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Phase 1 Trial of PF-06821497, a Potent and Selective Inhibitor of Enhancer of Zeste Homolog 2, in Follicular Lymphoma, Small-Cell Lung Cancer, and Castration-Resistant Prostate Cancer

Michael T Schweizer[1], Konstantin Penkov[2], Anthony Tolcher[3], Atish D Choudhury[4], Vadim Doronin[5], Raid Maki Aljumaily[6,15], Emiliano Calvo[7], Richard C Frank[8], John Hamm[9], Victor Moreno[10], Vladimir Vorobyev[11], Stephane Billotte[12], Timothy Bowler[13], Joseph Chen[14], Tess Lin[13], Li Liu[12], Arnab K Maity[12], Shikhar Sharma[12], Melissa Johnson[15]

[1]University of Washington Seattle, WA, and Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA, USA; [2]PHI "Clinical Hospital RZhD-Medicine St. Petersburg", St. Petersburg, Russia; [3]NEXT Oncology, San Antonio, TX, USA; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]State Budgetary Healthcare Institute of Moscow City Clinical Hospital №40, Moscow, Russia; [6]Stephenson Cancer Center, Oklahoma City, OK, and Sarah Cannon Research Institute, Nashville, TN, USA; [7]START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [8]Norwalk Hospital, Nuvance Health, Norwalk, CT, USA; [9]Norton Healthcare, Norton Cancer Institute, Louisville, KY, USA; [10]START Madrid-FJD, Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain; [11]Botkin Hospital, Moscow, Russia; [12]Pfizer Inc, San Diego, CA, USA; [13]Pfizer Inc, New York, NY, USA; - employee of Pfizer when this work was performed [14]Pfizer Inc, San Francisco, CA, USA; [15]Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN, USA

Objectives

- To evaluate the safety, PK, pharmacodynamics, and antitumor activity of PF-06821497 in an ongoing phase 1 trial in patients with FL, SCLC, and CRPC in Part 1A/B, (monotherapy) and in CRPC in Part 2A (in combination with enzalutamide).

Conclusions

- Durable objective tumor responses were observed in patients with FL treated with PF-06821497 and mCRPC treated with PF-06821497 in combination with enzalutamide.
- Treatment with PF-06821497 was associated with a favorable safety profile, with evidence of EZH2 pharmacodynamic inhibition and antitumor activity.

Background

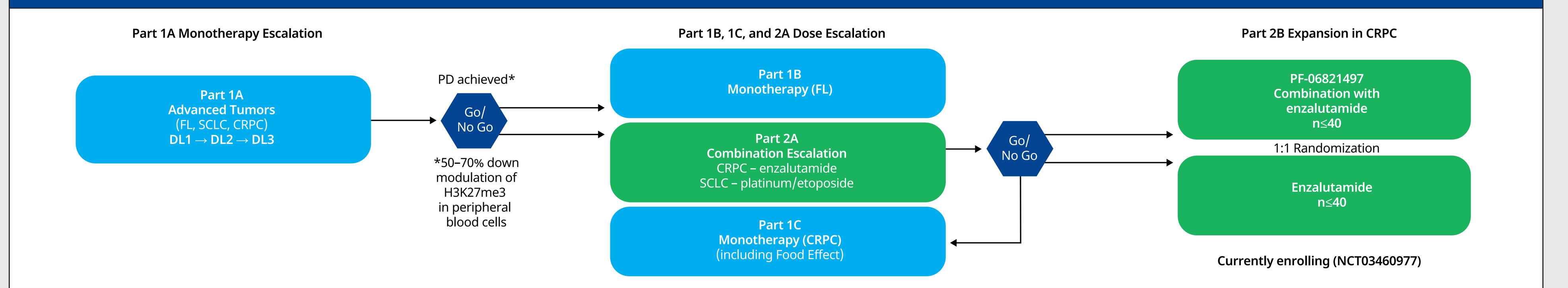
- Epigenetic dysregulation is a hallmark of many cancer types, including hematologic malignancies and solid tumors, and is implicated in the modulation of multiple key cellular processes, including gene transcription, DNA replication, and DNA repair.[1]
- The aberrant activity of epigenetic regulators in cancer, including histone methyltransferase and demethylase enzymes, has made them attractive targets for developing novel therapies for cancer.[2]
- The enhancer of zeste homolog 2 (*EZH2*) gene encodes the histone methyltransferase component of the polycomb repressive complex-2 (PRC2), inducing transcriptional silencing of target genes. Its activity is altered in cancers such as follicular lymphoma (FL), small-cell lung cancer (SCLC), and metastatic castration-resistant prostate cancer (mCRPC).
- EZH2 is overexpressed in CRPC, and its expression level has been shown to be an independent prognostic indicator of disease.[3] EZH2 activity has been implicated in the pathogenesis of CRPC through multiple mechanisms, including silencing of tumor suppressor genes, direct interaction with the *AR* gene and promoting development of neuroendocrine transdifferentiation associated with anti-androgen resistance.[4-8]
- PF-06821497 is a potent, selective S-adenosyl-L-methionine competitive EZH2 inhibitor that inhibits wild-type (WT) and EZH2 Y641N mutant enzymes, resulting in strong H3K27Me3 inhibition in preclinical models.

