unable to tolerate additional chemotherapy

Cohort 1b3 Endometrial Cancer

23.01) Histologically or cytologically confirmed recurrent or persistent endometrial cancer that is refractory to curative or established treatments

23.02) Progressive disease on or after at least one prior regimen of systemic chemotherapy, or unable to tolerate systemic chemotherapy

Cohort 1bC1 Ovarian Cancer

24.01) Histologically or cytologically confirmed diagnosis of recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma that is refractory to existing therapy(ies) known to provide clinical benefit

24.02) Progressive disease on or after at least two prior regimens of treatment including at least one platinum-containing regimen, *or* unable to tolerate additional chemotherapy

24.03) No prior therapy with an anti-PD1 or PD-L1-directed agent

No waivers will be granted for any of these inclusion criteria.

5.2 Eligibility Criteria

Exclusion Criteria (Phase 1a And Phase 1b)

Patients who meet ANY of the following criteria will be excluded from study entry:

1) Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent daily) must be discontinued at least two weeks before the first dose of study drug. Short courses of high dose steroids, continuous low dose (prednisone < 10 mg/day), inhaled, intranasal, intraocular, and joint injections of steroids are allowed
2) Decreased cardiac function with New York Heart Association (NYHA) > Class 2 at screening
3) Uncontrolled or significant heart disorder such as unstable angina
4) QT interval corrected for heart rate (QTc) per institutional guidelines> 450 msec for males or > 470 msec for females at screening
5) History of ADAs, , severe allergic, anaphylactic, or other infusion-related reaction to a previous biologic agent
6) Known hypersensitivity to any component of the investigational product (IP) formulation including active ingredient, sodium acetate, sucrose, and polysorbate 20 (refer to Section 6.1.1)

7) Vaccines (eg, human papilloma virus [HPV] vaccine) within 4 weeks before the first dose of study drug. The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (ie, pneumovax, varicella, etc.) may be permitted, but must be discussed with the Sponsor's Medical Monitor and may require a study drug washout period prior to and after administration of the vaccine.

8) Current unresolved infection or history of chronic, active, clinically significant infection (viral, bacterial, fungal, or other) which, in the opinion of the Investigator, would preclude the patient from exposure to a biologic agent or may pose a risk to patient safety.

9) Patients with abnormal serum chemistry values that in the opinion of the Investigator are considered to be clinically significant. This includes patients who show clinical signs and symptoms related to their abnormal serum chemistry values, as well as patients whose serum chemistry values are asymptomatic, but clinically significant according to the Investigator (eg, hypokalemia or hyponatremia).

10) Any uncontrolled medical condition or psychiatric disorder which, in the opinion of the Investigator, would pose a risk to patient safety or interfere with study participation or interpretation of individual patient results

11) Pregnant or breastfeeding

12) Active, known, or suspected autoimmune disease. Patients with Type I diabetes mellitus, hypothyroidism requiring only hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger, are permitted to enroll.

13) Known history of testing positive for human immunodeficiency virus (HIV) 1 or 2 or known acquired immunodeficiency syndrome (AIDS).

14) Positive test for hepatitis B virus surface antigen (HBsAg) or detectable hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection.

15) Ongoing adverse effects from prior treatment > Grade 1 (with the exception of Grade 2 alopecia or peripheral neuropathy) based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

16) Symptomatic interstitial lung disease or inflammatory pneumonitis.

17) Untreated or active CNS or leptomeningeal metastases. Patients are eligible if metastases have been treated and patients are neurologically returned to baseline or neurologically stable (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks before the first dose of study drug.

18) Evidence of coagulopathy or bleeding diathesis. Patients receiving stable therapeutic doses of anti-coagulants will be permitted.

19) Transfusion of blood or platelets completed within 72 hours before the first dose of study drug.
20) Any uncontrolled inflammatory GI disease including Crohn's Disease and ulcerative colitis
21) For Cohort 1b1 only: Patients with HER2 positive disease

No waivers will be granted for any of these exclusion criteria.

5.3 Lifestyle Restrictions

There is not enough information currently available to make any specific recommendations regarding lifestyle restrictions.

5.4 Screen Failures

Patients in the Phase 1a Dose Exploration and in Phase 1b Dose Expansion who test negative for B7-H4 will be considered Pre-Screen-Failures. Patients who test positive and enter the Screening Period, but do not enroll, will be considered Screen-Failed.

6 Treatments

6.1 Treatments Administered

6.1.1 FPA150 Identity

FPA150 drug product is supplied for IV administration as a sterile, aqueous, colorless to slightly yellowish, pyrogen-free solution supplied in single-use glass vials. The composition of the drug product contains 20 mg/mL active ingredient, 20 mM sodium acetate, 270 mM sucrose, 0.05% (w/v) polysorbate 20 at pH 5.0. The container-closure system consists of a 5 mL Type I glass vial, sealed with a bromobutyl rubber stopper, and a flip-off cap. The final drug product will be provided as 2° to 8°C refrigerated liquid protected from light which is diluted for administration according to instructions provided in a separate Pharmacy Manual.

A 20 mL vial will be available in the second half of 2019. The composition of the drug product contains 20 mg/mL active ingredient, 20 mM sodium acetate, 270 mM sucrose, 0.05% (w/v) polysorbate 20 at pH 5.0. The container-closure system consists of a 20 mL Type I glass vial, sealed with a bromobutyl rubber stopper, and a flip-off cap.

FPA150 will be supplied in a sterile vial for dilution into an IV bag for administration by the study center.

6.1.2 Pembrolizumab

Pembrolizumab for injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL solution. Each 1 mL solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg) and Water for Injection. For additional information, refer to the Keytruda® (pembrolizumab) Prescribing Information (Keytruda® USPI). FPA150 + pembrolizumab combination cohorts will only enroll in the United States.

Pembrolizumab is available for injection as a 50 mg lyophilized powder in single-use vial for reconstition and in 100 mg/4 mL (25 mg/mL) solution in single use vial.

The lyophilized powder is reconstituted by adding 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL). Slowly swirl the vial and allow up to 5 minoutes for the bubbles to cear. Do not shake the vial.

The injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. . Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg) and water for Injection. Please refer to pembrolizumab USPI

6.2 Treatment Packaging, Labeling, and Storage

6.2.1 FPA150

FPA150 will be packaged and labeled as a 5 mL or 20 mL (to be available in second half of 2019) fill in ISO 6R vials by the Sponsor (or designee) per applicable local regulatory requirements.

All FPA150 vials must be stored refrigerated at 2° to 8°C in accordance with the manufacturer's instructions as provided in the Pharmacy Manual. Until dispensed to patients, FPA150 will be stored in a securely locked area, accessible to authorized personnel only.

6.2.2 Pembrolizumab

For the combination cohorts pembrolizumab's .

packaging, labelling, and storage of pembrolizumab should be in accordance with the Keytruda® USPI , the Pharmacy Manual, and relevant local guidelines.

6.3 Administration and Preparation

6.3.1 FPA150

FPA150 will be administered as a 60-minute IV infusion Q3W in 21-day cycles until progressive disease or unacceptable toxicity. Proposed dose levels to be studied are outlined in Table 3 for Phase 1a Dose Escalation. Please refer to the pharmacy manual for any additional dosing instructions for dose levels below 1 mg/kg.

The dose of FPA150 will be based on body weight at Cycle 1 Day 1. After Cycle 1, the FPA150 dose will be recalculated at each infusion visit only if the patient's weight has changed > 10% from Cycle 1, Day 1.

Further instructions on drug preparation and administration are in the Pharmacy Manual.

There is no pre-specified maximum number of doses of FPA150 monotherapy. Patients may continue receiving FPA150 according to their study specified cohort/ dose until Investigator-assessed clinical progression, unacceptable toxicity, or until the patient meets any of the other protocol-specified withdrawal criteria.

A pharmacist (or other responsible person) will prepare FPA150 for administration. After calculating the number of vials based on the patient's weight, FPA150 will be diluted in a 0.9% sodium chloride solution or 5% dextrose in water solution. Prepared FPA150 should be administered ≤4 hours after preparation under ambient temperature.

FPA150 will be administered under medical supervision over approximately 60-minute (± 5 minutes) IV infusion via a peripheral vein or central venous catheter. The IV administration set for FPA150 infusion must contain a 0.22 µm in-line filter or a 0.22 µm syringe filter.

All patients must be monitored for at least 4 hours after the end of the first infusion of FPA150. Patients in whom intrapatient dose escalation is planned (ie, patients enrolled at dose levels below 1 mg/kg) should also be monitored for at least 4 hours after the end of infusion at each dose escalation. Infusion of FPA150 must be stopped, reduced, interrupted, or discontinued according to Section 6.4.4 (Dose Modification Criteria) and Section 6.4.6 (Dose Interruptions During Study Treatment Administration). If a patient experiences an infusion reaction, the patient's vital signs (temperature, blood pressure, pulse, and respiration rate) should be monitored during the infusion as well as every 30 minutes after the infusion for a minimum of 2 hours and until resolution of the infusion reaction.

6.3.2 Pembrolizumab

Pembrolizumab should be prepared according to the Keytruda® USPI.

Table 9 details the treatment regimen for the combination cohorts. Pembrolizumab will be administered after completion of the FPA150 IV infusion. Pembrolizumab will be administered at a dose of 200 mg by IV infusion over 30 minutes (± 5 minutes) starting on C1D1 and repeated Q3W on Day 1 of each 21-day cycle after all procedures and assessments have been completed. Pembrolizumab should not be co-administered with FPA150.

Further information regarding dosing and preparation of pembrolizumab can be found in the Keytruda® USPI.

Table 9: Study Treatment Regimen of Combined Treatment of FPA150 and Pembrolizumab

Study Treatment	Dosage Formulation	Unit Dose Strengths	Dosage Level (s)	Route of Administration	Regimen/ Treatment Period
FPA150	Solution for infusion	Single-use glass vials (5 mL and 20 mL) containing 20 mg/mL active ingredient	Table 4	60-minute (± 5 minutes) IV infusion	Day 1 of each cycle (Q3W) 30 to 60 minutes
Pembrolizumab	Solution for infusion or lyophilized powder	100 mg/vial containing 25 mg/mL active ingredient or 50 mg lyophilized powder in single use vial for reconstitution	200 mg	30-minute IV infusion	Day 1 of each 21-day cycle (Q3W) After FPA150

6.4 Dose Modifications

In Phase 1a the starting dose level of FPA150 is 0.01 mg/kg. Subsequent dose escalations between cohorts in Phase 1a are described in Section 4.1.1. The dose of FPA150 for Phase 1b will be determined by evaluation of the data from Phase 1a of the study, as described in Section 4.1.4.

All patients in the combination cohorts receive pembrolizumab 200 mg IV Q3W. Dose modifications for pembrolizumab are described in the package insert. Dose reductions for pembrolizumab are not permitted.

6.4.1 Dose Modification Based on Weight

A complete physical examination including height and weight will be performed at screening. The dose of FPA150 will be based on body weight at Cycle 1 Day 1. After Cycle 1, the FPA150 dose will be recalculated at each infusion visit only if the patient's weight has changed > 10% from Cycle 1, Day 1.

The dose of pembrolizumab will not be adjusted based on weight.

6.4.2 Dose Escalation within a Cohort

In Phase 1a, intrapatient dose escalation will be permitted in patients enrolled at dose levels below 1 mg/kg provided:

- The patient did not experience a DLT
- All other AEs have recovered to Grade 1 or lower prior to dose escalation
- The patient may only dose escalate by a maximum of 1 dose level every 21 days
- The patient cannot dose escalate beyond 1mg/kg dose level unless the dose level has been cleared according to the standard 3+3 dose escalation design as described in Section 4.1
- Patients treated at dose levels up to 1 mg/kg may be escalated to a higher dose level if the patient has had a radiographic response, subsequently progressed and the higher dose levels have cleared DLT.

Intrapatient dose escalation will only be permitted after a discussion between the sponsor medical monitor and treating physician taking into account the overall safety experience, PK and PD data available at the time of the request.

In Phase 1b, patients will be treated at the MTD and/or RD as determined from Phase 1a, and dose escalation will not be permitted.

6.4.3 Toxicity at Lowest Dose Level

If the MTD is unexpectedly exceeded at the first dose level of FPA150 (0.01 mg/kg), the dose may be reduced to 0.005 mg/kg (refer to Table 3 for an outline of FPA150 dose levels for Phase 1a). Decisions on how to next proceed will be based on safety, tolerability, and PK data, and will be determined by the CRC (refer to Section 4.1.1).

6.4.4 Dose Modification Criteria for FPA150

Dose reductions for FPA150 may be permitted for patients on treatment beyond the DLT Period and can be assessed using local laboratories. If a patient requires a dose reduction of FPA150 during the DLT period, they will be considered to have a DLT and be permanently discontinued from FPA150. Dose reductions for FPA150-related AEs should follow the guidelines outlined in Table 10. The treating physician may choose to interrupt or discontinue FPA150 at any time outside of these guidelines if they believe it is necessary to ensure patient safety. It is recommended that the treating physician disuss the proposed dosing modification with the FivePrime medical monitor prior to making the change. Patients may resume FPA150 if the event returns to baseline or ≤ Grade 1 in accordance with the guidelines outlined in Table 10. Any variations from these guidelines must be discussed with the FivePrime Medical Monitor prior to dosing and must take into consideration the overall benefit and risks for the patient of continued participation in the study.

