Phase 1b/2 first-in-class novel combination trial of next generation CDK4-selective inhibitor atirmociclib (PF-07220060) and next generation CDK2-selective inhibitor PF-07104091 in HR+ HER2− metastatic breast cancer and advanced solid tumors

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Declaration of interests

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Employee of: University of Texas MD Anderson Cancer Center, where I am Vice President, Head of Clinical Development in the Therapeutics Discovery Division, which has a commercial interest in DDR inhibitors (IACS30380/ART0380 was licensed to Artios).
Consultant for: 858 Therapeutics, AbbVie, Acrivon, Adagene, Aduro, Almac, Amgen Inc., Amphista, Artios, Astex, AstraZeneca, Athena, Atrin, Avenzo, Avoro, Axiom, Baptist Health Systems, Bayer, Beigene, BioCity Pharma, Blueprint, Boxer, BridGene Biosciences, Bristol Myers Squibb, C4 Therapeutics, Calithera, Cancer Research UK, Carrick Therapeutics, Circle Pharma, Clovis, Cybrexa, Daiichi Sankyo, Dark Blue Therapeutics, Debiopharm, Diffusion, Duke Street Bio, EcoR1 Capital, Ellipses Pharma, EMD Serono, Entos, FoRx Therapeutics AG, F-Star, Genesis Therapeutics, Genmab, GlaxoSmithKline, Glenmark, GLG, Globe Life Sciences, Grey Wolf Therapeutics, Guidepoint, Ideaya Biosciences, Idience, Ignyta, I-Mab, ImmuneSensor, Impact Therapeutics, Institut Gustave Roussy, Intellisphere, Jansen, Joint Scientific Committee for Phase I Trials in Hong Kong, Kyn, Kyowa Kirin, MEI pharma, Merck, Mereo, Merit, Monte Rosa Therapeutics, Natera, Nested Therapeutics, Nexys, Nimbus, Novocure, Odyssey Therapeutics, OHSU, OncoSec, Ono Pharma, Onxeo, PanAngium Therapeutics, Pegascy, PER, Pfizer, Piper-Sandler, Pliant Therapeutics, Prelude Therapeutics, Prolynx, Protai Bio, Radiopharma Theranostics, Repare, resTORbio, Roche, Ryvu Therapeutics, SAKK, Sanofi, Schrodinger, Servier, Synnovation, Synthis Therapeutics, Tango, TCG Crossover, TD2, Terremoto Biosciences, Tessellate Bio, Theragnostics, Terns Pharmaceuticals, Thryv Therapeutics, Tolremo, Tome, Trevarx Biomedical, Varian, Veeva, Versant, Vibliome, Voronoi Inc, Xinthera, Zai Labs and ZielBio.
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Stockholder in: Seagen.

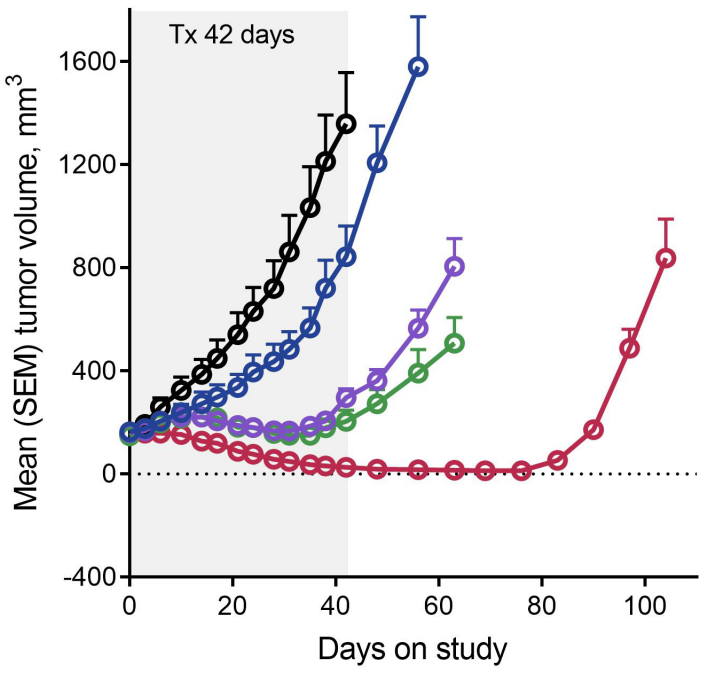
Combination of CDK4i/CDK2i may overcome CDK4/6i resistance

