A Phase 1a/1b Study of FPA008 in Combination with Nivolumab in Patients with Selected Advanced Cancers

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INTRODUCTION

FPA008 is a humanized IgG4 monoclonal antibody that binds to human colony stimulating factor 1 receptor (CSF1R), and blocks the ability of its ligands (IL34 and CSF1) to activate CSF1R expressed on macrophages. Macrophages are a major cellular component of murine and human tumors, where they are commonly termed tumor-associated macrophages (TAMs), and actively suppress antitumor immunity through multiple mechanisms. CSF1R signaling plays a major role in the trafficking, differentiation, and survival of TAMs. **Figure 1** shows the mechanism of action of FPA008.

Nivolumab is a fully-human IgG4 PD-1 immune checkpoint inhibitor approved by the FDA for the treatment of malignant melanoma and squamous NSCLC. PD-1 is expressed on activated lymphocytes, and is involved in a negative regulatory system to suppress the activated lymphocytes. Nivolumab blocks the interaction of PD-1 with its ligands (PD-L1 and PD-L2), preventing the negative regulatory signal mediated by the receptor-ligand interaction and thereby promoting the host immune response in which tumor cells are recognized as foreign and eliminated. **Figure 2** shows the mechanism of action of nivolumab.

Studies in preclinical tumor models have demonstrated that efficacy achieved with anti-PD-1 treatment is enhanced with concomitant CSF1R blockade. The combination of FPA008 with nivolumab is designed to remove multiple negative immune regulatory pathways and increase immune-mediated elimination of tumor cells.

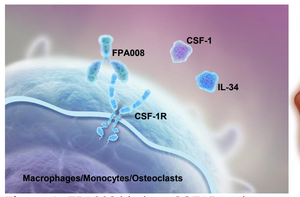

Figure 1: FPA008 binds to CSF1R and prevents binding of CSF1 and IL34

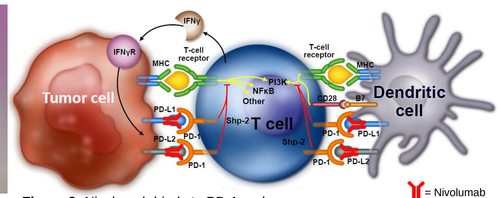

Figure 2: Nivolumab binds to PD-1 and prevents binding of PD-L1 and PD-L2

NIVOLUMAB EFFICACY SUMMARY

Nivolumab has shown efficacy in multiple tumor types, including those being explored in this study. A summary of the efficacy data from relevant nivolumab studies is shown in **Table 1**.

Table 1: Summary of Nivolumab Clinical Efficacy Data

Study Number	Study Drug	Comparator	Tumor Type	Response	
				ORR	OS
CA209003[a]	Nivolumab	None	Previously treated NSCLC	18%	-
CA209012[b]	Nivolumab	None	Previously treated NSCLC	22-36%	71-80% @ 12mo
CA209012[c]	Nivolumab + ipilimumab	None	1st line NSCLC	14-29%	-
CA209012[d]	Nivolumab + chemotherapy	None	1st line NSCLC	33-50%	59-87% @ 12mo
CA209012[e]	Nivolumab + erlotinib	None	Stage IIIB/IV EGFR mutant 1st line NSCLC	19%	73% @ 12mo
CA209017[f]	Nivolumab	Docetaxel	2nd line squamous NSCLC	20%	9.2 months (HR 0.59)
CA209063[g]	Nivolumab	None	Advanced, refractory, squamous NSCLC	14.5%	-
CA209003[h]	Nivolumab	None	Advanced Melanoma	31%	16.8 months
CA209004[i,j]	Nivolumab + ipilimumab	None	Advanced Melanoma	40%	85% @ 12mo
CA209037[k]	Nivolumab	Dacarbazine or paclitaxel + carboplatin	2nd line or later, advanced Melanoma	31.7%	-
CA209038[l]	Nivolumab	None	Advanced Melanoma	25%	-
CA209143[m]	Nivolumab	None	GBM (1st recurrence)	-	70% @ 6mo

a. Topalian et al, NEJM, 2012;366:2443
b. Gettinger et al, JCO, 2014;32(5s):abstr 8024
c. Antonia et al, JCO, 2014;32(5s):abstr 8023
d. Antonia et al, JCO, 2014;32(5s):abstr 8113
e. Rizvi et al, JCO, 2014;32(5s):abstr 8022
f. Brahmer et al, NEJM, 2015;373:123
g. Rizvi et al, Lancet Onc, 2015;16:257
h. Topalian et al, JCO, 2014;32:1020
i. Wolchok et al, NEJM, 2013;369:122
j. Kluger et al, ESMO, 2014;abstr 10850
k. Weber et al, Lancet Onc, 2015;16:375
l. Urba et al, Proc AACR, 2015; abstr 2855
m. Sampson et al, JCO, 2015;33:abstr 3010

STUDY DESIGN

The study design is shown in **Figure 3**.

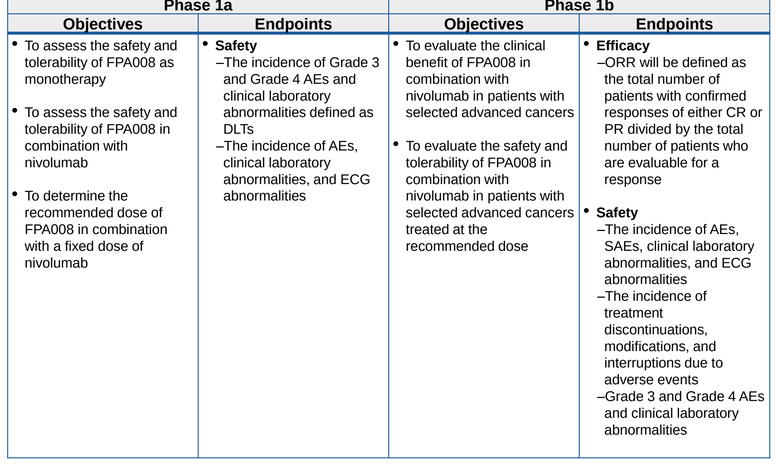

Figure 3: Overall Study Design

OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the study are shown in **Table 2**.