Table 10: Dose Modification Guidelines for FPA150 (Non-infusion Toxicity)

FPA150-related Toxicity Grade	Dose Schedule	New FPA150 Dose
Grade 1 or 2	No delay or missed dose required	100% of dose
Grade 3 (first occurrence)	Delay or miss dose until recovery to baseline or Grade 1	If recovery to baseline or Grade 1 within 28 days, may resume at 100% of starting dose or 1 dose lower[a]
Grade 3 (second occurrence)	Delay or miss dose until recovery to baseline or Grade 1	If recovery to baseline or Grade 1 within 28 days, may resume at 1 level lower[a] than previous dose or discontinue
Grade 3 (third occurrence) Grade 3 which does not recover to baseline or Grade 1 within 28 days Any Grade 4	Permanently Discontinue	N/A

[a] Eg, 1 dose level lower for patients treated at 20 mg/kg is 10 mg/kg; 1 dose level lower for patients treated at 10 mg/kg is 3 mg/kg; 1 dose level lower for patients treated at 3 mg/kg is 1 mg/kg.

There is a ± 3-day window for the first 3 scheduled FPA150 dosing visits. The first dose of each cycle is considered Day 1 of each cycle. Cycles will repeat every 21 days unless there is a treatment delay. Intrapatient dose escalation will not be permitted above 1mg/kg except as detailed in Section 6.4.2. Any patient whose dose of FPA150 is decreased cannot be subsequently increased.

6.4.5 Dose Modification Criteria (Pembrolizumab) including Immune Related AEs

Any dose modifications for pembrolizumab-related toxicity in patients enrolled on the Phase 1a Safety Lead-in will be considered a DLT and the patient will need to be replaced.

Dose modifications for pembrolizumab in the Phase 1b dose expansion will be allowed in accordance with the Keytruda® USPI. Dose reductions for pembrolizumab are not permitted. AEs associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. irAEs may be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. Dose modification and toxicity management for irAEs associated with pembrolizumab should be done in accordance with the guidelines provided in the Keytruda® USPI.

6.4.6 Dose Interruptions During Study Treatment Administration

FPA150: Infusion must be stopped if any AE ≥ Grade 3 occurs during the infusion. If bronchospasm or dyspnea occurs in a patient during the infusion, the infusion must be stopped.

In addition, at the Investigator's discretion, the infusion rate for FPA150 may be reduced or stopped if a less severe AE (Grade 1 or 2) occurs during the infusion. If a Grade 3 or less severe AE resolves within 4 hours, the infusion may be restarted at half the previous rate and promptly managed according to the discretion of the Investigator. If the same AE appears again with the same severity at any time during the restarted infusion, the infusion should be discontinued, and no further dosing of FPA150 will occur without consultation with the Sponsor or Sponsor's designee.

If a patient experiences an infusion reaction prior to completion of the infusion, the infusion must be stopped, and the patient should be promptly managed and monitored according to signs and symptoms, and local clinical protocol until there is a complete resolution of the event. Symptoms of infusion reactions may include: fever, chills, rigors, urticaria, hypotension and hypertension with headache, wheeze, breathlessness, hypoxia, and pulmonary infiltrates. For patients whose infusion-associated events were either Grade 1 or 2, and completely resolved on the day of the infusion, the infusion may be resumed at the discretion of the Investigator at a slower rate with premedication. All subsequent infusions for that patient should then be administered at the reduced rate of infusion with pre-medications. Pre-medications may include medications such as corticosteroids, diphenhydramine, acetaminophen and/or bronchodilators as indicated. FPA150 will be permanently discontinued for patients who have experienced Grade 3 or above infusion-associated AEs, and for patients who have recurrent infusion-associated reactions after restarting the infusion despite pre-medications and slower infusion.

If a patient experiences an infusion reaction, the patient's vital signs (temperature, blood pressure, pulse, and respiration rate) should be monitored during the infusion, as well as every 30 minutes after the infusion for a minimum of 2 hours and until resolution of the infusion reaction.

Pembrolizumab: Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management for infusion reactions associated with pembrolizumab should be in accordance with the guidelines provided in the Keytruda® USPI.

6.5 Maximum Duration of Treatment

There is no pre-specified maximum number of doses of FPA150 monotherapy or in combination. Patients may continue receiving FPA150 monotherapy according to their study specified cohort/dose until Investigator-assessed disease progression or the patient meets any of the other protocol-specified withdrawal criteria.

Patients may receive pembrolizumab therapy according to their study specified cohort/dose until Investigator-assessed disease progression, the patient meets any of the other protocol-specified withdrawal criteria or the patient completes approximately 24 months of pembrolizumab treatment.

If one of the two drugs have to be discontinued, patients may continue to receive the other drug alone.

6.6 Method of Treatment Assignment

Patients in Phase 1a Dose Escalation will be sequentially assigned to dose levels at the time of enrollment, as described in Section 4.1.2 Patients in Phase 1a Dose Exploration will be assigned to the dose level and schedule selected based on the results of the Phase 1a Dose Escalation, as described in Section 4.1.3. Patients in Phase 1b Dose Expansion will be assigned to the dose level and schedule selected based on the results of the Phase 1a Dose Escalation and Phase 1a Dose Exploration, as described in Section 4.1.4.

Procedures for informed consent, screening, and enrollment are outlined in Section 8.1.

6.7 Blinding

Blinding and breaking the blind are not applicable as this study is open label.

6.8 Study Drug Accountability

The Investigator or appropriately qualified staff is responsible for maintaining accurate study drug accountability records throughout the study.

The Investigator is responsible for returning all unused study drug to the Sponsor (or designee), and must verify that no remaining supplies are in the Investigator's possession. The study site is permitted to destroy used or partially used study drug vials according to the site policy once Sponsor approval of their documented destruction procedure has been obtained. On completion of the study, the number of FPA150 and/or pembrolizumab vials shipped, destroyed, and returned must be reconciled.

Details regarding preparation, storage, handling, and administration are provided in Sections 6.2 and 6.3.

6.9 Treatment Compliance

Only qualified study center personnel may administer FPA150 and/or pembrolizumab. Pharmacy personnel trained in the study requirements will monitor compliance with the treatment assignments. Records of study medication administered (date, time, and dose administered relative to time of preparation) will be recorded on the patient's electronic case report form (eCRF).

6.10 Concomitant Therapy

Supportive care (eg, anti-emetics, analgesics for pain control, bisphosphonates and denosumab) may be used at the Investigator's discretion and in accordance with institutional procedures. Hematopoietic stimulating agents may be used if indicated. Concomitant anti-cancer therapies of any kind are not permitted.

Rescue and supportive care medications that are allowed with pembrolizumab should be given in accordance with the guidelines provided in the Keytruda® USPI.

7 Discontinuation/ Withdrawal Criteria

7.1 Discontinuation of Study Treatment

Treatment with study drug may be discontinued for any of the following reasons:

- Consent withdrawal at the request of the patient or their legally authorized representative
- Progressive disease as assessed by the Investigator. Treatment beyond disease progression may be allowed in select patients with initial RECIST v1.1 defined progressive disease if the benefit/risk assessment favors continued administration of study treatment (eg, patients are continuing to experience clinical benefit as assessed by the Investigator, and tolerating treatment).
- Any event that would pose an unacceptable safety risk to the patient
- A concurrent illness that would affect assessments of the clinical status to a significant degree
- A positive pregnancy test at any time during the study
- 24 months of treatment with pembrolizumab
- Specific request of the Sponsor or its authorized representative (eg, if the study is terminated for reasons of patient safety)
- AE
- Investigator decision
- Patient decision, non-AE
- Other

7.2 Withdrawal from the Study

Any patient may be discontinued from the study for any of the following reasons:

- Consent withdrawal at the request of the patient or their legally authorized representative
- AE
- Death
- Investigator decision
- Lost to follow-up
- Significant noncompliance to protocol
- Study termination by Sponsor
- Other

The Sponsor or its designee must be notified if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records and case report form (CRF). When a patient withdraws from treatment, all safety data normally required at the end of the study (ie, the EOT visit and long-term follow-up) will be obtained if possible.

7.3 Patient Replacement

Patients in Phase 1a Dose Escalation or Phase 1a Combination Safety lead-in will be replaced if they are unevaluable for DLT (refer to Section 4.1.2.2). Patients in Phase 1a Dose Exploration or Phase 1b Dose Expansion will not be replaced.

7.4 Premature Termination of the Study

If the investigator, Sponsor, or Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- Discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure to enroll patients at an acceptable rate
- Decision on the part of the Sponsor to suspend or discontinue development of the drug

8 Study Assessments and Procedures

Descriptions of assessments are provided in Sections 8.1 through 8.14, below.

Additional guidance for study assessments and procedures is provided in the following appendices:

- Specific timing requirements for study assessments and procedures: Appendix 1 Schedule of Assessments.
- Guidance for the specific timing of PK, immunogenicity, and pharmacodynamic sample collection: Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collection.
- Specific pharmacodynamic analyses to be conducted: Appendix 3 List of Pharmacodynamic Samples for Analyses.
- Guidance for ECOG assessment: Appendix 4 Eastern Cooperative Oncology Group Performance Status.
- Specific clinical laboratory tests to be conducted: Appendix 5 Clinical Laboratory Tests.
- NYHA Classification: Appendix 6 New York Heart Association Classification.

8.1 Informed Consent, Screening, and Enrollment

Patients must be able to provide written informed consent and meet all eligibility criteria prior to enrollment.

Only patients who meet all eligibility criteria outlined in Section 5 will be enrolled in this study. No waivers of inclusion or exclusion criteria will be granted by the Investigator and Sponsor or its designee for any patient enrolled in the study. Patients who qualify for Phase 1a of the study will be enrolled into the first available cohort. A patient may be enrolled into either Phase 1a or Phase 1b of the study, but not both.

In both Phase 1a and 1b, the Investigator may repeat qualifying laboratory tests and vital signs/ ECGs prior to enrollment if a non-qualifying finding is considered an error, and/or if an acute finding is likely to meet eligibility criteria on repeat testing. Local hematology and blood chemistry test results must be obtained within 96 hours of dosing to confirm eligibility.

Refer to Section 8.1.1 below for specific informed consent requirements by study phase.

8.1.1 Informed Consent Requirements by Study Phase

All subjects in all monotherapy and combination therapy cohorts must sign and date the most recent IRB/IEC-approved informed consent form before any study procedures are performed.

Optional procedures may require separate subject consent, either within the main ICF or on a separate ICF, per IRB/IEC requirements. Subjects who screen fail must re-sign the informed consent, if any screening procedures will be performed outside of the 28-day screening window from the time of the first informed consent.

8.2 Medical History and Demographics

Patient medical and surgical history includes a thorough review of significant past medical and surgical history, current conditions, concomitant therapies, alcohol and smoking history, and smoking status.

Demographics including age, gender, race, and ethnicity will be recorded.

8.3 Safety Assessments

Unless otherwise specified, all safety assessments must be completed prior to start of study drug infusion on scheduled dosing days in accordance with the Schedule of Assessments (Appendix 1). Safety measures will include vital signs, body weight, physical examination, ECOG performance status, laboratory tests (hematology, serum chemistries, and urinalysis), ECGs, and monitoring of AEs and concomitant medications.

In Phase 1a, the CRC (refer to Section 4.1.1) will evaluate study safety data (AEs and serious adverse events [SAEs]) on a regular basis throughout the entire treatment phase (as described in the CRC Charter).

8.3.1 Physical Examinations, Height and Weight

A complete physical examination including height and weight will be performed at screening. A limited physical examination (eg, symptom-directed examination of specific organ systems/body area) should be conducted at the specified time points after screening in accordance with the Schedule of Assessments (Appendix 1). After Cycle 1, the FPA150 dose will be recalculated at each infusion visit only if the patient's weight has changed > 10% from Cycle 1, Day 1. Weight will also be recorded at the final EOT visit.

8.3.2 Vital Signs

Vital signs (blood pressure, pulse, respiration, and temperature after 5 minutes of rest) will be measured in accordance with the Schedule of Assessments (Appendix 1).

8.3.3 Electrocardiograms

Twelve-lead ECGs will be performed in accordance with the Schedule of Assessments (Appendix 1). To minimize variability, it is important that patients are in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG to prevent changes in heart rate. ECGs for each patient should be obtained from the same machine whenever possible. The ECGs should be reviewed promptly by a qualified physician and any clinically important finding should be recorded on the appropriate CRF. The Investigator is responsible for providing the interpretation of all ECGs. The results will include heart rate, PR interval, QRS interval, QT interval, and QTc interval.

