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Phase 1 Trial of PF-07799933 (ARRY-440), a Next-Generation BRAF Inhibitor for BRAF-Mutant Cancers

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Objective

- To evaluate the safety and tolerability, PK, and potential clinical benefits of PF-07799933 administered as monotherapy (Part 1) and in combination with binimetinib or cetuximab (Part 2) in patients with BRAF Class I, II, and III alteration solid tumors, with and without brain involvement, to determine the monotherapy MTD/RDE.

Conclusions

- PF-07799933 demonstrated anti-tumor activity in preclinical models of BRAF V600 and non-V600 mutations.
- PF-07799933 treatment demonstrated multiple responses in treatment-refractory BRAF V600 tumors, both systemically and in the brain.
- Presented here is the first-ever reported BRAF dimer inhibitor (PF-07799933) demonstrating clinical activity against documented treatment-acquired dimerizing resistance mutations (eg, p48 splice variant).
- The novel, rapid PK-informed dose escalation design provides a new paradigm for accelerating the testing of next-generation targeted therapies early in clinical development.

Electronic Poster and Supplementary Material

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References: 1. Agianian B, et al. J Med Chem 2018;61:5775-93. **2.** Wichmann J, et al. Clin Cancer Res 2022;28:770-80. **3.** Poulikakos P, et al. Nature 2012;464:427-30. **4.** Singh AK, et al. ACS Omega 2023;8:27819-44.

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Background

- Approved B-type RAF proto-oncogene (BRAF) inhibitors have transformed the treatment landscape for BRAF V600-mutant cancers but suffer 3 key liabilities: limited brain penetrance, BRAF dimer promoting resistance mutations, and toxicity from paradoxical signaling activation in BRAF wild-type cells.[1-3]
- Class I BRAF inhibitors are ineffective against BRAF Class II and III (homodimers and heterodimers).[4] Next-generation agents that cause pan-RAF inhibition may more broadly target BRAF mutants but are limited by a narrow therapeutic index.[1, 4]
- PF-07799933 (ARRY-440) is a highly selective ATP-competitive small molecule RAF kinase inhibitor currently under investigation in patients with BRAF V600 mutant and non-V600-altered advanced solid tumors; it is a brain-penetrant BRAF-selective monomer/dimer inhibitor that spares A-type RAF and C-type RAF proto-oncogene.

Methods

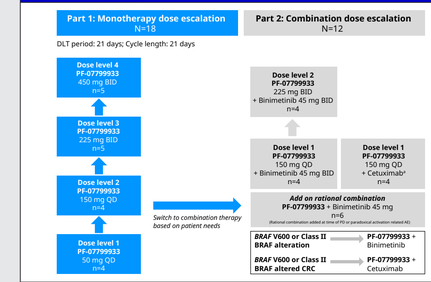
STUDY DESIGN

- PF-07799933 was characterized in patient-derived BRAF-mutant cancer cells in vitro and in vivo.
- PF-07799933 is being investigated in patients with refractory BRAF-mutant solid tumors using novel phase 1 design, enabling flexible, rapid dose escalation based on safety and pharmacokinetic (PK) assessments.
- This study comprises 3 parts; here we report on Parts 1 and 2 (**Figure 1**).
  - **Part 1:** Single-agent PF-07799933, dosed orally, in cohorts of 2–6 patients, with dose escalation starting at 50 mg once daily (QD), increasing to 150 mg QD, 225 mg twice daily (BID), and 450 mg BID, continuing until stopping criteria are met for maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE).
    - 3-fold dose escalation was enabled if the following safety criteria were met: no dose-limiting toxicities (DLTs) and margin of exposure ≤40 (assessed through drug exposure at a severely toxic dose in 10% of rats, compared with human PK parameters) in ≥2 or 3 participants in the dose level.
    - A patient initially on monotherapy may be transitioned to a specific combination therapy according to treatment needs.
  - **Part 2:** Combination therapy in dose escalation; PF-07799933, starting at 150 mg, dosed with binimetinib or cetuximab.
- In both parts, the number of evaluable patients at all dose levels for DLT was determined using a Bayesian logistic regression model (BLRM). Dose escalation was guided by BLRM, escalating with overdose control (EWOC) principles, safety, and PK parameters.