Table 2: Primary Objectives and Endpoints

Phase 1a		Phase 1b	
Objectives	Endpoints	Objectives	Endpoints
• To assess the safety and tolerability of FPA008 as monotherapy • To assess the safety and tolerability of FPA008 in combination with nivolumab • To determine the recommended dose of FPA008 in combination with a fixed dose of nivolumab	• **Safety** –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	• To evaluate the clinical benefit of FPA008 in combination with nivolumab in patients with selected advanced cancers • To evaluate the safety and tolerability of FPA008 in combination with nivolumab in patients with selected advanced cancers treated at the recommended dose	• **Efficacy** –ORR will be defined as the total number of patients with confirmed responses of either CR or PR divided by the total number of patients who are evaluable for a response • **Safety** –The incidence of AEs, SAEs, clinical laboratory abnormalities, and ECG abnormalities –The incidence of treatment discontinuations, modifications, and interruptions due to adverse events –Grade 3 and Grade 4 AEs and clinical laboratory abnormalities

ELIGIBILITY CRITERIA

The key global inclusion and exclusion criteria are shown in **Table 3** and **Table 4**. In addition to these, there are also specific inclusion and exclusion criteria for each of the eight cohorts for Phase 1b (see **Figure 3**).

Table 3: Key Inclusion Criteria for All Cohorts

- At least one measurable lesion at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) as per RECIST v1.1 criteria
- Progressive disease on, or refusal of, appropriate approved therapy for their tumor type unless otherwise specified in the cohort specific criteria
- All patients in Phase 1a and patients who consent to be biopsied in Phase 1b must have at least 1 tumor site that can be biopsied and be willing to have pre-treatment, on-treatment, and post-progression biopsies (except for patients in the Glioblastoma cohort)
- Age ≥ 18 years
- ECOG performance status of 0 or 1
- Hepatic Laboratory Values
  - AST or ALT ≤3x ULN
  - Bilirubin ≤1.5x ULN (except patients with Gilbert's syndrome, who must have total bilirubin <3 mg/dL)
  - Albumin >3.0 g/dL

Table 4: Key Exclusion Criteria for All Cohorts

- Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses >10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration except in the case of tumor-related AE treatment. Patients requiring chronic systemic treatment with either corticosteroids (inhaled or topical steroids and adrenal replacement steroid doses >10 mg/day prednisone equivalent) or other immunosuppressive medications within 2 weeks of treatment are permitted in the absence of active autoimmune disease.
- Decreased cardiac function with NYHA > Class 2
- Uncontrolled or significant heart disorder such as unstable angina
- Significant abnormalities on ECG at screening. QTcF >450 msec for males or >470 msec for females at screening
- Positive test for latent tuberculosis (TB) at screening (Quantiferon test) or evidence of active TB
- Abnormal serum chemistry values considered to be clinically significant
- Pregnant or breastfeeding
- 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
- Treatment with any cancer therapy or participation in another investigational drug or biologics trial within 28 days prior to first dose of study drug
- Symptomatic interstitial lung disease or inflammatory pneumonitis
- Untreated or active central nervous system (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 prior to first dose of study drug administration. In addition, patients must be either off corticosteroids, or on a stable dose or decreasing dose of <10 mg daily prednisone or prednisone equivalent.
- Prior exposure to any CSF1R pathway inhibitors

SAMPLE ANALYSIS

Tumor biopsy samples will be collected at Screening, on Study Day 29, and post-progression. For Phase 1b, at least 10 of the patients in each cohort will have pre-treatment and Study Day 29 biopsies collected. Blood samples will be collected at pre-specified time points.

The analyses to be performed on the biopsy and blood samples are shown in **Figure 4**.

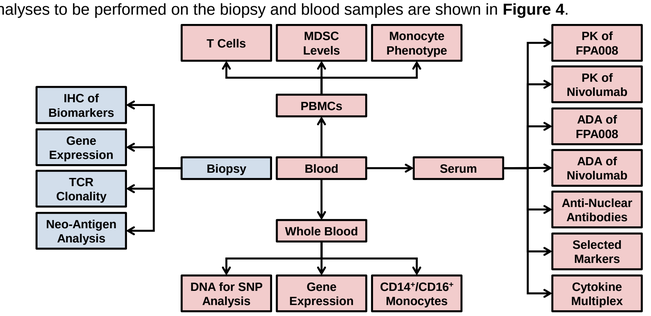

Figure 4: Sample Collection Overview

SUMMARY

- Scientific data support investigation of FPA008 in combination with nivolumab in multiple cancer types including melanoma, NSCLC, head and neck, pancreatic, colorectal, and glioma.
- Reprogramming the TAM compartment in tumors via FPA008-mediated CSF1R blockade could reduce immunosuppressive TAMs in the tumor microenvironment and increase CD8+ T-cell anti-tumor responses.
- PD-L1 expression in the tumor microenvironment could act to restrain the anti-tumor CD8 response and the addition of an anti-PD-1 agent, such as nivolumab, could remove the negative effect of the PD-L1 upregulation.