ECGs should be performed before the PK blood draw on days where both are done. Additional ECGs should be obtained at any time if serum creatine kinase (CK) or cardiac troponin is elevated, or if ECG is abnormal (excluding sinus tachycardia; ECGs should be obtained [if clinically indicated] until the abnormality is resolved or clinically stable). Additional ECGs may be obtained at any time, if clinically indicated (eg, in case of elevated creatinine kinase [CK] or troponin).

Any clinically significant changes in ECGs that occur during the study should be reported as an AE in the eCRF.

8.3.3.1 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed in all patients in accordance with the Schedule of Assessments (Appendix 1). The ECOG performance scale is provided in Appendix 4 Eastern Cooperative Oncology Group Performance Status.

The ECOG performance status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

8.4 Tumor Tissue

Tumor tissue should be collected in accordance with the Schedule of Assessments (Appendix 1). Requirements for archival tumor tissue and fresh biopsies by phase of study is detailed in Section 4.1.

8.4.1 Archival Tissue

Mandatory archival tumor tissue from an excisional, incisional or core needle biopsy (or patient must undergo a fresh tumor biopsy during screening if archival tissue is not available; fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses) will be collected as follows:

- Archival tumor block (preferred) or 10 unstained sections from an archival tumor block must be provided during screening by all patients in the study for exploratory biomarker analyses
- Five unstained sections from an archival tumor block must be provided during pre-screening from patients in the Phase 1a Monotherapy Dose Exploration, Phase 1a Combination Safety Lead-in, Phase 1b Monotherapy Dose Expansion, and Phase 1b Combination Dose Expansion for evaluation of B7-H4 expression by IHC.

8.4.2 Procedures for Fresh Biopsy

All patients in Phase 1a Monotherapy Dose Exploration cohorts, and at least 15 patients per 30 patient cohort in Phase 1b Dose Expansion cohorts (monotherapy and in combination with pembrolizumab) will be required to undergo a fresh tumor biopsy during screening and just prior to drug administration at Cycle 3. For the patient's convenience, the biopsy required prior to Cycle 3 Day 1 is flexible as long as the biopsy is obtained after Cycle 2 Day 15 and prior to study drug administration on Cycle 3 Day 1.

The following guidelines apply to patients who consent for tumor biopsy:

- All patients that consent to a pre-treatment biopsy must have at least one tumor site that can be biopsied and be willing to have pre-treatment and on-treatment biopsies, from the same lesion where feasible.
- Patients in Phase 1a Monotherapy Dose Escalation who do not have archival tissue require a fresh tissue biopsy for enrollment.
- Biopsies will be performed according to the treating institution's own guidelines. These biopsies must be excisional, incisional or core needle biopsies, as fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses.
- If a pre-treatment biopsy has been performed as part of the patient's standard of care within 28 days prior Cycle 1 Day 1 and the sample can be made available to study Sponsor, the pre-treatment biopsy does not need to be repeated.
- Sites for biopsy must be distinct from target lesions used for efficacy assessment
- Patient must have recovered from any acute adverse effects of the biopsy procedure prior to dosing

8.5 Clinical Safety Laboratory Assessments

Laboratory assessments will be performed in accordance with the Schedule of Assessments (Appendix 1). Laboratory assessments will be performed locally at each study center's laboratory by means of their established methods. Before starting the study, the Investigator will provide the Sponsor (or designee) with a list of the normal ranges and units of measurement. Testing HbsAg, HbcAb and HCV RNA will be performed at screening and if clinically indicated on study. Blood samples should be taken using standard techniques.

Abnormal laboratory results that lead to a change in patient treatment management (eg, dose delay, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and will be recorded on the AE page of the eCRF. Laboratory test values that meet SAE criteria must be reported as SAEs. Refer to Section 8.12.2 for details regarding the reporting of abnormal laboratory findings as AEs.

If either AST or ALT is elevated, obtain total serum bilirubin and alkaline phosphatase; repeat daily or other interval, as clinically indicated, until resolved or stable. Additional tests to rule out drug-induced liver injury (eg, abdominal ultrasound, serum gamma- glutamyl transferase (GGT), hepatitis serology) may be obtained at any time, if clinically indicated.

8.6 Efficacy Assessments

8.6.1 Tumor Assessment

The first on-study imaging assessment should be performed within 28 days from C1D1. Subsequent tumor assessments will be performed in accordance with the Schedule of Assessments (Appendix 1) and should consist of clinical examination and appropriate imaging techniques (preferably computed tomography (CT) scans with appropriate slice thickness per RECIST v1.1, magnetic resonance imaging (MRI) acceptable). The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

Tumor response assessment will be performed every 6 weeks for 6 months and then every 12 weeks by the Investigator per the Schedule of Assessments (Appendix 1) using RECIST v1.1 guidelines (Appendix 4) (Eisenhauer 2009).

If patient terminates prior to scheduled CT/MRI scans, patient should have scans done at the EOT visits (does not need to be repeated if performed within 8 weeks prior to the EOT visits, or if tumor progression was previously determined). After discontinuation of study treatment for reasons other than progressive disease, or withdrawal of consent, or initiation of additional anti-cancer therapy, tumor assessments will continue approximately every 12 weeks until disease progression, withdrawal of consent or start of new anti-cancer therapy.

8.7 Pregnancy

Pregnancy testing (serum or urine) should be conducted in accordance with the Schedule of Assessments (Appendix 1).

8.7.1 Pregnancy Testing

Pregnancy is an exclusion criterion and women of child bearing potential must not be considering pregnancy during the study. Pregnancy tests should be performed for any woman of childbearing potential. Serum ß-hCG (evaluated by local laboratories) and urine pregnancy tests will be performed only on women of child bearing potential.

8.7.2 Pregnancy on Study

In the event of suspected pregnancy, a serum pregnancy test should be repeated. Patients who become pregnant during the study must discontinue study treatment immediately.

The Sponsor must be notified of any patient who becomes pregnant while participating in this study. Although pregnancy is not an AE, all pregnancies must be followed to conclusion to determine their outcome. It is the responsibility of the Investigator or designee to report any pregnancy in a patient that occurs during the study by completing the Pregnancy Reporting Form. Please contact the study monitor to receive the Pregnancy Reporting Form on learning of a pregnancy.

Notification of the pregnancy including the anticipated date of birth should be submitted on a Pregnancy Reporting Form within 24 hours of awareness and reported using the same procedure as described for reporting SAEs (Section 8.12.6). If the pregnancy is to be terminated, the anticipated date of termination should be provided.

The patient will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriages, premature termination of the pregnancy, and congenital abnormalities will be reported as SAEs. Information on the status of the mother and child will be forwarded to the Sponsor. Follow-up will be in accordance with regulatory guidance and at least 6 to 8 weeks after the estimated delivery date.

Pregnancies that occur during the first 6 months of the Follow-up period should be reported to the Sponsor, and followed as described above.

Refer to https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf for additional guidelines regarding pregnancy and contraception for pembrolizumab.

8.8 Pharmacokinetics

Samples for PK assessment will be collected and processed according to instructions provided in a separate laboratory manual. FPA150 concentration in serum will be determined using an enzyme linked immunosorbent assay (ELISA) method. Additional guidance for sampling and procedures is provided in Appendix 2.

The PK parameters (AUC, C_{max}, C_{trough}, CL, $t_{1/2}$, V_{ss}) for FPA150 will be derived from serum FPA150 concentration-time data using non-compartmental analysis (NCA) when appropriate and applicable. Alternative methods may be considered. Other parameters, such as dose proportionality, accumulation ratio, attainment of steady state, will also be calculated if the data are available. The impact of immunogenicity on FPA150 exposure will be assessed.

Samples for PK analysis for any of the cohorts of FPA150 in combination with pembrolizumab will be collected and held at a central laboratory. Individual and mean (±SD) serum concentration-time data for FPA150 and pembrolizumab may be tabulated and plotted by dose level/cohort. PK parameters for the combination may be tabulated and summarized by dose level/cohort when appropriate and applicable.

8.9 Pharmacodynamics

Samples for pharmacodynamic assessment will be collected and processed according to instructions provided in a separate laboratory manual. Additional guidance for sampling and procedures is provided in the following appendices:

- Specific timing requirements for study assessments and procedures: Appendix 1 Schedule of Assessments.
- Guidance for the specific timing of pharmacodynamic sample collection: Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collection.
- Specific pharmacodynamic analyses to be conducted: Appendix 3 List of Pharmacodynamic Samples for Analyses.

Blood and tumor samples will be collected at baseline and on treatment for exploratory pharmacodynamic biomarker analysis, to determine the effect of study drug on target cells and target biology, and to confirm mechanism of action in human disease.

8.10 Immunogenicity Assessments

Samples for immunogenicity assessment will be collected and processed according to instructions provided in a separate laboratory manual. Additional guidance for sampling and procedures is provided in the following appendices:

- Specific timing requirements for study assessments and procedures: Appendix 1 Schedule of Assessments.
- Guidance for the specific timing of immunogenicity sample collection: Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collection.

Immunogenicity, defined as an ADA immune response to FPA150, will be assessed by measurement of total anti-FPA150 antibodies from all patients. Immunogenicity testing will consist of screening, confirmation, and titration of anti-FPA150 antibodies. Additional characterization of a confirmed anti-FPA150 antibody response may be considered.

Immunogenicity, defined as an ADA immune response to pembrolizumab, will be assessed by measurement of total anti-pembrolizumab antibodies from all patients. Immunogenicity testing will consist of screening, confirmation, and titration of anti-pembrolizumab antibodies. Additional characterization of a confirmed anti-pembrolizumab antibody response may be considered.

8.11 Predictive and Pharmacodynamic Biomarkers

Samples for predictive and pharmacodynamic biomarker assessment will be collected and processed according to instructions provided in a separate laboratory manual. Additional guidance for sampling and procedures is provided in the following appendices:

- Specific timing requirements for study assessments and procedures: Appendix 1 Schedule of Assessments.
- Guidance for the specific timing of PK, immunogenicity, and pharmacodynamic sample collection: Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collection.
- Specific pharmacodynamic analyses to be conducted: Appendix 3 List of Pharmacodynamic Samples for Analyses.

A variety of endpoints that could monitor drug activity and potentially predict clinical response to FPA150 may be investigated in peripheral blood and archival and/or fresh tumor specimens, collected from patients prior to and during treatment. Data from these analyses will be evaluated for association with response and/or safety data.

Exploratory biomarker analysis will be conducted to investigate the relationship between baseline target levels, tumor immune phenotype, pharmacodynamic response within the tumor and in the periphery, and efficacy.

8.11.1 Analysis of B7-H4 Expression

Samples for analysis of B7-H4 expression will be collected and processed according to instructions provided in a separate laboratory manual. Additional guidance for sampling and procedures is provided in the following appendices:

- Specific timing requirements for study assessments and procedures: Appendix 1 Schedule of Assessments.
- Specific pharmacodynamic analyses to be conducted: Appendix 3 List of Pharmacodynamic Samples for Analyses.

Five Prime has developed an IHC assay based on a monoclonal anti-B7-H4 antibody, whose specificity and sensitivity has been evaluated (refer to Section 2.2.1 for additional information regarding FPA150 and B7-H4). Baseline tumor samples (archival or recent biopsy if archival is not available) for B7-H4 expression by IHC must be available prior to enrollment for

patients in the Phase 1a Monotherapy Dose Exploration, Phase 1a Combination Safety Lead-in, Phase 1b Monotherapy Dose Expansion and Phase 1b Combination Dose Expansion cohorts. Archival tissue for patients enrolled in Cohort 1b1 (Breast Cancer) must be within 24 months prior to pre-screening.

Because it is predicted that patients whose tumors have high levels of expression of the target B7-H4 protein are more likely to respond to FPA150, patients in the Phase 1a Dose Exploration,Phase 1a Combination Safety Lead-in, and in Phase 1b Dose Expansion will be selected based on B7-H4 expression by an IHC test.

Prevalence studies conducted at Five Prime with the IHC assay using archival tissue has shown a variety of cancers express high levels of B7-H4 including breast, ovarian, endometrial and urothelial carcinoma.

8.11.3 Tumor Marker [redacted]

Samples for tumor markers [redacted] will be collected and processed according to instructions provided in a separate laboratory manual. Additional guidance for sampling and procedures is provided in the following appendices:

- Specific timing requirements for study assessments and procedures: Appendix 1 Schedule of Assessments.
- Guidance for the specific timing of PK, immunogenicity, and pharmacodynamic sample collection: Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collection.

- Specific pharmacodynamic analyses to be conducted: Appendix 3 List of Pharmacodynamic Samples for Analyses.

Blood samples will be processed to collect plasma and stored frozen prior to analysis. In addition to the PK and ADA analyses, plasma samples may be analyzed to determine the pharmacodynamic effect of study drugs on [redacted] or circulating tumor marker concentrations. Samples may be assessed by ELISA, seromics, and/or other relevant multiplex-based protein assay methods.