KEY INCLUSION CRITERIA

- Patients aged >16 years; ECOG PS 0 or 1, or ECOG PS 2 if related to underlying cancer.
- Histological or cytological diagnosis of advanced/metastatic solid tumor including primary brain tumor; and prior to enrollment, confirmation of sufficient availability of archival tissue samples for submission.
- Documented evidence of a qualifying BRAF alteration.
- All participants with BRAF V600 mutation must have progressed on prior BRAF inhibitor +/- mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor.
- All participants for whom immune checkpoint inhibitor (ICI) therapy is standard of care must have been previously treated with a minimum of 1 line of ICI.

Figure 1: Study design



[a]Initial binimetinib dose is 45 mg BID orally. Initial cetuximab dose is 400 mg/m² as a 120-min IV infusion, then 250 mg/m² as a 60-min IV infusion once weekly (subsequent doses). AE=adverse event; BID=twice daily; BRAF=B-type RAF proto-oncogene; CRC=colorectal cancer; DLT=dose-limiting toxicity; MTD=maximal tolerated dose; PD=progressive disease; QD=once daily; RDE=recommended dose for expansion

Results

PRECLINICAL

- PF-07799933 inhibited signaling in vitro, disrupted BRAF-containing homo- and heterodimers, and caused less paradoxical signaling compared with approved agents (**Supplementary Figure**).
- PF-07799933 alone and in combination with binimetinib inhibited tumor growth systemically and in the brain in mouse xenografts harboring de novo and acquired BRAF dimer-forming mutations (**Figure 2**).

PATIENTS

- In this ongoing study, 30 patients with BRAF-mutant cancers started PF-07799933 treatment, from the data cutoff of August 24, 2023.
  - 18 patients (60%) received escalating doses of PF-07799933 50 mg QD to 450 mg BID as monotherapy.
  - 12 patients (40%) received PF-07799933 in combination with binimetinib (27%) or cetuximab (all colorectal cancer [CRC]) (13%).
    - 6 of 18 patients (33%) initially receiving PF-07799933 monotherapy transitioned to combination therapy with PF-07799933 and binimetinib.
- Patients had the following tumor types: melanoma (43%), CRC (17%), primary brain tumor (PBT) (13%), thyroid (10%), and other (n=5 [3%] each; **Table 1**).
- BRAF mutations included Class I (V600E) (73%), Class II (10%), and Class III (13%; **Table 1**).
- All BRAF V600E+ patients with cancer were previously treated with ≥1 approved BRAF inhibitor with MEK inhibitor, and all BRAF V600E+ patients with melanoma also were previously treated with ≥1 immune checkpoint inhibitor.

SAFETY

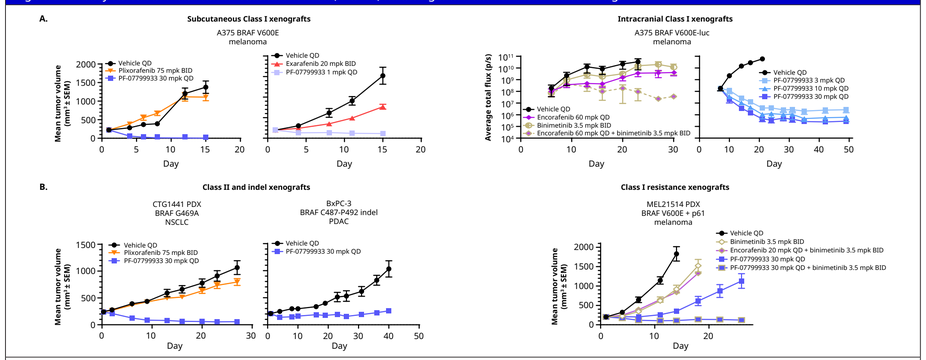
- PF-07799933 was well-tolerated as monotherapy or combination.
- There were no DLTs, and the MTD was not reached.
- Treatment-emergent adverse events (TEAEs) in ≥3 patients for monotherapy for any grade/grade ≥3, respectively, were fatigue (44%/0%), headache (28%/0%), vision blurred (22%/6%), and lipase increased (17%/0%; **Table 2**).
- The most common TEAEs for combination therapy for any grade/grade ≥3, respectively, were peripheral edema (33%/0%), acneiform rash, diarrhea, and fatigue (each 28%/0%; **Table 2**) and were most often attributed to binimetinib or cetuximab.
- The AE profile for PF-07799933 was consistent with less paradoxical signaling activation (eg, limited rash observed).