- CDK4/6i combined with endocrine therapy have improved survival outcomes in patients with HR+ HER2− mBC[1]
  - However, on-target toxicity is common with CDK4/6i, and resistance can occur via loss of the Rb tumor suppressor or upregulation of cyclin E1 protein expression and subsequent activation of CDK2[2,3]
- Atirmociclib (PF-07220060) is a selective CDK4i with significant sparing of CDK6 that is associated with less neutropenia than CDK4/6i
- PF-07104091 is a first-in-class selective CDK2i that is being investigated in HR+ HER2− mBC
- The combination of atirmociclib (PF-07220060), PF-07104091, and endocrine therapy may overcome resistance to prior CDK4/6i
- A phase 1b/2, open-label, multicenter, dose-escalation and dose-expansion study is evaluating the combination of atirmociclib (PF-07220060), PF-07104091, and endocrine therapy in patients with mBC or other advanced solid tumors (NCT05262400)

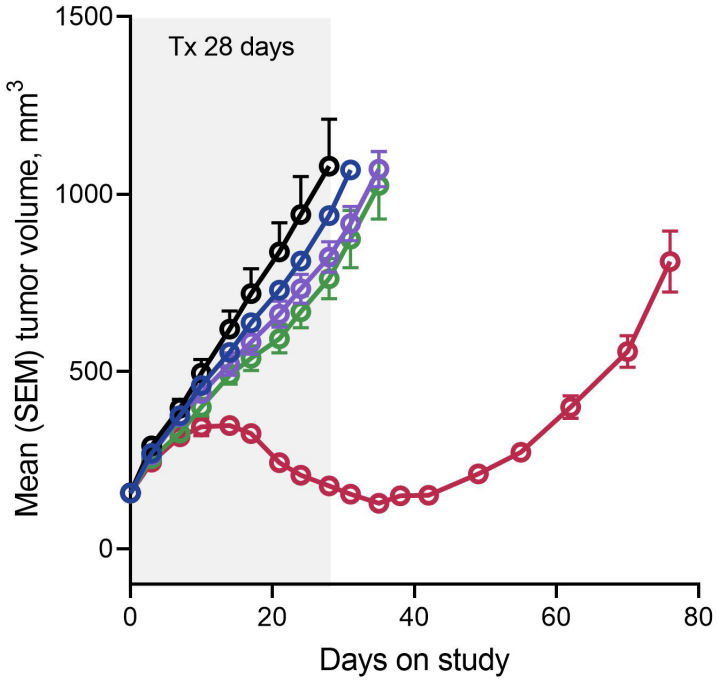
1. Spring LM, et al. Lancet 2020;395(10226):817-27. 2. DeMichele A, et al. Clin Cancer Res 2015;21(5):995-1001. 3. Jhaveri K, et al. Expert Rev Anticancer Ther 2021;21(10):1105-24.
CDK=cyclin-dependent kinase; CDK2/4/6i=CDK2/4/6 inhibitor(s); HER2−=human epidermal growth factor receptor 2-negative; HR+=hormone receptor-positive; mBC=metastatic breast cancer

Atirmociclib (PF-07220060) and PF-07104091 combination shows synergy in palbociclib-sensitive and -resistant ER+ mBC models

HCC1428 xenografts
(palbociclib treatment-naïve HR+ BC)



ST941PBR xenografts
(palbociclib-resistant HR+ BC)