Methods

STUDY DESIGN AND TREATMENT

- In an ongoing, open-label, multicenter, multi-dose phase 1 dose-escalation and dose expansion study, PF-06821497 was administered orally in adult patients as a single agent (for FL, SCLC, and mCRPC) or in combination with standard-of-care (SOC) treatment for SCLC (chemotherapy) or mCRPC (enzalutamide).
  - Data for the SCLC in combination with SOC cohorts are not reported here.

Figure 1: Study Design


Part 1A Monotherapy Escalation
Part 1A
Advanced Tumors
(FL, SCLC, CRPC)
DL1 → DL2 → DL3
PD achieved*
Go/
No Go
*50–70% down modulation of H3K27me3 in peripheral blood cells
Part 1B, 1C, and 2A Dose Escalation
Part 1B
Monotherapy (FL)
Part 2A
Combination Escalation
CRPC – enzalutamide
SCLC – platinum/etoposide
Part 1C
Monotherapy (CRPC)
(including Food Effect)
Go/
No Go
Part 2B Expansion in CRPC
PF-06821497
Combination with
enzalutamide
n≤40
1:1 Randomization
Enzalutamide
n≤40
Currently enrolling (NCT03460977)

Part 1C may be opened at the sponsor's discretion.
CRPC=castration-resistant prostate cancer; DL=dose level; FL=follicular lymphoma; PD=pharmacodynamics; SCLC=small-cell lung cancer

- The study is comprised of 2 parts (**Figure 1**).
  - Part 1: Single-agent PF-06821497 dosed orally twice daily (BID) in a continuous regimen (6 escalation cohorts: 75, 150, 250, 375, 500 and 625 mg). Part 1A was to establish safety and target modulation information in order to commence monotherapy Part 1B and combination Part 2A dose escalation.
  - Part 2A: Combination therapy in dose escalation; PF-06821497 (150, 250, 375, 500, 625, 750, 875 and 1250 mg) dosed with enzalutamide (in mCRPC, 8 escalation cohorts).
  - Part 2B: Randomized, open-label prostate cancer expansion cohort testing PF-06821497 (1250 mg BID) plus enzalutamide vs. enzalutamide only in mCRPC. Data not reported.
- For all dose escalation in Parts 1 and 2A, a modified toxicity probability interval method, targeting a dose-limiting toxicity (DLT) rate of 27.5% with an equivalence interval of (22.5%, 32.5%), was used to determine maximum tolerated dose.

KEY INCLUSION CRITERIA

- Histologic or cytologic diagnosis of advanced/metastatic solid tumor with the following tumor types in individual study parts:
- Part 1A: Advanced/unresectable or metastatic FL, SCLC, or mCRPC refractory to/intolerable of standard treatment, or for which no curative treatment is available. Patients with FL (Parts 1A and 1B, dose-finding) had exhausted all SOC therapies.
- Part 1B: Patients with FL who had exhausted all curative therapies, and have relapsed or refractory disease.
- Part 2A: Patients with mCRPC with prior abiraterone and/or enzalutamide treatment and evidence of cancer progression.
- Age ≥18 years; ECOG PS 0 or 1, and adequate bone marrow, renal, and liver function. Resolved acute effects of any prior therapy to baseline levels.

ASSESSMENTS

- Primary objectives:
  - Part 1: Assess the overall safety of PF-06821497 in patients with FL, SCLC, or mCRPC, and determine the expansion dose of monotherapy.
  - Part 2A: Determine safety and tolerability at increasing dose levels of PF-06821497 in combination with enzalutamide in patients with mCRPC to determine the expansion dose for combination therapy.
- Secondary objectives, Parts 1 and 2A:
  - Evaluate preliminary antitumor activity of PF-06821497: objective response, lymphoma response, prostate cancer response, and assessment of prostate-specific antigen (PSA) levels.
  - Characterize pharmacokinetics (PK) of single and multiple-dose PF-06821497.

Results

PATIENTS

- As of the data cut-off of September 30, 2021, 57 patients were treated in dose-escalation: n=25, Part 1; n=32, Part 2A CRPC.
- Mean age was 67 years, and 91% were White (**Table 1**).