[redacted]

8.11.5 Gene Expression Profiling

Samples for gene expression profiling will be collected and processed according to instructions provided in a separate laboratory manual. Additional guidance for sampling and procedures is provided in the following appendices:

- Specific timing requirements for study assessments and procedures: Appendix 1 Schedule of Assessments.
- Guidance for the specific timing of PK, immunogenicity, and pharmacodynamic sample collection: Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collection.
- Specific pharmacodynamic analyses to be conducted: Appendix 3 List of Pharmacodynamic Samples for Analyses.

Whole blood and tumor tissue for exploratory biomarker analysis will be collected at the time points indicated in the Schedule of Assessments (Appendix 1) [redacted]

8.12 Adverse Events

Adverse events should be collected/ recorded in accordance with the Schedule of Assessments (Appendix 1).

8.12.1 Method of Detecting and Reporting Adverse Events and Serious Adverse Events

In Phase 1a and Phase 1b, any new symptoms, injury or worsening of symptoms that occur during the Screening Period, ie, following signing of the ICF but prior to first infusion (Cycle 1 Day 1), will be considered pretreatment events and reported on the Medical History page of the eCRF, unless they directly correlate to a study-related procedure in which case they will be reported on the AE eCRF page. Otherwise, AE reporting will begin at the time of infusion of Cycle 1, Day 1 (day of first infusion) and continue until completion of the End of Treatment visit or until 4 weeks (28 days) after the last dose of study treatment.

Patients in Phase 1b will undergo long-term follow-up for survival by clinic visit or by telephone approximately every 3 months ± 28 days after the EOT visit until up to 24 months after the last patient is enrolled into the study.

SAEs occurring after the EOT visit should be reported to the Sponsor by the Investigator only if the Investigator considers a causal relationship with FPA150. SAEs should always be recorded on the AE eCRF.

8.12.2 Adverse Event Definitions

An AE is any untoward medical occurrence that occurs in a patient administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to the product. Abnormal laboratory findings that are not considered clinically significant will be recorded only on the laboratory eCRF pages and not on the AE pages. Abnormal laboratory results that are considered clinically significant in the Investigator's opinion are also to be recorded on the AE eCRF. Relationship (reasonable causal relationship) to drug therapy and counter measures undertaken will be noted on the eCRF.

All AEs including intercurrent illnesses that occur during the study, from the time of administration of study treatment, will be documented on the AE eCRF. Concomitant illnesses, which existed prior to the day of the first study infusion, will not be considered AEs

unless they worsen by at least one grade during the treatment period. Intensity (severity) grade will be defined according to the NCI-CTCAE, version 4.03. Pre-existing conditions will be recorded on the Medical History eCRF.

A treatment-emergent adverse event (TEAE) will be defined as an AE that begins or worsens in severity after at least one dose of study treatment (FPA150) has been administered.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, will not be reported as an AE, but the procedure and/or therapeutic treatment should be recorded on the appropriate eCRF. The medical condition for which the procedure was performed must be reported as an AE (or as part of the patient's medical history, if the procedure precedes the initiation of study-prescribed treatment). Disease progression is an efficacy endpoint and not an AE or SAE. Concurrent signs and symptoms clearly associated with disease progression itself should not be reported as an AE or SAE.

8.12.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to seriousness, intensity (severity), causality and the outcome and action taken. All AEs, regardless of the relationship to study treatment, will be recorded on the AE eCRF. This includes potential end-organ toxicity, eg, renal (proteinuria), hepatic, and cardiovascular (increased blood pressure) effects, and effects on wound healing. All AE reports should contain a brief description of the event, date of onset, ongoing or date of resolution, intensity, treatment required, relationship to study treatment, action taken with the study treatment, outcome, and whether the event is classified as serious as described below.

8.12.3.1 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death. Death may occur as a result of the underlying disease process. All events other than progression of underlying disease that result in death during the reporting period up to 28 days following the last dose of study treatment must be treated as an SAE and reported as such
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medically significant events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to

prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether a case is considered medically significant or serious and whether expedited reporting is appropriate.

Hospitalization for an event solely related to progressive disease is not considered an SAE. Hospitalization for an elective or planned procedure to treat a pre-existing condition is not considered an SAE unless it results in one of the outcomes listed above.

8.12.3.2 Intensity (Severity)

Investigators need to assess the severity of AEs according to the guidelines provided in NCI-CTCAE, version 4.03.

CTCAE v 4.03 Severity Grades are:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; mild AE
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living; moderate AE
- Grade 3: Severe or medically significant but non-immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; severe AE
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Fatal AE

If the AE is not specified in the CTCAE or the study protocol, the grading of severity will be assessed as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or death due to the AE (Grade 5) using the following definitions:

- Mild: The patient is aware of the event or symptom, but the event or symptom is easily tolerated.
- Moderate: The patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- Severe: Significant impairment of functioning: the patient is unable to carry out usual activities.
- Very severe (life-threatening): The patient's life is at risk from the event.

8.12.3.3 Causality

The Investigator will assess the causality/relationship between the study treatment and the AE and record that assessment on the eCRF.

The most likely cause of an SAE (eg, disease under treatment, concomitant disease, concomitant medication, other) will be indicated on the eCRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to study treatment will be assessed by means of a question: 'Is there a reasonable possibility that the AE may have been caused by the study treatment?' Answer Yes or No.

The description below provides guiding principles for the Investigator to make casualty assessments.

- Yes, there is a reasonable possibility that the AE may have been caused by the study treatment:
  - Follows a reasonable temporal sequence from administration of the study treatment
  - Could not be reasonably explained by the patient's clinical state, environmental or toxic factors, or other therapies administered to the patient
  - Disappears or decreases on cessation or reduction in dose of the study treatment
  - Follows a known pattern of response to the study treatment
  - Reappears or worsens on re-challenge
- No, there is no reasonable possibility that the AE may have been caused by the study treatment:
  - Does not follow a reasonable temporal sequence from administration of the study treatment
  - Could be reasonably explained by the patient's clinical state, environmental or toxic factors, or other therapies administered to the patient
  - Does not follow a known pattern of response to the study treatment
  - Does not reappear or worsen on re-challenge

The relatedness for SAEs will also be assessed and documented on the AE eCRF.

8.12.3.4 Outcome and Action Taken

The Investigator will record the action taken and outcome for each AE in the eCRF according to the following criteria:

- Action Taken
  - Dose Not Changed
  - Drug Interrupted
  - Drug Withdrawn
  - Not Applicable
  - Unknown
- Outcome
  - Fatal
  - Not Recovered/Not Resolved
  - Recovered/Resolved
  - Recovered/Resolved with Sequelae
  - Recovering/Resolving

8.12.4 Follow-up of Adverse Events and Serious Adverse Events

All treatment-related SAEs experienced by a study patient, will be monitored until the event has resolved or stabilized, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Sponsor, there is a satisfactory explanation for the changes observed, or the patient is lost to follow-up.

All unresolved AEs should be followed by the Investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained. The Investigator should notify the study Sponsor of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. The Sponsor should also be notified if the Investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that has participated in this study.

8.12.5 Treatment of Overdose

8.12.5.1 FPA150

In the event of a medical emergency due to suspected FPA150 overdose the Medical Monitor should be contacted as soon as possible. Monitoring and reporting a suspected treatment overdose should follow guidelines for AEs and SAEs. No specific antidote is available for

treating overdose with FPA150. Management of any AEs due to overdose should be managed per Institutional practice.

8.12.5.2 Pembrolizumab

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.12.6 Regulatory Reporting Requirements for Serious Adverse Events

Any SAEs, whether or not considered related to treatment with FPA150, must be reported by the Investigator to the Sponsor or Sponsor's designee within 24 hours of the Investigator becoming aware of the event and must be recorded on both the Electronic Serious Adverse Event Form (eSAE Form) and AE eCRF. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and outcome/resolution of the event will be recorded on the eSAE form. Paper forms for reporting SAEs will also be provided to the study centers for SAE reporting in case the eSAE system is down.

A digital copy of the eSAE form must be e-mailed **within 24 hours** to the attention of the ICON Pharmacovigilance Safety Specialist Email: icon-mads@iconplc.com:

If the eSAE form is down or unavailable, the use of a paper SAE form or a digital copy is acceptable. The form must be faxed or emailed within 24 hours to the attention of the ICON Pharmacovigilance Safety Specialist:

ICON Medical and Safety Services
Fax number: +1-866-955-7492
SAE Hotline: +1-888-723-9952
icon-mads@iconplc.com

The Investigator should not wait to receive additional information to fully document the event before notification of a SAE, though additional information may be requested. The minimum information that is required for an initial SAE report is as follows:

- Patient number
- Investigator name and study center number
- Event term
- Event onset date
- Serious criteria
- Relationship to study treatment(s)

As applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Serious AEs occurring after the EOT visit should be reported to the Sponsor by the Investigator if the Investigator considers there is a causal relationship with the study treatment.

The Investigator and Sponsor will review each SAE report and evaluate the seriousness and causal relationship of the event to study treatment. In the event of a disagreement about causality, the most conservative assessment will be used. In addition, the Sponsor will evaluate the expectedness according to the FPA150 IB. Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

The Sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the Food and Drug Administration (FDA), per 21 Code of Federal Regulations (CFR) 312.32, and to other regulatory authorities, according to national law and/or local regulations. All Investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC.

The Sponsor or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

8.13 Concomitant Medication Recording

Concomitant medications should be collected/ recorded in accordance with the Schedule of Assessments (Appendix 1).

All medications that were used from 14 days prior to enrollment through the end of study participation will be recorded in the eCRF. These are to include prescription and nonprescription medications, transfusions, vitamins and nutritional supplements, and other remedies. Excluded prior medications are excluded via the eligibility criteria (Section 5.2). Additional guidance regarding concomitant medication is provided in Section 6.10.

8.14 End of Treatment Follow-Up

End of treatment follow-up should be done in accordance with the Schedule of Assessments (Appendix 1). There is no pre-specified maximum number of doses of FPA150. Patients may continue receiving FPA150 as monotherapy according to their study specified cohort/ dose until Investigator-assessed disease, progression or the patient meets any of the other protocol-specified withdrawal criteria (refer to Section 7). Patients receiving pembrolizumab can continue receiving drug according to their study specified cohort/dose until Investigator-assessed disease progression, the patient meets any of the other protocol-specified withdrawal criteria (refer to Section 7) or the patient completes approximately 24 months of treatment.

If one of the two drugs have to be discontinued, patients may continue to receive the other drug alone. Treatment beyond disease progression may be allowed in select patients with initial RECIST v1.1 defined progressive disease if the benefit/risk assessment favors continued administration of study treatment (eg, patients are continuing to experience clinical benefit as assessed by the Investigator, and tolerating treatment).

Each patient is required to complete an EOT follow-up period which will include visits at approximately 28 (±7) days and 100 (±7) days after the last dose (refer to Appendix 1).

8.14.1 Long-Term Follow-Up

Long-term follow-up should be done in accordance with the Schedule of Assessments (Appendix 1). Patients enrolled in Phase 1b will be required to enter into long-term follow-up after they have permanently discontinued study drug (refer to Section 7) until death, withdrawal of consent or study termination. During long-term follow-up, patients should be contacted every 12 (±2) weeks for survival status. Patients should have tumor scans every 12 (±2) weeks, if tumor progression was not previously determined and/or use of alternative anti-cancer therapy has not been initiated. Any new anti-cancer therapy should be documented.

9 Statistical Considerations

Before database lock, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final integrated study report.

9.1 Sample Size Determination

For Phase 1a, this study is designed as a dose escalation study with objectives that include determination of an MTD and/or RD for FPA150 monotherapy and FPA150 combined with pembrolizumab. It will also include assessments of the safety and tolerability of FPA150 monotherapy and in combination with pembrolizumab. The sample size of this study was not determined by strict statistical considerations. The total number of patients planned for this study is estimated to be up to 278.

Phase 1a will enroll up to 68 patients. The 68 patients include 23 to 26 patients in the Phase 1a Monotherapy Dose Escalation cohorts, 6 to 22 patients in the Phase 1a Combination Safety Lead-in cohort andup to 20 additional patients in the Phase 1a Monotherapy Dose Exploration cohorts to further evaluate safety, PK, pharmacodynamics, and clinical activity at 1 or more dose levels (to be conditional upon the dose level clearing DLT criteria).

For the objective of estimating the ORR of FPA150 in the Phase 1b Monotherapy and Combination Dose Expansion cohorts, it is estimated that up to 30 patients will be enrolled to ensure 25 evaluable patients in each cohort. The following table displays the corresponding 2-sided 90% confidence interval (CI) and the precision for the various observed response rates based on 25 evaluable patients. The sample size of 25 is chosen to ensure that it will allow to exclude 10% when the observed ORR is 24% or higher (Agresti 1998).

Phase 1b will enroll up to 210 patients with specific tumor types. Up to 30 patients are planned for each of the 3 FPA150 Monotherapy Dose Expansion cohorts, and one additional cohort of FPA150 in combination with pembrolizumab. Additional cohorts of up to 30 patients each may be enrolled, based on emerging clinical and translational data.