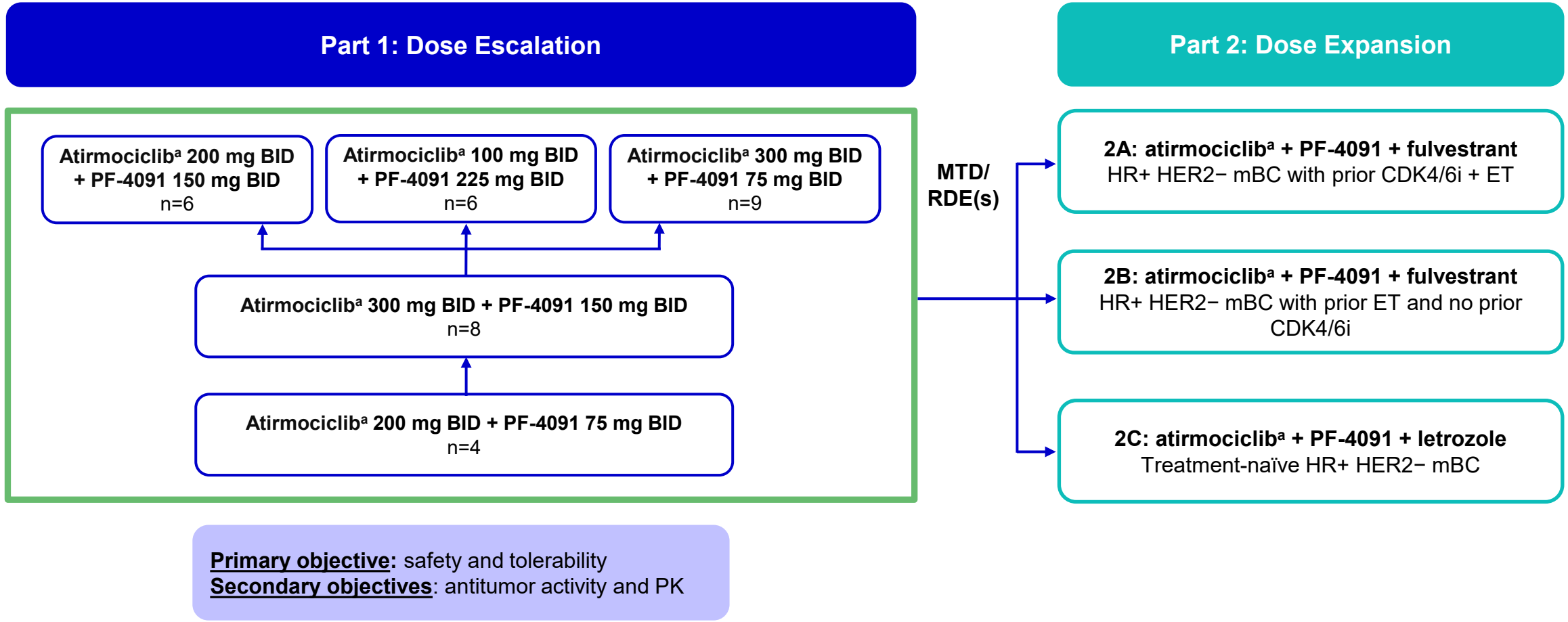


- Combination treatment results in better TGI than treatment with palbociclib or single agent atirmociclib[a] or PF-07104091 in these models
- See poster #5719 for additional preclinical characterization data

- Vehicle
- Palbociclib 10 mpk BID
- PF-07104091 150 mpk BID
- Atirmociclib[a] 60 mpk BID
- Atirmociclib[a] 60 / PF-07104091 150 mpk BID

[a] Atirmociclib (PF-07220060).
BC=breast cancer; BID=twice daily; ER+=estrogen receptor-positive; mpk=mg per kg; TGI=tumor growth inhibition; Tx=treatment

A phase 1b/2 study of atirmociclib (PF-07220060) and PF-07104091 is currently ongoing



Fulvestrant was allowed in Part 1 after ≥2 cycles of the doublet combination in patients with HR+ HER2− mBC. [a] Atirmociclib (PF-07220060).
ET=endocrine therapy; MTD=maximum tolerated dose; PF-4091=PF-07104091; PK=pharmacokinetics; RDE=recommended dose for expansion