Table 1: Demographic Characteristics, SAS (N=57)

Characteristic	Part 1A (n=11)	Part 1B (n=14)	Part 2A CRPC (n=32)	Total (N=57)
Age, mean (standard deviation), y	69.8 (8.2)	58.5 (12.2)	69.7 (8.2)	67.0 (10.4)
Race, n (%)				
White	10 (90.9)	14 (100)	28.0 (87.5)	52 (91.2)
Black or African American	1 (9.1)	0	2.0 (6.3)	3 (5.3)
Asian	0	0	1.0 (3.1)	1 (1.8)
Not reported	0	0	1.0 (3.1)	1 (1.8)
Diagnosis				
Follicular Lymphoma, n	1	14	0	15
Duration since onset, median, range (min, max), y	8.0 (8.0, 8.0)	3.6 (0.8, 21.0)		3.6 (0.8, 21.0)
Castration-resistant prostate cancer, n	8	0	32	40
Duration since onset, median, range (min, max), y	7.4 (5.8, 19.7)	-	5.7 (1.4, 21.8)	6.2 (1.4, 21.8)
Small-cell lung cancer, n	2	0	0	2
Duration since onset, median, range (min, max), y	1.3 (0.5, 2.0)	-	-	1.3 (0.5, 2.0)
Patients with any prior anticancer drug therapy, n (%)	11 (100)	14 (100)	32 (100)	57 (100)
Number of regimens, n (%)[a]				
1	2 (18.2)	2 (14.3)	3 (9.4)	7 (12.3)
2	1 (9.1)	3 (21.4)	8 (25.0)	12 (21.1)
3	2 (18.2)	2 (14.3)	9 (28.1)	13 (22.8)
4	2 (18.2)	3 (21.4)	5 (15.6)	10 (17.5)
5	1 (9.1)	4 (28.6)	5 (15.6)	10 (17.5)
≥6	3 (27.3)	0	2 (6.3)	5 (8.8)
Patients with ≥1prior radiation therapy, n (%)	8 (72.7)	2 (14.3)	17 (53.1)	27 (47.4)
Patients with ≥1prior surgery, n (%)	10 (90.9)	3 (21.4)	18 (56.3)	31 (54.4)

[a] No patients were reported to have prior treatment with EZH2i.
CRPC=castration-resistant prostate cancer; min max, minimum maximum; SAS=safety analysis set

SAFETY

Pooled: Parts 1A, 1B, and 2A

- Overall, the most common treatment-related adverse events (TRAEs) were nausea (26.3%), fatigue (24.6%), and diarrhea (22.8%); the majority were grade 1–2 (**Table 2**).
  - Serious adverse events occurred in 17 patients, 1 was treatment-related (grade 5 hepatic failure and grade 4 sepsis).
  - One patient with FL treated in Part 1 had a DLT of grade 4 thrombocytopenia.

Table 2: TRAEs Occurring in >15% Patients by Grade (Treatment Related to PF-06821497): Pooled Part 1A, 1B, and 2A CRPC, SAS (N=57)

AEs by PT, n (%)	Grade 1	Grade 2	Grade ≥3[a]	Total
With any PF-06821497-related AEs	9 (15.8)	23 (40.4)	7 (12.3)	39 (68.4)
Nausea	13 (22.8)	2 (3.5)	0	15 (26.3)
Fatigue	7 (12.3)	6 (10.5)	1 (1.8)	14 (24.6)
Diarrhea	9 (15.8)	4 (7.0)	0	13 (22.8)
Decreased appetite	7 (12.3)	5 (8.8)	0	12 (21.1)
Dysgeusia	9 (15.8)	3 (5.3)	0	12 (21.1)

[a] Includes one patient with metastatic CRPC treated with 150 mg BID PF-06821497 monotherapy with a treatment-related SAE of grade 5 hepatic failure and grade 4 sepsis; no other treatment-related SAEs were reported.
AE=adverse event; CRCP=castration-resistant prostate cancer; PT=preferred term; SAE=serious adverse event; SAS=safety analysis set; TRAE=treatment-related adverse event

Parts 1A & 1B

- The most common TRAEs of any grade were nausea (36.0%); alopecia, anemia, diarrhea, dysgeusia, fatigue (20% each); decreased appetite (16.0%); and thrombocytopenia (16.0%). The majority of TRAEs were grade 1–2.

Part 2A

- In Part 2A only, the most common TRAEs of any grade were fatigue (28.1%), decreased appetite or diarrhea (25.0% each), and dysgeusia (21.9%) (**Table 3**).