Table 11: Two-Sided 90% Confidence Intervals of the Observed Response Rates

Sample Size	Observed Response Rate	90% CI	Precision (longest one-sided CI length*)
25	5/25 (20%)	(8%, 38%)	18%
	6/25 (24%)	(11%, 42%)	18%
	7/25 (28%)	(14%, 46%)	18%
	8/25 (32%)	(17%, 50%)	18%
	9/25 (36%)	(20%, 54%)	18%
	10/25 (40%)	(24%, 58%)	18%

Abbreviations: CI = confidence interval.
*Distance from the observed response rate to the lower or upper CI boundary.

Considering it is possible to open successive cohorts after data is reviewed, up to 210 patients may be enrolled in Phase 1b (not to exceed 30 patients in any individual cohort).

A 2-stage design will be used to determine the actual enrolled subjects. Sponsor will evaluate efficacy in phase 1b on an ongoing basis and may suspend or terminate enrollment in specific cohorts if <=1 response (CR or PR per RECIST 1.1) is observed in the first 16 patients enrolled in each cohort. In this case, the probability of early termination is 0.81 with 0.05 responder rate for futility and 0.2 responder rate for efficacy.

9.2 Populations for Analyses

The following analysis populations are defined for the study:

- Safety Population—all patients who have received any portion of at least one dose of FPA150.
- DLT-Evaluable Population—all patients enrolled into Phase 1 monotherapy and in combination with pembrolizumab who received at least two doses of FPA150 and completed Cycle 1 of treatment, or who experienced a DLT in Cycle 1.
- Pharmcokinetic Full Analysis Population: All patients who received at least one dose of FPA150 and had at least one FPA150 serum concentration result.
- Pharmacokinetic -Evaluable Population—all patients in the PK Full Analysis Population who had sufficient PK sample for the calculation of at least one PK parameter on at least one Study Day.
- Efficacy-Evaluable Population—all patients who met eligibility criteria, received at least one dose of FPA150, have measurable tumor lesions at baseline, and have at least one post-baseline disease assessment unless the death and clinical progressive disease occurred prior to the first post baseline disease assessment.

9.3 General Considerations

All analyses will be descriptive and will be presented by phase, dose group, cohort and overall as appropriate. In addition, all patients dosed at the MTD and/or RD will also be summarized as appropriate. Data collected in this study will be presented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of valid cases, arithmetic mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.4 Statistical Analyses

9.4.1 Safety Analyses

Safety analyses will be performed separately within both phases of the study and for all patients combined. Data from all patients that receive any portion of at least one dose of FPA150 as monotherapy or one dose of FPA150 in combination with pembrolizumab will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, weight, ECGs, and concomitant medications/procedures will be tabulated and summarized. In addition, the incidence of DLTs in Phase 1a will be summarized.

Subject incidence of AEs will be summarized overall and with separate summaries for serious AEs, AEs leading to discontinuation, AEs leading to death, and NCI CTCAE Grade 3 or higher AEs. The patients' worst grade for each preferred term will be used for the summary of AEs by CTCAE grade. Treatment-related AEs and SAEs will also be summarized similarly.

Weight and vital signs will be summarized descriptively (N, mean, SD, median, minimum, and maximum). ECOG performance status will be summarized categorically and descriptively.

Shift tables displaying patient counts and percentages classified by baseline grade and maximum grade on treatment will be provided for laboratory data by cohort and overall as appropriate.

9.4.2 Efficacy Analyses

The ORR will be summarized with frequencies and percentages with 90% CI by each dose/cohort. The duration of response (DOR) for complete response (CR) and partial response (PR) patients and PFS for all treated patients will be summarized with descriptive statistics (N, arithmetic mean, SD, median, minimum, and maximum). The ORR, DOR, and PFS will

be determined using RECIST v1.1. Kaplan-Meier methodology will be used to estimate median DOR and PFS and corresponding 95% CI.

ORR, DOR, and PFS are defined below.

ORR: defined as the total number of patients with confirmed responses of either CR or PR per RECIST v1.1 divided by the total number of patients who are evaluable for a response.

DOR: defined as the time from onset of response (CR or PR) that is subsequently confirmed to the first observation of progressive disease or death due to any cause. Patients who are alive and progression-free at the time of data analysis will be censored at the time of their last assessment for tumor response.

PFS: defined as the time from the patient's first dose to the first observation of progressive disease or death due to any cause. Patients who are alive and progression-free at the time of data analysis will be censored at the time of their last assessment for tumor response.

More details of censoring rule for DOR and PFS will be outlined in SAP.

9.4.3 Pharmacokinetic Analyses

Individual and mean (±SD) serum FPA150 concentration-time data from monotherapy or in combination with pembrolizumab will be tabulated and plotted by dose level. Estimated individual and mean (±SD) PK parameters (eg, AUC, C_{max}, C_{min}, CL, $t_{1/2}$, V_{ss}) will be tabulated and summarized by dose level. Other descriptive statistics might be reported for serum FPA150 when appropriate and applicable.

For cohorts of FPA150 in combination with pembrolizumab samples for PK analysis will be collected and held at a central laboratory. Individual and mean (±SD) serum concentration-time data for FPA150 and pembrolizumab may be tabulated and plotted by dose level/cohort. Other parameters, such as dose proportionality, accumulation ratio, and attainment of steady state, may be evaluated, tabulated, and summarized by dose level/cohort if the data is available. The impact of immunogenicity on FPA150 exposure will be assessed, tabulated, and summerized by dose level as data allow.

9.4.4 Immunogenicity Analyses

A baseline ADA-positive subject is defined as a subject who has an ADA positive sample at baseline. An ADA-positive subject is a subject with at least one ADA-positive sample relative to baseline after initiation of the treatment. The frequency distribution of baseline ADA-positive subjects and ADA-positive subjects after initiation of the treatment will be summarized for FPA150 and pembrolizumab, respectively.

9.4.5 Pharmacodynamic Analyses

A list of potential pharmacodynamic analyses is provided in Appendix 3. Selected pharmacodynamic biomarkers will be assessed for meaningful changes between pretreatment and on-treatment tumor and peripheral blood samples.

9.4.6 Interim Analyses

Safety data will be reviewed on a routine basis by the Sponsor, contract research organization (CRO), and/or the CRC. In Phase 1a, the Sponsor (and/or designee) and Investigator(s) will review safety data from each dose cohort prior to dose escalation or de-escalation. AE data from the treatment period following the DLT window will be presented to the Medical Monitors when available. A 2-stage design will be used as described in Section 9.1.

10 Ethical, Legal, and Administrative Aspects

10.1 Data Quality Assurance

The Sponsor (or designee) may conduct a site visit prior to study initiation at a site to verify the qualifications of each investigator, inspect the site facilities, and inform the investigator of responsibilities and for ensuring study compliance and procedures for adequate and correct documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other pertinent data for each study patient. All information recorded on the eCRFs for this study must be consistent with the patients' source documentation (ie, medical records).

10.2 Electronic Case Report Forms and Source Documentation

All data obtained during this study should be entered in the eCRFs promptly. All source documents from which eCRF entries are derived should be placed in the patient's medical records. eCRF fields for which source documents will typically be needed include laboratory assessments, physical examination reports, nursing notes, ECG recordings, hospital records, CT scans, and/or MRI) reports.

The eCRFs for each patient will be checked against source documents at the study site by the site monitor. Instances of missing or uninterpretable data will be discussed with the investigator for resolution.

10.3 Access to Source Data

During the study, a monitor will perform routine site visits to review protocol compliance, compare eCRFs and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

In accordance with ICH Good Clinical Practices (GCP) guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents. Moreover, regulatory authorities, IRBs, IECs, and/or the Sponsor's Quality Assurance group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The investigator assures that the Sponsor and/or Sponsor's designee will receive the necessary support to complete these activities.

All participating centers should take particular care in ensuring that original imaging source data (CT images, MRI images, echo images, etc.) are maintained and accessible for monitoring, and that these original source data are then archived on a long-term basis in compliance with ICH GCP Section 8. These images must be stored in a secure location until the Sponsor or Sponsor's designee authorizes their destruction, and must be retrievable by study patient number in the event of an audit.

10.4 Data Processing

The Data Management Plan, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. All processes for data processing and query handling will be described in the Data Management Plan.

10.5 Archiving Study Records

Each study site will maintain a study file, which should contain, at minimum, the IB, the protocol and any amendments, the protocol for tissue sampling, drug accountability records, correspondence with the IEC/IRB and the Sponsor (or designee), and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the Sponsor or its designees.

The investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In addition, the investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of the Sponsor. Should the investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing of the new responsible person and/or the new location. Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

10.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and investigator abide by GCP guidelines of the ICH and the Declaration of Helsinki (1989). The study also will be carried out in compliance with local legal requirements.

10.7 Informed Consent

All information about the clinical study, including the patient information and the ICFs, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki.

The ICFs, prepared by the investigator with the assistance of the Sponsor, must be approved along with the study protocol by the IEC/IRB and be acceptable to the Sponsor before each patient is enrolled on the study; written informed consent will be obtained according to the regulatory and legal requirements. Copies of the signed ICFs will be retained by the patient and the original will be filed in the investigator's study center file, unless otherwise agreed.

The investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must be documented in the source documents and in the eCRF.

If a protocol amendment is required, the ICFs may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IRB/IEC and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

10.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/IEC, in accordance with local legal requirements. The Sponsor, Sponsor's agents, and investigator must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC approval prior to implementation. The protocol amendment will be submitted to the IND application / Clinical Trial Application under which the study is being conducted.

10.9 Clinical Study Report and Publications

The data collected during this study are confidential and proprietary to FivePrime. Any publications or abstracts arising from this study require approval by FivePrime prior to publication or presentation and must adhere to the Sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the

Sponsor at the earliest practicable time for review, but in any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. FivePrime shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10.10 Confidentiality

All study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on eCRFs and other documents submitted to the Sponsor or Sponsor's designee by their patient number, initials, and/or birth date. Study patients are not to be identified by name, and any information sent to the Sponsor or Sponsor's designee should have patient identifiers redacted, and replaced with patient identification. Documents that include the name of the patient (eg, the signed informed consent) must be maintained in confidence by the investigator. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

10.11 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to applicable regulatory authorities and investigators. Investigators will then notify local IRB/IECs as deemed appropriate based on individual IRB/IEC policy. A significant safety issue is one that has a significant impact on the course of the clinical trial or program (including the potential for suspension of the trial program or amendments to protocols) or warrants immediate update of informed consent.

11 References

Adams, S., S. Loi, D. Toppmeyer, *et al.* 2017. "Phase 2 Study of Pembrolizumab as First-Line Therapy for PD-L1-Positive Metastatic Triple-Negative Breast Cancer (mTNBC): Preliminary Data from KEYNOTE-086 Cohort B." Journal of Clinical Oncology. http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.1088#affiliationsContainer.

Aghajanian, C., M. Sill, K. Darcy, *et al.* 2011. "Phase II Trial of Bevacizumab in Recurrent or Persistent Endometrial Cancer: A Gynecologic Oncology Group Study." *Journal of Clinical Oncology* 29 (16):2259-2265.

Agresti, A. and B. Coull. 1998. "Approximate is Better than "Exact" for Interval Estimation of Binomial Proportions." *The American Statistician* 52 (2):119-126.

Cortes, J., J. O'Shaughnessy, D. Leosch, *et al.* 2011. "Eribulin Monotherapy Versus Treatment of Physician's Choice in Patients with Metastatic Breast Cancer (EMBRACE): A Phase 3 Open-Label Randomised Study." *Lancet* 377:914-923.

Eisenhauer, E. A., P. Bogaerts, L. H. Schwartz, *et al.* 2009. "New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1)." *European Journal of Cancer* 45:228-247.

Fan, M., Q. Zhuang, Y. Chen, *et al.* 2014. "B7-H4 Expression is Correlated with Tumor Progression and Clinical Outcome in Urothelial Cell Carcinoma." *Int J Clin Exp Pathol* 7 (10):6768-6775.

Fumoleau, P., R. Largillier, C. Clippe, *et al.* 2004. "Multicentre, Phase II Study Evaluating Capecitabine Monotherapy in Patients with Anthracycline- and Taxane-Pretreated Metastatic Breast Cancer." *European Journal of Cancer* 40:536-542.

Hamanishi, J., M. Mandai, T. Ikeda, *et al.* 2015. "Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients with Platinum-Resistant Ovarian Cancer." *Journal of Clinical Oncology* 33 (34):4015-4022.

Hanker, L., S. Loibl, N. Buchardi, *et al.* 2012. "The Impact of Second to Sixth Line Therapy on Survival of Relapsed Ovarian Cancer After Primary Taxane/ Platinum-Based Therapy." *Annals of Oncology* 23:2605-2612.

He, C., H. Qiao, H. Jiang, *et al.* 2011. "The Inhibitory Role of B7-H4 in Antitumor Immunity: Association with Cancer Progression and Survival." *Clinical and Developmental Immunology* 2011:1-8.