Table 1: Demographics and baseline characteristics

	Part 1	Part 2			
	PF-07799933 monotherapy	PF-07799933 150 mg QD + cetuximab[a]	PF-07799933 150 mg QD + binimetinib 45 mg BID	PF-07799933 225 mg BID + binimetinib 45 mg BID	Overall
	(N=18)	(N=4)	(N=4)	(N=4)	(N=30)
Age, y					
18–44	9 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (30.0)
45–64	5 (27.8)	2 (50.0)	2 (50.0)	4 (100.0)	13 (43.3)
≥65	4 (22.2)	2 (50.0)	2 (50.0)	0 (0.0)	8 (26.7)
Sex					
Female	8 (44.4)	3 (75.0)	1 (25.0)	4 (100.0)	16 (53.3)
Male	10 (55.6)	1 (25.0)	3 (75.0)	0 (0.0)	14 (46.7)
Race					
White	17 (94.4)	2 (50.0)	4 (100.0)	3 (75.0)	26 (86.7)
Asian	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (3.3)
Not reported	1 (5.6)	1 (25.0)	0 (0.0)	1 (25.0)	3 (10.0)
Tumor type					
Melanoma	8 (44.4)	0 (0.0)	3 (75.0)	2 (50.0)	13 (43.3)
Colorectal cancer	1 (5.6)	4 (100.0)	0 (0.0)	0 (0.0)	5 (16.6)
Primary brain	4 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (13.3)
Thyroid	3 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.0)
Other	2 (11.1)	0 (0.0)	1 (25.0)	2 (50.0)	5 (16.6)
BRAF mutation class					
Class I	14 (77.8)	3 (75.0)	2 (50.0)	3 (75.0)	22 (73.3)
Class II	2 (11.1)	1 (25.0)	0 (0.0)	0 (0.0)	3 (10.0)
Class III	2 (11.1)	0 (0.0)	1 (25.0)	1 (25.0)	4 (13.3)
BRAF fusion	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (3.3)

Data are n (%). [a] Initial cetuximab dose is 400 mg/m² as a 120-min IV infusion, then 250 mg/m² as a 60-min IV infusion once weekly (subsequent doses). BID=twice daily; QD=once daily

Figure 2: Efficacy curves of mean tumor volumes in mice (n=8–10) following oral treatment with indicated agents



(A) Subcutaneous xenografts (left) and flux measurements of intracranial xenografts (right) of Class I A375 (BRAF V600E) melanoma cells. (B) Subcutaneous patient-derived or cell line xenografts of Class II, indel, and Class I acquired resistance models. BID=twice daily; mpk=mg/kg; p/s=photon per second; QD=once daily; SEM=standard error of the mean

Table 2: Treatment-emergent adverse events for patients taking PF-07799933 as monotherapy and in combination with binimetinib or cetuximab

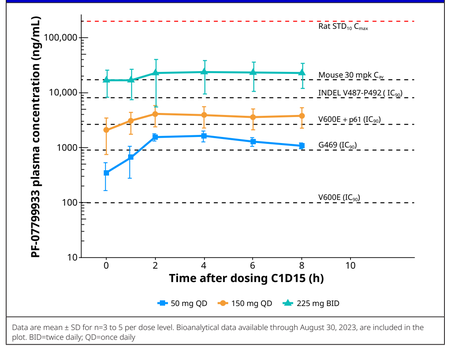
	Part 1: PF-07799933 monotherapy (N=18)	
TEAE, n (%)	Any grade	Grade ≥3
Fatigue	8 (44.4)	0 (0.0)
Headache	5 (27.7)	0 (0.0)
Blurry vision	4 (22.2)	1 (5.5)
Increased lipase levels	3 (16.6)	0 (0.0)
Part 2: PF-07799933 combination therapy (N=18)[a]		
Peripheral edema	6 (33.3)	0 (0.0)
Acneiform rash	5 (27.7)	0 (0.0)
Diarrhea	5 (27.7)	0 (0.0)
Fatigue	5 (27.7)	0 (0.0)

[a] Patient number is a collation of 12 patients who started combination therapy and 6 patients who switched to combination therapy based on treatment need.
TEAE=treatment-emergent adverse event

PHARMACOKINETICS

- PK-guided dose escalation enabled PF-07799933 Cycle 1 Day 15 plasma concentrations to exceed the IC_{90} for key BRAF mutations by dose level 3 (225 mg BID; **Figure 3**).