Table 3: TRAEs Occurring in >15% of Patients by Grade (Treatment Related to PF-06821497): Part 2A CRPC, SAS (n=32)

AEs by PT, n (%)	Grade 1	Grade 2	Grade ≥3[a]	Total
With any PF-06821497-related AEs	4 (12.5)	12 (37.5)	2 (6.3)	18 (56.3)
Fatigue	4 (12.5)	5 (15.6)	0	9 (28.1)
Decreased appetite	5 (15.6)	3 (9.4)	0	8 (25.0)
Diarrhea	6 (18.8)	2 (6.3)	0	8 (25.0)
Dysgeusia	7 (21.9)	0	0	7 (21.9)
Nausea	6 (18.8)	0	0	6 (18.8)
Vomiting	5 (15.6)	0	0	5 (15.6)

[a] No grade 4 or 5 AEs were recorded.
AE=adverse event; CRPC=castrate resistant prostate cancer; PT=preferred term; SAS=safety analysis set; TRAE=treatment-related adverse event

EFFICACY

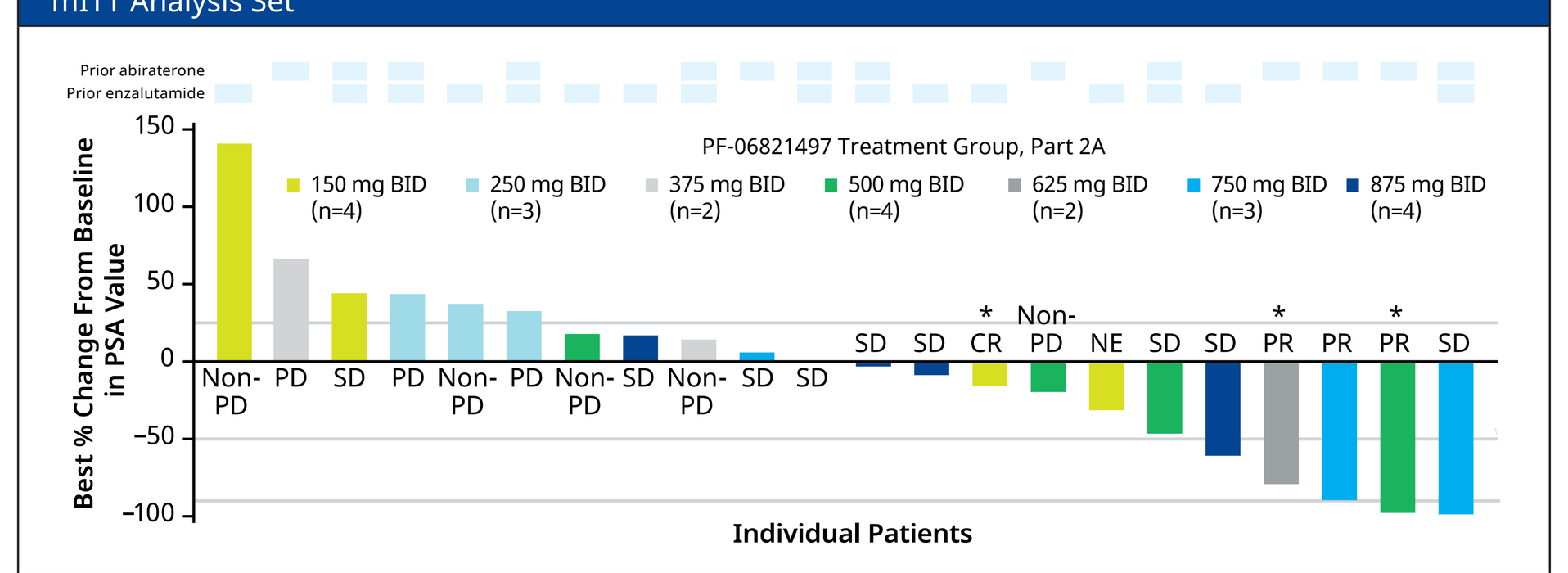
Part 1

- Among patients with FL (n=15) in Part 1, all were included in the modified intent-to-treat (mITT) efficacy analysis, and all had measurable disease at baseline.
- There were 4 partial responses (2 confirmed), 6 minor responses (6 confirmed), 1 stable disease (SD), and 1 progressive disease (PD), per RECIL[9]; 3 patients were not evaluable (n=2 best overall response of SD prior to 58 days on study, n=1 no post baseline assessment due to COVID-19-related death).
- In Part 1 patients with CRPC (n=8), all patients were included in the mITT efficacy analysis, and 2 patients had measurable disease at baseline. There were 2 patients with SD, 2 non–complete response (CR)/non-PD, and 4 PD per PCWG3[10] criteria.

Part 2A

- All patients with CRPC (n=32) in Part 2A had prior treatment with abiraterone and/or enzalutamide.
- Per mITT, 4 of the 32 patients with CRPC in Part 2A dosed with PF-06821497 were not included in the response analysis: n=1 withdrawal by subject, n=1 adverse event, n=2 data cut-off prior to first on-study assessment.
- Among the mITT evaluable patients (n=28), PSA reductions ≥50% (PSA50 response) were observed in 5 (17.9%) patients (n=2, prior enzalutamide; n=3, enzalutamide-naïve) (**Figure 2**).