Kryczek, I., S. Wei, G. Zhu, *et al.* 2007. "Relationship Between B7-H4, Regulatory T Cells, and Patient Outcome in Human Ovarian Carcinoma." *American Association for Cancer Research* 67 (18):8900-8905.

Liu, W., Y. Chen, S. Zhu, *et al.* 2014. "B7-H4 Expression in Bladder Urothelial Carcinoma and Immune Escape Mechanisms." *Oncology Letters* 8:2527-2534.

Martin, M., A. Ruiz, M. Munoz, *et al.* 2007. "Gemcitabine Plus Vinorelbine Versus Vinorelbine Monotherapy in Patients with Metastatic Breast Cancer Previously Treated With Anthracyclines and Taxanes: Final Results of the Phase III Spanish Breast Cancer Research Group (GEICAM) Trial." *Lancet Oncology* 8:219-225.

Miyatake, T., B. Tringler, W. Liu, *et al.* 2007. "B7-H4 (DD-O110) is Overexpressed in High Risk Uterine Endometrioid Adenocarcinomas and Inversely Correlated with Tumor T-Cell Infiltration." *Gynecologic Oncology* 106:119-127.

Pujade-Lauraine, E., F. Hilpert, B. Weber, *et al.* 2014. "Bevacizumab Combined with Chemotherapy for Platinum Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomised Phase III Trial." *Journal of Clinical Oncology* 32 (13):1302-1308.

Saber, H., R. Gudi, M. Manning, *et al.* 2016. "An FDA Oncology Analysis of Immune Activating Products and First-In-Human Dose Selection." *Regulatory Toxicology and Pharmacology* 81:448-456.

Schmid, P., S. Adams, H. S. Rugo, *et al.* 2018. "Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer." *N Engl J Med* 379 (22):2108-2121.

Simon, I., D. Katsaros, I. Rigault de la Longrais, *et al.* 2007. "B7-H4 is Over-Expressed in Early-Stage Ovarian Cancer and is Independent of CA125 Expression." *Gynecologic Oncology* 106:334-341.

12 Appendices

The following appendices are provided for this protocol.

APPENDIX 1: SCHEDULE OF ASSESSMENTS

Table 12: Schedule of Assessments: Phase 1a and Phase 1b (Monotherapy and Combination Cohorts)

Procedure[a,b]	Pre-Screening	Screening	Cycle 1		Cycle 2	Subsequent Cycles	End of Treatment Follow-up Period		LTFU Period[p]
		Day –28 to Day 0	Day 1[q] ± 3 days	Day 8 ± 3 days	Day 1 ± 3 days	Day 1 ± 3 days	28 (±7) days post-last dose	100 (±7) days post-last dose	
Informed Consent	x[i]	x							
Review / Confirm Eligibility Criteria		x	x						
Medical History / Demographics		x	x						
Physical Examination[c]		x	x	x	x	x	x	x	
Height and Weight[c,d]		x	x		x	x	x	x	
Vital Signs[e]		x	x	x	x	x	x	x	
12-Lead ECG[f]		x					x	x	
ECOG Performance Status[g]		x	x		x	x	x	x	
Fresh Biopsy[h]		x				x			
Archival Tissue for IHC Testing for B7-H4 and Exploratory Biomarker Analyses[i]	x	x							
Clinical Safety Laboratory Tests[j]		x	x	x	x	x	x	x	
Hepatitis B (HBsAg and HBcAb), and Hepatitis C (HCV RNA)		x							
CT/MRI Tumor Assessment[k,]		x				x	x		x
Tumor Markers [l]	Refer to Appendix 2 for specific days and times								
Pregnancy Test[m]		x	x			x	x		
Sampling for PK, ADA, and Pharmacodynamics[n]	Refer to Appendix 2 for specific days and times								

Procedure[a,b]	Pre-Screening	Screening	Cycle 1		Cycle 2	Subsequent Cycles	End of Treatment Follow-up Period		LTFU Period[p]
		Day –28 to Day 0	Day 1[q] ± 3 days	Day 8 ± 3 days	Day 1 ± 3 days	Day 1 ± 3 days	28 (±7) days post-last dose	100 (±7) days post-last dose	
Study Drug(s)[o]			x		x	x			
Adverse Events[s]			x	x	x	x	x		
Prior/Concomitant Medications			x	x	x	x	x		
Thyroid Function Testing[r]			x			x			
Long-Term Follow-up Contact[p]									x

Abbreviations (for the Schedule of Assessments and Footnotes): ADA = anti-drug antibody; AE = adverse events; ALT = alanine transaminase; AST = aspartate transaminase; B7-H4 = transmembrane protein of the B7 family also known as B7S1, B7x, or VTCN1; CK = creatinine kinase; CT = computerized tomography; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; HBsAg = hepatitis B surface antigen; HCV = hepatitis C antibody; IV = intravenous; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetics; Q3W = once every 3 weeks; Q12W = once every 12 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

Additional guidance for sampling and procedures is provided in the following appendices:

- Guidance for the specific timing of PK, immunogenicity, and pharmacodynamic sample collection: Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collection.
- Specific pharmacodynamic analyses to be conducted: Appendix 3 List of Pharmacodynamic.
- Guidance for ECOG assessment: Appendix 4 Eastern Cooperative Oncology Group Performance Status.
- Specific clinical laboratory tests to be conducted: Appendix 5 Clinical Laboratory Tests.
- NYHA Classification: Appendix 6 New York Heart Association Classification.

Footnotes for Schedule of Assessments (additional assessment and procedure details are provided in Protocol Section 8):

a. Unless specified, procedure is to be completed within ± 72 hours of scheduled time point and performed prior to administration of study drug.

b. Any clinical assessment, laboratory test, or additional non-specified test may be obtained at any time, if clinically indicated.

c. A complete physical examination including height and weight will be performed at screening. A limited physical examination (e.g., symptom-directed examination of specific organ systems/body area) should be conducted at the specified time points after screening.

d. Height is only required to be recorded at screening. Weight is required to be recorded pre-dose at Day 1 of each cycle. After Cycle 1, the FPA150 dose will be recalculated at each infusion visit only if the patient's weight has changed > 10% from Cycle 1, Day 1. Weight will also be recorded at the final EOT visit.

e. Vital signs include pulse, respiratory rate, blood pressure, and temperature in a resting position. Measure vital signs prior to dosing and after completion of each IV infusion at the following time points: 5 minutes (± 3 min), 15 minutes (± 3 min), 30 minutes (± 3 min), and 1 hour post-dose (± 15 min). In addition, measure vital signs at 2, 3 and 4 hours post-dose (± 15 min) in patients that are being monitored for up to 4 hours post-dose (ie, after 1st infusion of FPA150 or after the end of infusion at each intrapatient dose escalation).

f. The exact time of the ECG should be recorded. The results will include heart rate, PR interval, QRS interval, QT interval, and QTc interval. Additional ECGs should be obtained at any time, if serum CK or cardiac troponin is elevated; if abnormal (excluding sinus tachycardia), ECGs should be obtained (if clinically indicated), until the abnormality is resolved or clinically stable. Additional ECGs may be obtained at any time, if clinically indicated. ECGs for each patient should be obtained from the same machine whenever possible. ECGs should be performed before the PK blood draw on days where both are done. To minimize variability, it is important that patients be in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (eg, television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. Any clinically significant changes in ECGs that occur during the study should be reported as an AE in the eCRF.

g. ECOG status is to be assessed at Screening, within 72 hours prior to dosing on Day 1 of each cycle, and at EOT.

h. A biopsy will be collected from the primary tumor or metastatic tumor site in patients enrolled in Phase 1a Monotherapy Dose Exploration, and a subset of patients (15 patients per 30-patient dose cohort) in Phase 1b Monotherapy Dose Expansion and Phase 1b Combination Dose Expansion cohorts; this will be done at screening and prior to the Cycle 3, Day 1 dose, from the same lesion where feasible. Refer to Section 8.4 for details regarding analyses of tumor tissue (fresh or archival).

i. B7-H4 expression results must be available prior to enrollment for all patients in Phase 1a Monotherapy Dose Exploration, Phase 1a Combination Safety Lead-in, and all patients in Phase 1b Dose Expansion (monotherapy and in combination with pembrolizumab). Archival tissue for patients enrolled in Cohort 1b1 (Breast cancer) must be within 24 months prior to pre-screening. Five unstained sections from an archival tumor block must be provided during pre-screening of patients in Phase 1a Dose Exploration and in Phase 1b Dose Expansion for evaluation of B7-H4 expression by IHC. Archival tumor block (preferred) or 10 unstained sections from an archival tumor block must be provided during screening in all patients for exploratory biomarker analyses.

j. **Refer to Appendix 5 for a listing of all Clinical Safety Laboratory Tests to be conducted**. Local hematology and blood chemistry test results must be obtained within 96 hours of dosing to confirm eligibility. **All serum chemistries will be assessed locally.**

k. CT/MRI of the tumor sites should be measured according to RECIST v1.1. Tumor assessment should be performed at screening, then every 6 weeks [±1] week for the first 6 months for patients who remain on treatment (and every 12 [±2] weeks, thereafter). If patient terminates prior to scheduled CT/MRI scans, patient should have scans done at the EOT visits (does not need to be repeated if performed within 6 weeks prior to the End of Treatment visits, or if tumor progression was previously determined). Patients who enter LTFU while showing clinical benefit should have tumor assessments Q12W for DOR. The same measuring modality should be used by the site to maintain consistency across the various time points.

l. Tumor markers will be assessed at a central laboratory. Tumor markers will be collected Day 1 of Cycles 1, 2, 3, 4, 5, 7, and 9. After Cycle 9 tumor markers will be collected every 12 weeks (every 4 cycles). Tumor markers will be collected at the times noted in Appendix 2.

m. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. A serum or urine pregnancy test will be performed at Cycle 1 Day 1 and every 6 weeks during treatment, and at the EOT visits.

n. Samples will be collected for PK, ADA, and pharmacodynamic analyses. All ADA and all PK samples should be collected prior to dosing. Not all visits will require collection of all 3 samples (PK, ADA, and Pharmacodynamic); refer to Appendix 2 for the collection schedule; refer to Appendix 3 for a list of the pharmacodynamic analyses. FPA150 samples for PK, ADA, and pharmacodynamic analyses will be assessed at a central laboratory. For cohorts of FPA150 in combination with pembrolizumb samples for PK will be collected and held at a central laboratory. In addition to the visits noted in Schedule of Assessments, PK and PD samples will be drawn on Day 4 and PK samples will be drawn on Day 15 of Cycle 1 for all cohorts.

o. FPA150 will be administered as a 60-minute (± 5 minutes) IV infusion Q3W in 21-day cycles until progressive disease or unacceptable toxicity. For FPA150 in combination with pembrolizumab cohorts, pembrolizumab will be administered after completion of the FPA150 IV infusion. Pembrolizumab will be administered at a dose of 200 mg by IV infusion over 30 minutes (± 5 minutes) starting on C1D1 and repeated Q3W on Day 1 of each 21-day cycle after all procedures and assessments have been completed. Pembrolizumab should not be co-administered with FPA150 through the same IV line. All patients must be monitored for at least 4 hours after the end of the first infusion of FPA150 and/or pembrolizumab. Patients may continue receiving FPA150 monotherapy or both drugs in combination according to their study specified cohort/dose until Investigator-assessed disease progression or the patient meets any of the other protocol-specified withdrawal criteria (refer to Section 7)

p. Only applicable for patients enrolled in Phase 1b cohorts, or the patient completes approximately 2 years of pembrolizumab. If one of the two drugs have to be discontinued, patients may continue to receive the other drug alone (based on Investigator discretion). Patients should be contacted every 12 (±2) weeks for survival status for up to 2 years. Patients should have tumor scans every 12 (±2) weeks, if tumor progression was not previously determined and/or use of alternative anti-cancer therapy has not been initiated. Any new anti-cancer therapy should be documented.

q. To minimize lab draws for patients, any labs obtained during screening that fall within the window of 3 days prior to C1D1 can be used for dosing purposes.

r. Thyroid function testing should be performed every 6 weeks while on treatment. Thyroid panel should include: Triiodothyronine (T3) or Free Triiodothyronine (FT3), Free thyroxine (FT4), and Thyroid stimulating hormone (TSH). Safety labs are done locally.

s. Adverse events should be collected only through the EOT Day 28 visit.