Figure 3: Preliminary plasma concentrations as function of time during monotherapy PF-07799933 dose escalation on Cycle 1 Day 15 (C1D15)



Data are mean ± SD for n=3 to 5 per dose level. Bioanalytical data available through August 30, 2023, are included in the plot. BID=twice daily; QD=once daily

EFFICACY

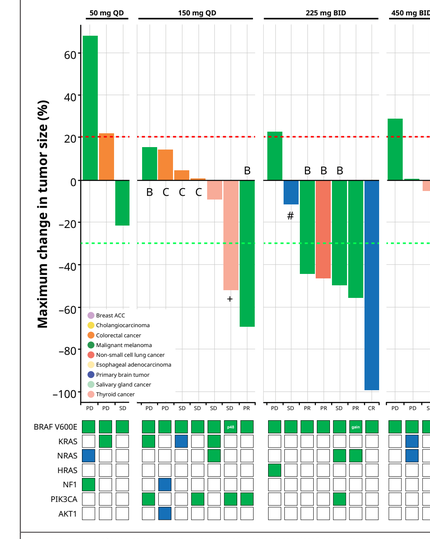
- Multiple confirmed responses in BRAF V600E+ patients with cancer both systemically and in the brain were seen in 4 of 7 patients at 225 mg BID ± binimetinib, including 1 complete response (CR) in a BRAF V600E+ PBT patient.
  - The CR response occurred in a patient taking PF-07799933 monotherapy (225 mg BID), based on the Response Assessment in Neuro-Oncology (RANO) investigator assessment (**Table 3**).
- A 5th confirmed response (second BRAF V600E+ PBT patient) occurred after data cutoff resulting in 5 of 7 responses.
- To our knowledge, this study includes the first evidence of efficacy in a patient with BRAF V600E+ thyroid cancer with identification of a dimerizing BRAF splice variant (**Figure 4**).
- PF-07799933 shows early evidence of anti-tumor activity in BRAF non-V600 tumors, as evidenced by a patient with BRAF G466E+ (Class III) adenoid cystic carcinoma with a sustained molecular CR in ctDNA.

Table 3: Summary of confirmed best overall response based on investigator assessment (RECIST v1.1)

	PF-07799933 monotherapy	PF-07799933 150 mg QD + cetuximab[a]	PF-07799933 150 mg QD + binimetinib 45 mg BID	PF-07799933 225 mg BID + binimetinib 45 mg BID
n (%)	(N=14)	(N=4)	(N=4)	(N=4)
Complete response (CR)	1 (7.1)[b]	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	1 (7.1)	0 (0.0)	1 (25.0)	2 (50.0)
Stable disease	7 (50.0)[c]	2 (50.0)	1 (25.0)	2 (50.0)
Progressive disease (PD)	5 (35.7)	2 (50.0)	2 (50.0)	0 (0.0)
Non-CR/non-PD	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Initial cetuximab dose is 400 mg/m² as a 120-min IV infusion, then 250 mg/m² as a 60-min IV infusion once weekly (subsequent doses). [b] CR occurred in a patient with primary brain tumor taking PF-07799933 monotherapy (225 mg BID), based on investigator assessment using the Response Assessment in Neuro-Oncology (RANO). [c] A sustained PR (tumor volume reduction –50%) occurred in a patient with thyroid cancer, after the addition of binimetinib for disease progression; per RECIST best observed response in this setting is SD. CR=complete response; PD=progressive disease

Figure 4: Waterfall plot of maximum change in tumor size by treatment, dose, and tumor for patients with BRAF V600E/Class I mutant cancer



Preliminary summary of select co-occurring mutations (activating oncogenes or inactivating tumor suppressors) is shown at the bottom (green=tumor; blue=ctDNA). B indicates Part 1 participant enrolled into monotherapy dose escalation who added on binimetinib; B or C indicates Part 2 participant enrolled into combination dose escalation with either binimetinib or cetuximab.
+ p48 dimerizing splice variant identified on archival tissue biopsy obtained after progression on BRAF inhibitor.
# Participant with primary brain tumor and confirmed PR after data cutoff (–92% tumor volume reduction, per RANO).
ACC=adenoid cystic carcinoma; BID=twice daily; QD=once daily