Figure 2: Waterfall Plot for Best Percent Change From Baseline in PSA Value: Part 2A CRPC, mITT Analysis Set



- Fourteen patients in the mITT analysis set had target lesions at baseline.
  - There were 4 objective responses (14.3%): 2 confirmed and 1 unconfirmed partial responses (enzalutamide-naive) (**Figure 3**) and 1 confirmed CR in a patient with non-target lesions (prior enzalutamide) (**Figure 4**); 10 patients had SD, 5 non-CR/non-PD, 5 clinical/radiographic progressive disease, and 4 patients were not evaluable (n=1 no evidence of disease at baseline, n=3 BOR of SD prior to 58 days on study).

Figure 3: Waterfall Plot for Best Percent Change From Baseline in Sum of Diameters for Target Lesions (PCWG3): Part 2A CRPC, mITT Analysis Set

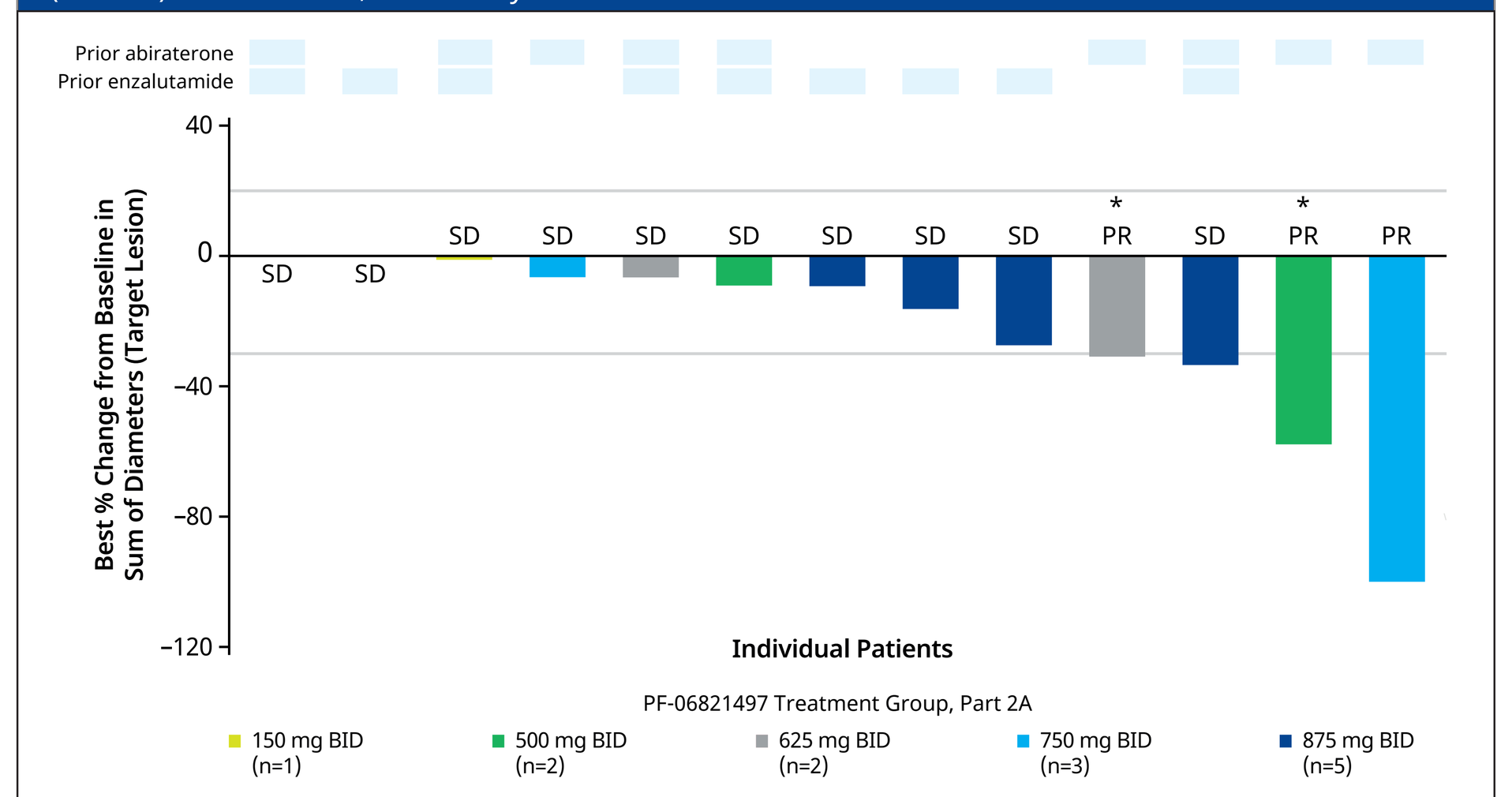
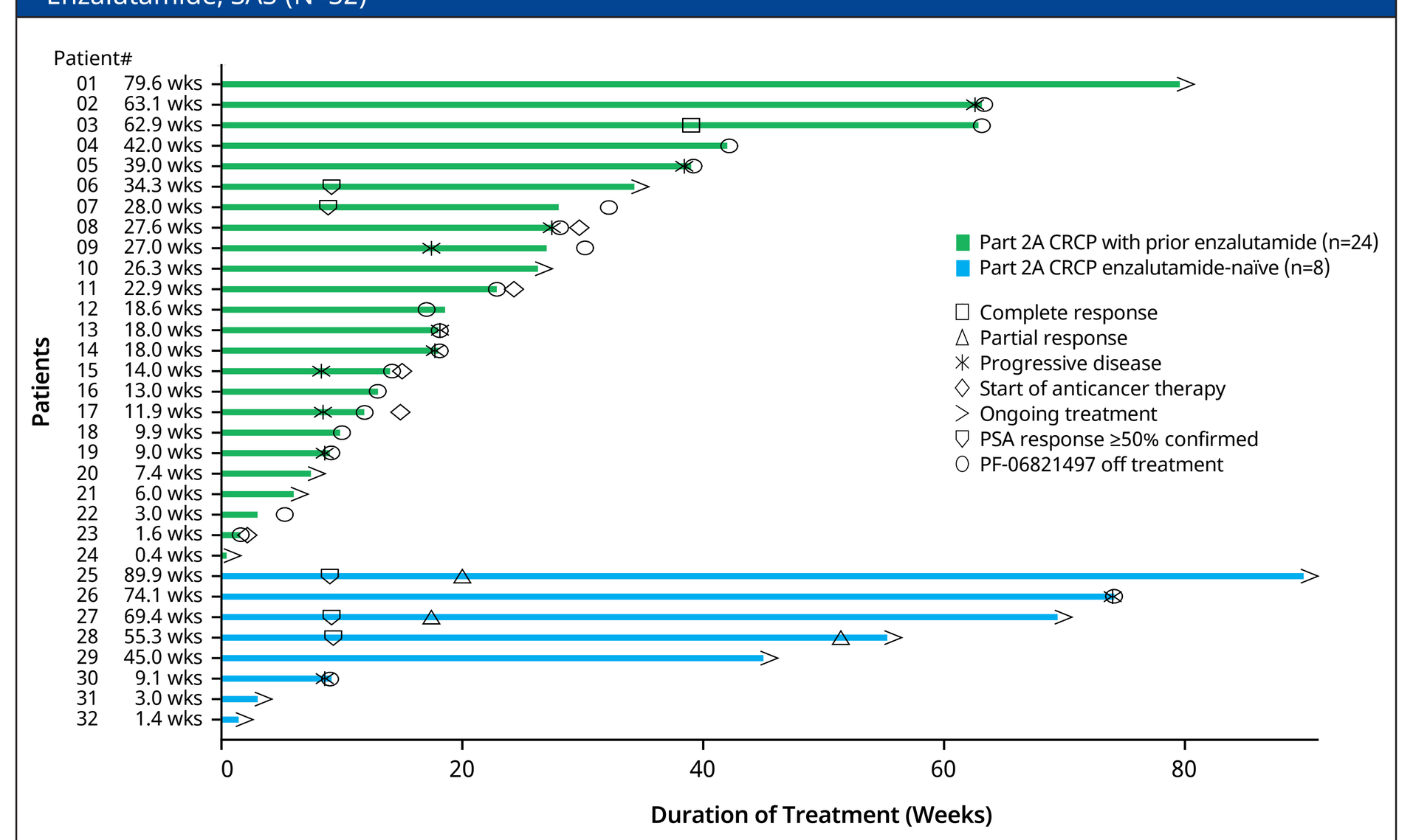
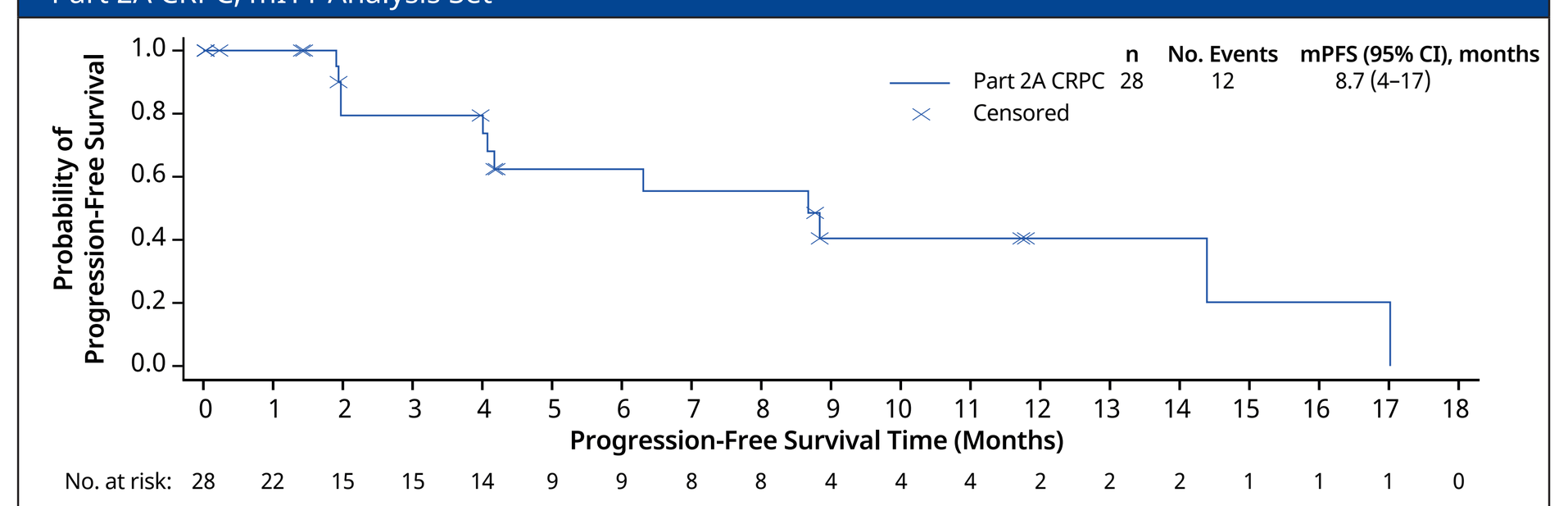