APPENDIX 2: SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND PHARMACODYNAMIC BLOOD SAMPLE COLLECTION

Table 13: Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collection

Study Cycle	Study Day	Time Point	Type of Sample
Screening	Screening (Day-28)	Screening	Tumor Biopsy
Cycle 1	Day 1	Prior to infusion	FPA150 and/or pembrolizumab PK (serum) (≤ 4 hours prior to dosing)
			FPA150 and/or pembrolizumab ADA (serum)
			FPA150 and/or pembrolizumab pharmacodynamics, (plasma) [redacted]
			FPA150 and/or pembrolizumab pharmacodynamics, [redacted]
			FPA150 and/or pembrolizumab pharmacodynamics, [redacted]
			FPA150 and/or pembrolizumab pharmacodynamics, [redacted]
			FPA150 and/or pembrolizumab Tumor Markers (serum)
		15 minutes after end of infusion	FPA150 and/or pembrolizumab PK (serum) (± 10 min)
		4 hours after end of infusion	FPA150 PK (serum) (± 30 min)
	Day 2	24 hours after end of infusion ± 3 hours	FPA150 PK (serum)
	Day 4	72 hours after end of infusion ± 3 hours	FPA150 PK (serum)
			FPA150 pharmacodynamics, [redacted]
	Day 8	168 hours after end of infusion ± 3 hours	FPA150 PK (serum)
			FPA150 and/or pembrolizumab pharmacodynamics, [redacted]
			FPA150 and/or pembrolizumab pharmacodynamics, [redacted]
			FPA150 and/or pembrolizumab pharmacodynamics [redacted]
	Day 15		FPA150 PK (serum) (within ± 1 day)

Study Cycle	Study Day	Time Point	Type of Sample
Cycles 2, 3, 4, 5, 7, 9	Day 1	Prior to infusion	Tumor Biopsy (**Cycle 3 only**)
			FPA150 PK (serum) (≤ 4 hours prior to dosing) For pembrolizumab PK at Cycles 2, 3, and 7 only)
			FPA150 ADA (serum) (Cycles 2, 3,5, 9 only For pembrolizumab ADA at Cycles 2, 3, and 7 only)
			FPA150 and/or pembrolizumab pharmacodynamics, [redacted]
			FPA150 and/or pembrolizumab pharmacodynamics, [redacted]
			FPA150 and/or pembrolizumab pharmacodynamics, [redacted]
			FPA150 and/or pembrolizumab pharmacodynamics [redacted]
			FPA150 and/or pembrolizumab Tumor Markers (serum)
		15 minutes after end of infusion	FPA150 PK (serum) (± 10 min)
Every 4th dose (12 weeks) after Cycle 9	Day 1	Prior to infusion	FPA150 PK (serum) (≤ 4 hours prior to dosing)
			FPA150 ADA (serum) (prior to dose for Cycles 13, 17 and every 8th dose [24 weeks] after Cycle 17)
			FPA150 and/or pembrolizumab Tumor Markers (serum) (cycles 13, 17, 21, and 25 only)
End of Treatment Follow-up Period (28 [±7] days and 100 [±7] days post-last dose)	Study discontinuation/ Progressive disease	Post treatment	FPA150 and/or pembrolizumab PK (serum)
			FPA150 and/or pembrolizumab ADA (serum)
			FPA150 pharmacodynamics, [redacted]
			FPA150 and/or pembrolizumab pharmacodynamics, [redacted]
			FPA150 and/or pembrolizumab pharmacodynamics, [redacted]

Abbreviations: ADA = anti-drug antibody; [redacted] PK = pharmacokinetics

APPENDIX 3: LIST OF POTENTIAL PHARMACODYNAMIC SAMPLES FOR ANALYSES

Pharmacodynamic samples for analyses may include, but are not limited to, the following:

- Tumor biopsy samples
  - Immunohistochemistry (IHC) analysis of selected biomarkers
  - [redacted]
- Blood samples
  - [redacted]
  - [redacted]
  - [redacted]

APPENDIX 4: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Table 14: Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status Criteria
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature (light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX 5: CLINICAL LABORATORY TESTS

The laboratory parameters outlined in Table 15 will be determined in accordance with the Schedule of Assessments and will be performed locally.

Table 15: Clinical Laboratory Tests

Hematology:	
Complete blood cell (CBC) with differential:	
white blood cells (WBC)	platelets
ANC	hemoglobin
neutrophils (%)	hematocrit
eosinophils (%)	red blood cells (RBC)
basophils (%)	
lymphocytes (%)	
monocytes (%)	
Urinalysis:	
Dipstick (appearance, color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood)	
If dipstick is positive (2+ or greater) for blood or protein, perform a microscopic examination.	
Clinical chemistry:	
Albumin	
alkaline phosphatase	glucose
ALT (SGPT)	lactate dehydrogenase (LDH)
AST (SGOT)	phosphate
blood urea nitrogen (BUN)	potassium
calcium	sodium
chloride	total bilirubin
carbon dioxide (CO_2 [bicarbonate])	total cholesterol
creatinine	total protein
direct bilirubin	uric acid
magnesium	
Screening laboratory tests include: Serology for Hepatitis B (HBsAg and HBcAb), and Hepatitis C (HCV RNA)	
Serum pregnancy test: In women of childbearing potential only.	
Urine pregnancy test: In women of childbearing potential only.	
Coagulation: INR and APTT	

Abbreviations for Table 11 and for notes: ADA = anti-drug antibodies; ALT = alanine transaminase; ANC = absolute neutrophil count; APTT = activated partial thromboplastin time; AST = aspartate transaminase; BUN = blood urea nitrogen; CBC = complete blood count; GGT = gamma-glutamyltransferase; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; INR = international normalized ratio; LDH = lactate dehydrogenase; PK = pharmacokinetics; RBC = red blood cell; RNA = ribonucleic acid; WBC = white blood cells.

Notes:

- Local hematology and blood chemistry test results must be obtained within 96 hours of dosing to confirm eligibility.
- If either AST or ALT is elevated, obtain total serum bilirubin and alkaline phosphatase; repeat daily or other interval, as clinically indicated, until resolved or stable.
- Additional tests to rule out drug-induced liver injury (eg, abdominal ultrasound, serum GGT, hepatitis serology) may be obtained at any time, if clinically indicated.

- Samples for PK, ADA, and pharmacodynamic analyses will be assessed at a central laboratory. Tumor markers will be assessed at a central laboratory. **All other (safety) laboratory tests will be assessed locally**.

APPENDIX 6: NEW YORK HEART ASSOCIATION CLASSIFICATION

Table 16: New York Heart Association Classification

Class I	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

APPENDIX 7: PROTOCOL AMENDMENT HISTORY

Document	Date
Amendment 2	04 February 2019
Amendment 1	23 January 2018
Original Protocol	31 October 2017

AMENDMENT 2 (05 FEBRUARY 2019)

Overall Rationale for the Amendment:

The protocol was updated to include language for FPA150 in combination with pembrolizumab cohorts and to incorporate additional updates and clarifications to study procedures that have been identified. These changes are summarized below. Additional changes were made to correct formatting and typographical errors.

Table 17: Document History

Section # and Name	Description of Change	Brief Rationale
Section 1 Protocol Synopsis, Objectives and Endpoints and Section; Table 2	• Included language to incorporate for FPA150 in combination with pembrolizumab and to clarify existing objectives or endpoints for FPA150 monotherapy.	• Objectives and Endpoints for Safety, Pharmacokinetic, Immunogenicity, Efficacy, Exploratory Pharmacokinetics, Exploratory Immunogenicity, and Exploratory Pharmacodynamic Biomarkers for Phase 1a and Phase 1b have been changed to further clarify for monotherapy cohorts and to include for combination cohorts
	• Abbreviations from below the table have been removed to avoid duplication of definitions	• Removed abbreviations
Section 1 Protocol Synopsis, Investigational Product; Section 6.1 Treatments Administered	• To provide details of pembrolizumab formulation and dosing for combination cohorts	• Addition of pembrolizumab investigational product description and dosing
	• To provide details of any updates to FPA150 investigational product	• Addition of larger FPA150 investigational product vial size
Section 1 Protocol Synopsis, Study Design; Section 4 Study Design	• Added clarified language and tables for the FPA150 in combination with pembrolizumab cohorts.	• Addition of combination cohorts
	• Clarified language around what the requirements are for archival tumor tissue and/or fresh biopsies for the FPA150 monotherapy cohorts and for the FPA150 in combination with pembrolizumab cohorts	• Clarification of requirements for archival tumor tissue and fresh biopsies for all cohorts
	• Clarified the naming conventions for each of the monotherapy and combination cohorts and removed the Phase 1b monotherapy urothelial cohort	• Addition of monotherapy dose exploration cohort

Section # and Name	Description of Change	Brief Rationale
	• Added cohort specific details for additional FPA150 monotherapy dose exploration cohort and FPA150 in combination with pembrolizumab cohorts	• Clarification of monotherapy treatment cohorts
	• Updated the number of patients and the sample size based on the addition of the combination cohorts	• Update the number of patients and sample size
Section 1 Protocol Synopsis, Eligibility Criteria; Section 5.1 Inclusion Criteria; 5.2 Eligibility Criteria	• Specified that inclusion criteria will be applicable for both monotherapy and combination therapy for phase 1a and phase 1b	• Inclusion criteria have been clarified
	• Added language to further clarify the inclusion criteria for phase 1b monotherapy breast cancer to include specifics for triple negative breast and HR+	• Inclusion criteria for disease specific cohorts have been added
	• Added inclusion criteria for the phase 1b FPA150 in combination with pembrolizumab ovarian cohort	• Additional Inclusion criteria have been added.
	• Added exclusion criteria	• Additional Exclusion Criteria have been added
Section 1 Protocol Synopsis, Statistical Methods; Section 9.1 Sample Size Determination	• Patient numbers were revised to align with the additional number of patients enrolling in the 4 lower dose cohorts	• Sample size determination has been changed.
Section 1 Protocol Synopsis, Safety Analysis	• Added clarified language that this study includes both monotherapy and combination therapy	• Clarification of cohorts has been added
Section 1 Protocol Synopsis, Efficacy Analysis	• Added language for Simon's 2-stage design	• Clarification of criteria for closing cohorts with limited activity
Section 1 Protocol Synopsis, Pharmacokinetic Analysis; Section 8.8 Pharmacokinetics; Section 9.4.3 Pharmacokinetic Analyses	• Added language about what will happen to the pembrolizumab PK samples for patients enrolled into the FPA150 in combination cohorts.	• Addition of analysis for combination samples
List of Abbreviations	• New terms were added as a result of the combination cohorts	• Addition of new terms from new text
	• Rearranged terms so that all are in alphabetical order	• Moved terms so that they are alphabetical
	• Clarification of list of abbreviations	• Removed terms that are not in the protocol

Section # and Name	Description of Change	Brief Rationale
Section 2.1 Study Rationale	• Added language to support the combination cohorts • Removed urothelial as one of the Phase 1b monotherapy cohorts	• Addition of Combination • Removed one of the Phase 1b monotherapy cohorts
Section 2.2.5 Clinical Experience with FPA150	• Added limited safety data from our completed cohorts in Phase 1a FPA150 monotherapy to support the MTD/RD of FPA150	• Addition of safety data from Phase 1a
Section 2.2.6 Pembrolizumab Background	• Added background information on Pembrolizumab for the combination cohorts	• Added Pembrolizumab language
Section 2.2.7 Rationale for Combination with Pembrolizumab	• Added language from research to support the addition of the pembrolizumab combination with FPA150 cohorts	• Added Pembrolizumab combination rationale
Section 2.3 Benefit/Risk Assessment	• Added supporting language regarding safety from Phase 1a Monotherapy Dose Escalation • Additional monitoring of patients after first infusion of FPA150	• Clarified that additional guidance on FPA150 dosing is located in other study documents • Clarified duration of post first infusion monitoring window of patients.
Section 4 Study Design; Figure 4	• Added updated study schema for monotherapy cohorts • Added updated study schema for combination cohorts	• Updated schema based on completed cohorts • Added new schema
Section 1 Protocol Synopsis; Section 4.1.2.2 Definition of a Dose-Limiting Toxicity	• Added language and tables to specifically define Dose Limiting Toxicities for monotherapy and combination cohorts.	• Added to include pembrolizumab
Section 4.5 Scientific Rationale for Study Design	• Added language that defines when to initiate the combination cohorts based on emerging data from the ongoing phase 1a monotherapy cohorts and from preclinical studies	• Clarified timing to initiate the FPA150 in combination with pembrolizumab cohorts
Section 4.6 Justification for Dose and Dosing Regimen	• Clarified language for the starting dose and dosing regimen of FPA150 Phase 1a Dose Escalation cohorts • Added language for the proposed dose of pembrolizumab	• Added rationale to how the starting dose was defined • To provide guidance for pembrolizumab
Section 4.7 Patient Selection	• Added language to include the combination cohorts and edited existing language to clarify the patient selection	• Added to include pembrolizumab