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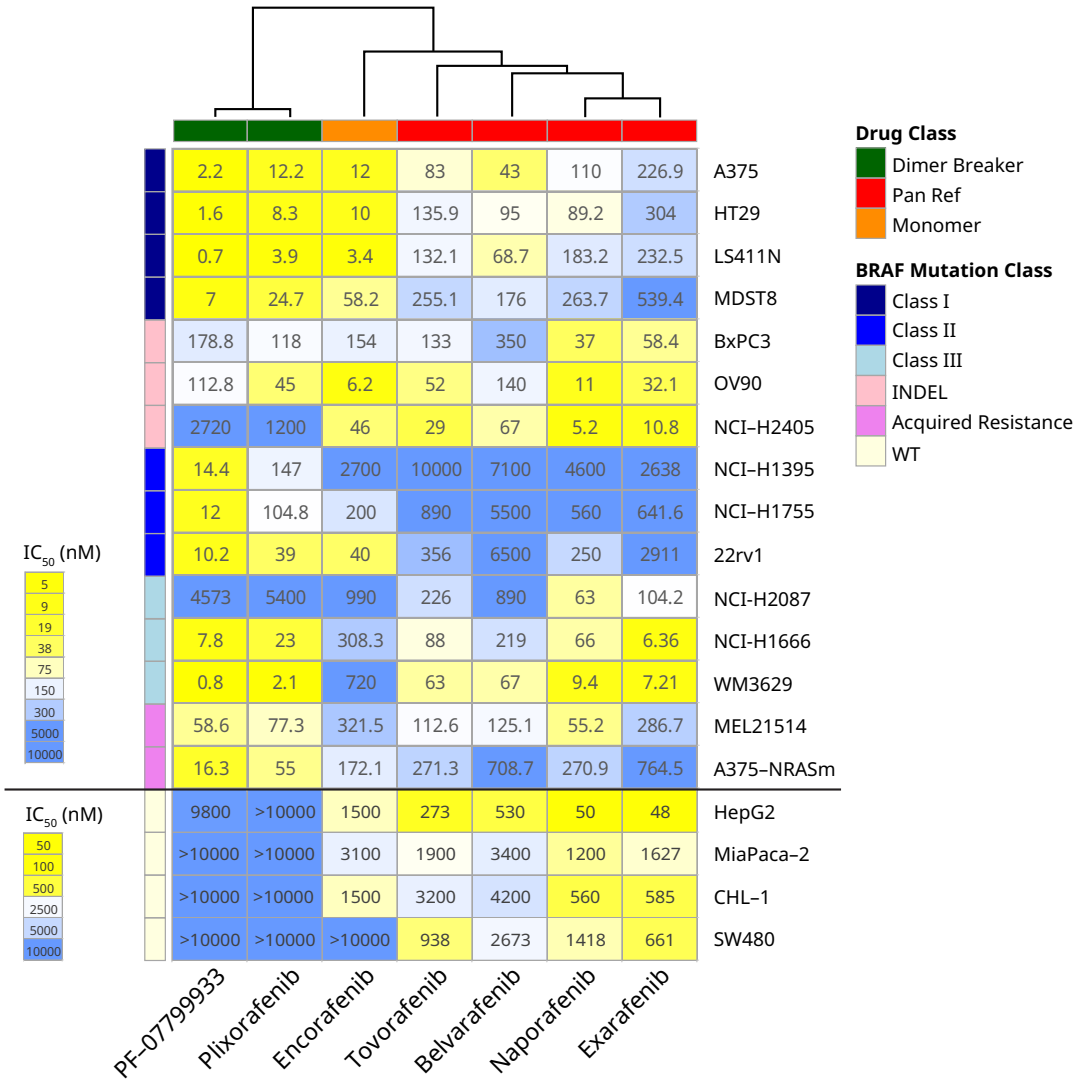
Supplementary Material

Supplementary Figure: Heatmap of 50% inhibitory concentration (IC_{50}) values after 1-h treatment with PF-07799933 or comparator RAF inhibitors in a panel of BRAF-mutant/WT cell lines



IC_{50} values derived from dose–response curves measured by In-Cell Western for inhibition of phospho-ERK. Data are representative of 2 or 3 independent experiments and are averaged over 3 technical replicates. BRAF=B-type RAF proto-oncogene; IC=inhibitory concentration; INDEL=insertion/deletion; NRASm=NRAS mutant; WT=wild type