Figure 4: Swimmer Plot of Duration of Treatment: Part 2A CRPC, Enzalutamide-naive vs Prior Enzalutamide, SAS (N=32)



- PFS, mITT analysis set for patients with CRPC in Part 2A: the median Kaplan–Meier estimate of time to event in months (95% CI) was 8.7 (4.0–17.0) (**Figure 5**).

Figure 5: Kaplan–Meier Plot of Progression-Free Survival Based on Investigator Assessment (PCWG3[10]): Part 2A CRPC, mITT Analysis Set

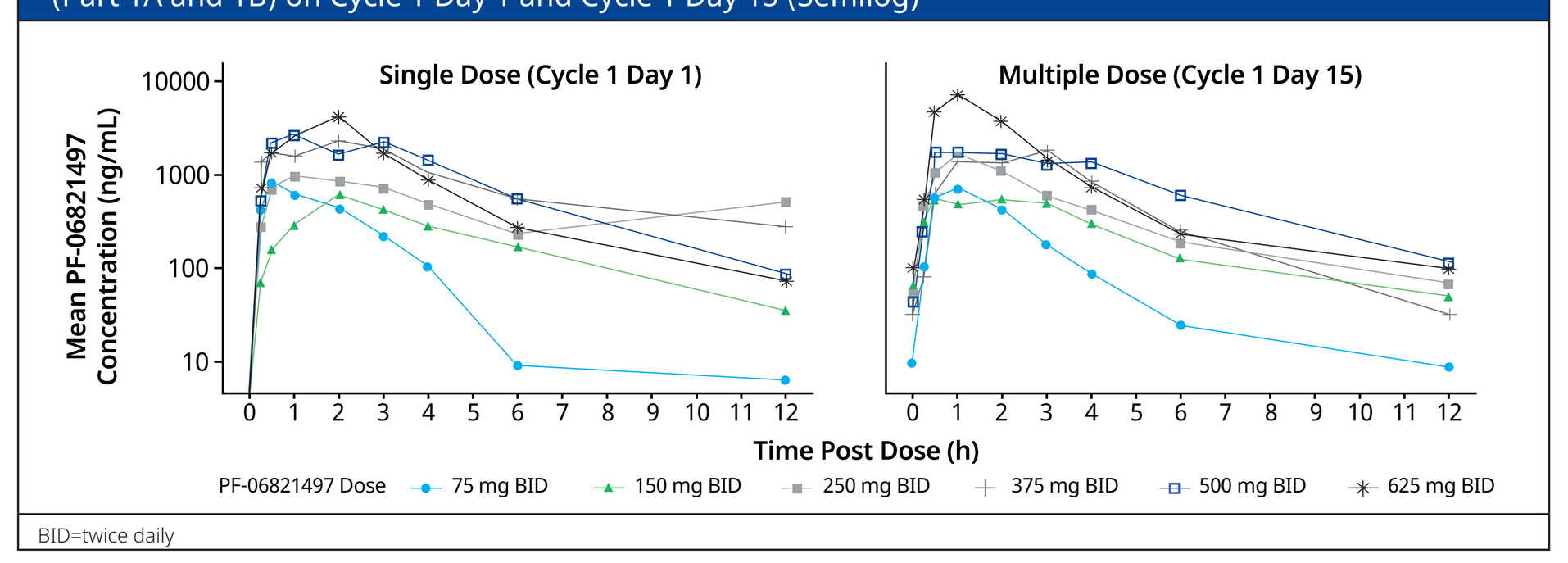


CRPC=castration-resistant prostate cancer; mITT=modified intent-to-treat; mPFS=median progression-free survival; PCWG3=Prostate Cancer Working Group

PHARMACOKINETICS

- Interim PK data revealed dose-dependent increases in PF-06821497 total exposure (area under the curve to the end of the dosing period), and peak concentrations were rapidly achieved with multiple-dose oral administration of 75 to 625 mg BID monotherapy (**Figure 6**).

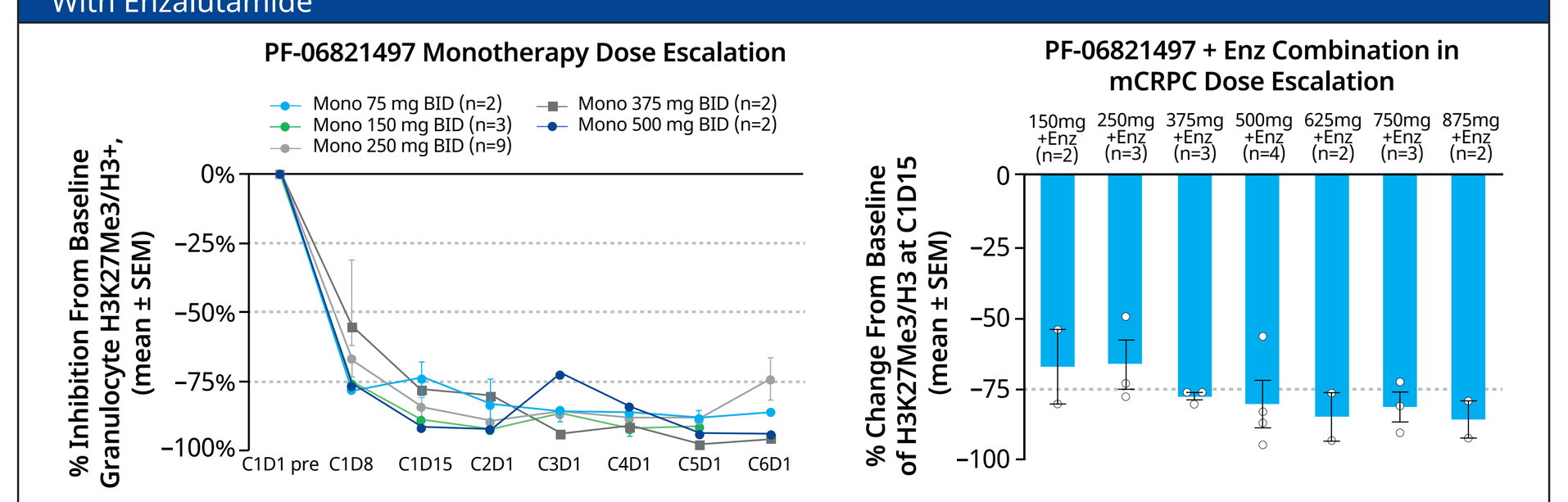
Figure 6: Mean Plasma PF-06821497 Concentrations After Oral Administration in Monotherapy (Part 1A and 1B) on Cycle 1 Day 1 and Cycle 1 Day 15 (Semilog)



BID=twice daily

- Maximal decrease (≥75%) in H3K27me3 in peripheral granulocytes was achieved with PF-06821497 monotherapy at all dose levels and by combination with enzalutamide at 375 mg BID or higher (**Figure 7**).

Figure 7: H3K27Me3 Inhibition in Peripheral Granulocytes by PF-06821497 Alone and in Combination With Enzalutamide


PF-06821497 Monotherapy Dose Escalation
Mono 75 mg BID (n=2)
Mono 150 mg BID (n=3)
Mono 250 mg BID (n=9)
Mono 375 mg BID (n=2)
Mono 500 mg BID (n=2)
PF-06821497 + Enz Combination in mCRPC Dose Escalation
150mg +Enz (n=2)
250mg +Enz (n=3)
375mg +Enz (n=3)
500mg +Enz (n=4)
625mg +Enz (n=2)
750mg +Enz (n=3)
875mg +Enz (n=2)

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For information, contact, Dr Michael T Schweizer, schweize@uw.edu

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