Section # and Name	Description of Change	Brief Rationale
Section 6.3.2 Table 10 Study Treatment Regimen of Combined Treatment of FPA150 and Pembrolizumab	• Addition of a table to show the treatment regimen for combination therapy	• Added to clarify the treatment for pembrolizumab combination cohorts
Section 6.4 Dose Modifications	• Added dose modification language and criteria for the combination cohorts. • Added language regarding Dose Escalations if there is radiographic response	• Added to include for pembrolizumab combination cohorts • Added clarification for escalation within a cohort
Section 6.5 Maximum Duration of Treatment	• Added language to define the maximum number of doses and/or duration of treatment for FPA150 and pembrolizumab • Added language to specify actions to take in combination cohorts if one of the two drugs has been discontinued; the patient may continue to receive the other drug as monotherapy	• Clarified how long a patient on FPA150 monotherapy or pembrolizumab can be on treatment • Clarified that monotherapy treatment can continue if one of the drugs in the combination therapy is stopped.
Section 6.8 Study Drug Accountability	• Added language to specify that accountability will be performed for FPA150 and/or pembrolizumab	• Clarified that drug accountability applies to both FPA150 and pembrolizumab
Section 6.9 Treatment Compliance	• Added language to include pembrolizumab to treatment compliance	• Clarified that treatment compliance applies to both FPA150 and pembrolizumab
Section 6.10 Concomitant Therapy	• Added language for pembrolizumab stating that the guidance from the package insert should be followed	• Clarified that the package insert for pembrolizumab should be followed
Section 7.1 Discontinuation of Study Treatment	• Added language that pembrolizumab treatment can continue up to 24 months	• Patients can only be on pembrolizumab for 24 months
Section 8.1.1 Informed Consent Requirements by Study Phase	• Clarified and simplified ICF requirement language for all monotherapy and combination therapy cohorts	• Clarified that sites should be having subjects sign the most recent approved ICFs
Section 8.4 Tumor Tissue	• Added clarification of what the requirements are regarding archival tissue or tumor tissue for all monotherapy and combination therapy cohorts • Added updated the number of patients who will require a fresh biopsy at screening and prior to Cycle 3 Day 1. • Added clarified language of when the biopsy may be done for the	• Clarified what and when archival and fresh biopsies are required for each cohort • Clarified the subset of patients that will require a fresh biopsy at screening

Section # and Name	Description of Change	Brief Rationale
	sample required prior to Cycle 3 Day 1	• Clarified when the biopsy for Cycle 3 Day 1 should be collected
Section 8.6 Efficacy Assessments	• Added language stating the first on study imaging assessment should be performed within 28 Days of Cycle 1 Day 1 • Changed the frequency of tumor scans to every 6 weeks for the first 6 months and then every 12 weeks	• Clarified when tumor assessment scan needs to occur • Clarified the scan frequency for tumor assessments to shorten the duration to determine patient tumor status earlier
Section 8.7.2 Pregnancy on Study	• Added language to reference the pembrolizumab USPI	• Clarifying to ensure sites remember to refer to the pembrolizumab package insert
Section 8.10 Immunogenicity Assessments	• Added immunogenicity language for pembrolizumab	• Clarifying that immunogenicity for pembrolizumab is also included
Section 8.12.5 Treatment of Overdose	• Added language regarding overdose while on treatment with pembrolizumab	• Clarifying overdose for pembrolizumab
Section 8.14 End of Treatment Follow-Up	• Added language to clarify that this is for both monotherapy and combination therapy • Added language for overdose of pembrolizumab	• Clarification of cohorts • Clarified addition of pembrolizumab for overdoses
Appendix 1: Schedule of Assessments	• Clarified that Schedule of Assessments is applicable to both monotherapy and combination therapy • Removed superscript from “subsequent cycles” • Clarified EOT 28 Days and EOT 100 Days by adding an additional column and having each visit have their own column. • Added HBcAb to Hepatitis B testing • Clarified that for tumor markers sites should refer to Appendix 2 for additional information and specific sampling times • Clarified that adverse events and concomitant medication should only be followed up until EOT 28 Days • Added a row for thyroid function testing • Added time windows for footnote e	• Added clarification of applicable cohorts • Corrected transcription error • Clarified study procedures • Clarified study procedures • Clarified study procedures • Clarified study procedures • Clarified study procedures • Clarified study procedures

Section # and Name	Description of Change	Brief Rationale
	• Clarified that ECGs should be down before PK draws in footnote f	• Clarified study procedures
	• Added language to clarify cohort names for monotherapy and combination therapy in footnote h	• Clarified study procedure
	• Clarified which monotherapy and combination therapy cohorts will require B7-H4 expression results in footnote i	• Clarified study procedures
	• Updated CT/MRI collection frequency from 9 weeks to 6 weeks in footnote k	• Clarified study procedures
	• Updated the schedule of tumor marker collection in footnote l	• Clarified study procedures
	• Added clarified language for PK collection requirements for monotherapy and combination therapy in footnote n	• Clarified study procedures
	• Added dosing guidance for pembrolizumab in footnote o	• Clarified study procedures
	• Clarified requirements for footnote p	• Clarified study procedures
	• Added footnote q regarding when to complete screening assessments	• Clarified study procedures
	• Added footnote r for thyroid testing	• Clarified study procedures
	• Added footnote s to clarify that adverse events and concomitant medication should be followed through EOT 28 Days	• Clarified study procedures
Appendix 2: Schedule of pharmacokinetic, immunogenicity, and pharmacodynamic blood sample collection; Table 9	• Added language to include pembrolizumab to all impacted samples	• Addition of pembrolizumab
	•	
	• Added pembrolizumab PK and ADA samples to be collected only at Cycles 1, 2, 3, and 7 prior to infusion and 15 min post infusion.	• Clarified study procedures
	• Added pembrolizumab ADA samples to be collected only at	• Clarified study procedures
	• Cycles 1, 2, and 3 prior to infusion and 15 min post infusion.	• Clarified study procedures
	• Clarified requirements for pharmacodynamics samples on Cycle 1 Day 4	• Clarified study procedures
	• Clarified requirement for [redacted] on Cycle 1 Day 8	• Clarified study procedures

Section # and Name	Description of Change	Brief Rationale
	• Clarified Tumor biopsy is required only at Cycle 3	• Clarified study procedures
	• Clarified requirement [redacted] at Cycle 2, 3, 4, 5, 7, and 9	• Clarified study procedures
	• Added language [redacted] at Cycle 3	• Clarified study procedures
	• Clarified that tumor markers are required at Cycles 2, 3, 4, 5, 7, and 9	• Clarified study procedures
	• Added windows for PK collection	• Clarified study procedures
	• Clarified tumor markers requirements after cycle 9	• Clarified study procedures
	• Clarified tumor biopsy requirement at EOT 28 Days	• Clarified study procedures
	• Added language [redacted] at EOT 28 Days	• Clarified study procedures
Appendix 3: List of Potential Pharmacodynamic samples for analyses	• Added clarification that the list provided is only a sample of what analyses may be included but it is not limited to only those	• Clarified study procedures
	• [redacted]	• Clarified study procedures
Appendix 5: Clinical laboratory tests	• Clarified what the required clinical chemistries are	• Clarified study procedures
	• Added additional abbreviations	• Clarified study procedures
	• Clarified what sample analysis will be completed at central laboratory	• Clarified study procedures

AMENDMENT 1 (23 JANUARY 2018)

Overall Rationale for the Amendment:

The protocol was updated to clarify the patient population and study procedures. These changes are summarized below. Additional changes were made to correct formatting and typographical errors.

Table 13: Document History

Section # and Name	Description of Change	Brief Rationale
Section 1 Protocol Synopsis, Section 5.1.1 Phase 1a Inclusion Criteria, and Section 5.1.3 Additional Cohort-Specific Inclusion Criteria for Phase 1b	• Inclusion Criteria #4 has been changed to patients should be refractory to or intolerant of existing therapy(ies) known to provide clinical benefit for their condition.	• Eligibility criteria changed to clarify prior treatment requirements
	• Inclusion #15 has been changed to clarify Hepatic safety labs must meet the following criteria: AST and ALT ≤ 3× ULN (AST and ALT < 5× ULN in patients with liver metastases is permitted)	• Allow a higher cut-off for liver enzyme elevations in patients with liver metastases which are likely to be common in the solid tumor population being evaluated in this study
	• Additional Inclusion Criteria for Cohort 1b1 Breast Carcinoma patients to include HER2 negative disease.	• Eligibility criteria changed to include only patients with HER2 negative breast cancer
	• Clarification of Cohort 1b2 Ovarian Carcinoma Inclusion Criteria to include diagnosis that is refractory to existing therapy(ies) known to provide clinical benefit.	• Eligibility criteria changed to clarify prior treatment requirements
	• All criteria have been sequentially numbered.	• For data management purposes

Section # and Name	Description of Change	Brief Rationale
Section 1 Protocol Synopsis and Section 5.2 Exclusion Criteria Phase 1a and Phase 1b	• Clarified that inhaled, intranasal, intraocular, and joint injections of steroids are exceptions to exclusion criteria #1 • Specfied the components of the investigational drug product formulation in exclusion criteria #6	• Specification of the types of steroid formulations allowable on study • To provide formulation details within exclusion criterion for criterion
Section 1 Protocol Synopsis, Section 4.1 Overall Design, and Section 4.1.2 Study Design: Phase 1a Dose Escalation	• Addition of lower dose initial accelerated titration design	• Phase 1a Dose Escalation design was revised to include 4 additional lower dose cohorts (0.01, 0.03, 0.1, and 0.3 mg/kg) to collect additional safety data
Section 1 Protocol Synopsis and Section 4.1.2.2 Dose-Limiting Toxicity Evaluation and Dose Escalation	• Language explaining the accelerated dose escalation titration design for additional 4 lower dose cohorts	• 4 additional lower dose cohorts (0.01, 0.03, 0.1, and 0.3 mg/kg) have been added at an accelerated titration design has been added to collect additional safety data at lower doses
Section 1 Protocol Synopsis, Section 4.3 Number of Patients, and Section 9.1 Sample Size Determination	• Updated number of patients	• Patient numbers were revised to align with the additional number of patients enrolling in the 4 lower dose cohorts
Section 4.1.2.1 Definition of a Dose-Limiting Toxicity	• Revised DLT definition to include adverse events regardless of attribution (except for those events clearly due to the underlying disease or extraneous causes) and included Grade 4 neutropenia that lasts more than 7 days.	• DLT criteria were revised to clarify the adverse events that should be considered for DLT determinations
Section 4.2.2 Phase 1a Dose Exploration	• Clarified that fresh biopsies are acceptable in the instance that archival tumor tissue is not available.	• Clarified that fresh or archival tumor tissue is acceptable

Section # and Name	Description of Change	Brief Rationale
Section 4.2.3 Phase 1b Dose Expansion	• Clarified that fresh biopsies are acceptable in the instance that archival tumor tissue is not available.	• Clarified that fresh or archival tumor tissue is acceptable
Section 4.7 Justification for Dose and Dosing Regimen	• Correction of the safe starting dose in humans and the upper value of C_{max} • Added "cells" after CT26	• Corrected transcription error • To clarifiy details of experimental model used
Section 6.1.3 FPA150 Administration	• Additional guidance for available dosing instructions • Additional monitoring of patients after first infusion of FPA150	• Clarified that additional guidance on FPA150 dosing is located in other study documents • Clarified duration of post first infusion monitoring window of patients.
Section 6.2.2 Dose Escalation within a Cohort	• Addition of intrapatient dose escalation	• Clarified that intrapatient dose escalation will be permitted for patients in dose cohorts up to 1mg/kg
Section 6.2.3 Toxicity at Lowest Dose Level	• Clarified first dose level • Clarified dose reduction	• Clarification of the lowest dose level to align with the new lowest dose level. • Clarification that the dose can be reduced from 0.1 mg/kg down to 0.005 mg/kg
Section 6.7 Concomitant Therapy	• Addition of bisphosphonates and denosumab as permitted concomitant medications	• Clarified that bisphosphonates and denosumab are permitted supportive care medications on study
Section 7.4 Premature Termination of the Study	• Added section for early stopping rules in cases of excessive toxicity or deaths.	• Clarified reasons for which the Sponsor could terminate the study early

Section # and Name	Description of Change	Brief Rationale
Section 8.12.2 Adverse Event Definitions	• Clarified language that Disease Progression is not an AE or SAE and that concurrent signs and symptoms clearly associated with disease progression itself should not be reported as an AE or SAE	• Clarification of reporting requirements for signs and symptoms of Disease Progression
Section 10 Ethical, Legal, and Administrative Aspects	• Added section with standard legal and regulatory content	• Section was added to adhere to ICH E6 requirements
Appendix 1 Schedule of Assessments	• Added visit windows to Cycle 1, Cycle 2 and Subsequent Cycles • Clarified language in footnote h that the biopsy should be taken at the EOT day 28 visit • Removed screening from footnote l to clarify that tumor markers should only be done at Day 1 of each every cycle • Clarified that serum pregnancy test can also be performed in footnote m • Added B7-H4 to Screening visit • Clarified visit for Tumor Markers [redacted] • Clarified language in footnote e that patients should be monitored post dose	• Standard visit windows were previously missing for some visits • Clarification of study procedures • Clarification of study procedures • Clarification of study procedures • Clarification of study procedures • Clarification of study procedures • Clarification of study procedures

Section # and Name	Description of Change	Brief Rationale
Appendix 2 Schedule of pharmacokinetic, immunogenicity, and pharmacodynamic blood sample collection	• Clarified language regarding sample collection to mimic what is listed in the body of the protocol. • Added sample collection window	• Clarification of study procedures • Standard sample collection windows were previously missing for some timepoints