Demographics and baseline characteristics

	Atirmociclib (PF-07220060) / PF-07104091 dose					
	200 / 75 mg BID n=4	300 / 150 mg BID n=8	200 / 150 mg BID n=6	100 / 225 mg BID n=6	300 / 75 mg BID n=9	Total N=33
Age, median (range), y	51.5 (45–58)	50.5 (46–75)	70.5 (50–76)	57.0 (38–65)	59.0 (42–67)	56.0 (38–76)
Female, n (%)	4 (100.0)	7 (87.5)	4 (66.7)	6 (100.0)	9 (100.0)	30 (90.9)
Race[a], n (%)						
White	1 (25.0)	4 (50.0)	6 (100.0)	5 (83.3)	7 (77.8)	23 (69.7)
Asian	0	0	0	1 (16.7)	1 (11.1)	2 (6.1)
ECOG performance status[a], n (%)						
0	0	2 (25.0)	1 (16.7)	2 (33.3)	3 (33.3)	8 (24.2)
1	3 (75.0)	6 (75.0)	5 (83.3)	3 (50.0)	6 (66.7)	23 (69.7)
HR+ HER2− breast cancer, n (%)	4 (100.0)	5 (62.5)	3 (50.0)	6 (100.0)	8 (88.9)	26 (78.8)
Number of prior lines of systemic therapy for breast cancer[b], median (range)	1.5 (1–3)	4.0 (2–7)	1.0 (1–7)	2.5 (1–6)	3.0 (2–14)	3.0 (1–14)
Prior CDK4/6i[b], n (%)	4 (100.0)	5 (100.0)	3 (100.0)	6 (100.0)	8 (100.0)	26 (100.0)
Prior fulvestrant[b], n (%)	3 (75.0)	5 (100.0)	2 (66.7)	4 (66.7)	7 (87.5)	21 (80.8)
Prior chemotherapy[b], n (%)	2 (50.0)	3 (60.0)	1 (33.3)	2 (33.3)	5 (62.5)	13 (50.0)

Other tumor types enrolled were HR+ HER2+ breast cancer, small cell cancer (lung, other), ovarian cancer, liposarcoma, prostate cancer, and uterine sarcoma (n=1 each).
[a] Race not reported in 8 patients and ECOG performance status not reported in 2 patients. [b] In advanced/metastatic setting. ECOG=Eastern Cooperative Oncology Group

Atirmociclib (PF-07220060) and PF-07104091 combination shows manageable safety profile at the two RDEs selected

Grade ≥3 treatment-related TEAEs in ≥30%[a] of patients, n (%)	Atirmociclib (PF-07220060) / PF-07104091 dose					Total N=33
	200 / 75 mg BID n=4	300 / 150 mg BID n=8	200 / 150 mg BID n=6	100 / 225 mg BID n=6	300 / 75 mg BID n=9	
Neutropenia	2 (50.0)	2 (25.0)	1 (16.7)	3 (50.0)	1 (11.1)	9 (27.3)
Leukopenia	2 (50.0)	2 (25.0)	3 (50.0)	0	1 (11.1)	8 (24.2)
Anemia	0	1 (12.5)	2 (33.3)	1 (16.7)	0	4 (12.1)
Fatigue	0	2 (25.0)	1 (16.7)	1 (16.7)	0	4 (12.1)
Lymphopenia	1 (25.0)	0	2 (33.3)	1 (16.7)	0	4 (12.1)
Thrombocytopenia	0	2 (25.0)	1 (16.7)	0	0	3 (9.1)
Nausea	0	0	1 (16.7)	0	0	1 (3.0)
Diarrhea	0	0	0	0	1 (11.1)	1 (3.0)
Vomiting	0	0	0	0	0	0

DLTs in 2 patients receiving atirmociclib[b] 200 mg BID + PF-07104091 150 mg BID:

- 1 G2–3 hematologic AEs
- 1 G3 nausea

DLTs in 3 patients receiving atirmociclib[b] 300 mg BID + PF-07104091 150 mg BID:

- 1 G4 thrombocytopenia
- 1 G3 fatigue
- 1 G2–3 fatigue and GI AEs

2 RDEs were selected based on safety data (no DLTs at these doses):

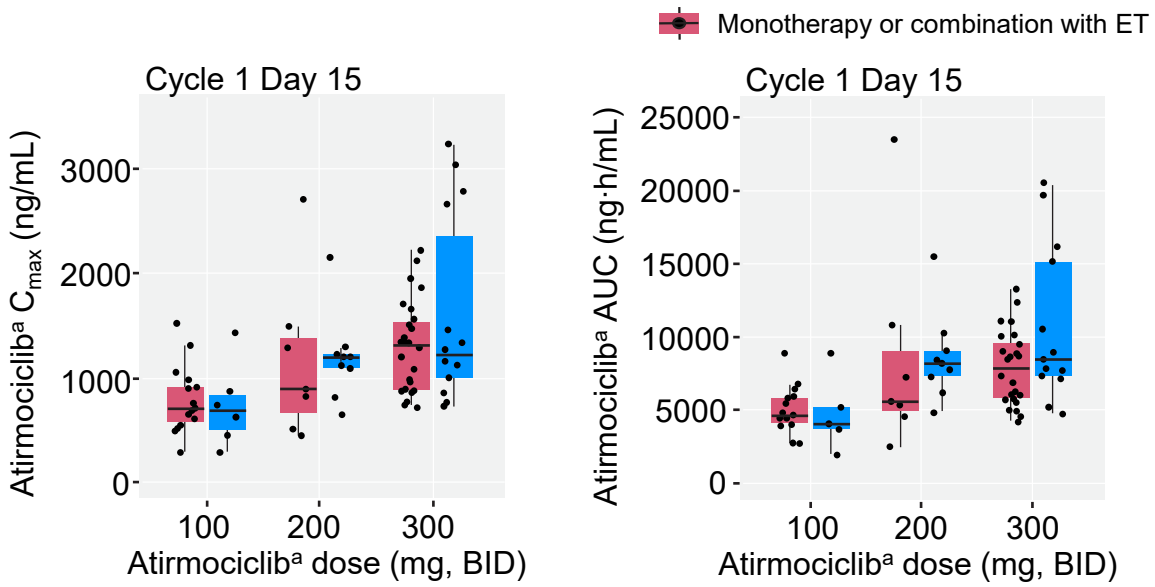
- Atirmociclib[b] 100 mg BID + PF-07104091 225 mg BID
- Atirmociclib[b] 300 mg BID + PF-07104091 75 mg BID

[a] Based on all-grade TEAEs. [b] Atirmociclib (PF-07220060).
AE=adverse event; DLT=dose-limiting toxicity; G=grade; GI=gastrointestinal; TEAE=treatment-emergent adverse event

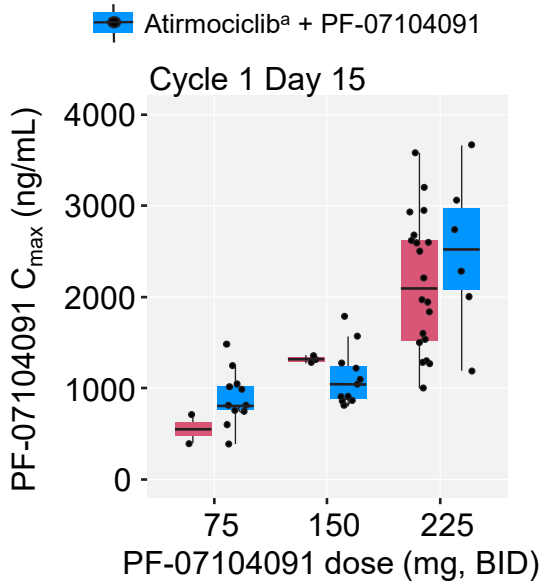
Preliminary PK results showed no obvious drug-drug interaction between atirmociclib (PF-07220060) and PF-07104091

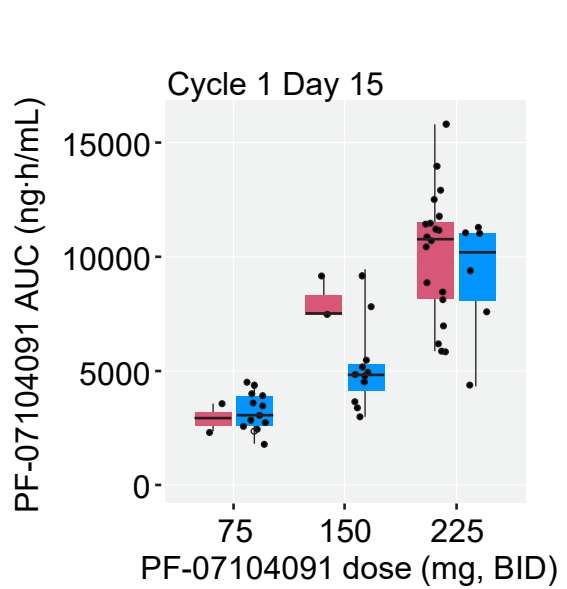
- Preliminary PK results were compared with results from 2 prior studies that evaluated atirmociclib[a] (C4391001) and PF-07104091 (C4161001) as monotherapy or in combination with ET
- Steady-state exposures were comparable to monotherapy

Steady state exposure of atirmociclib[a]



Steady state exposure of PF-07104091

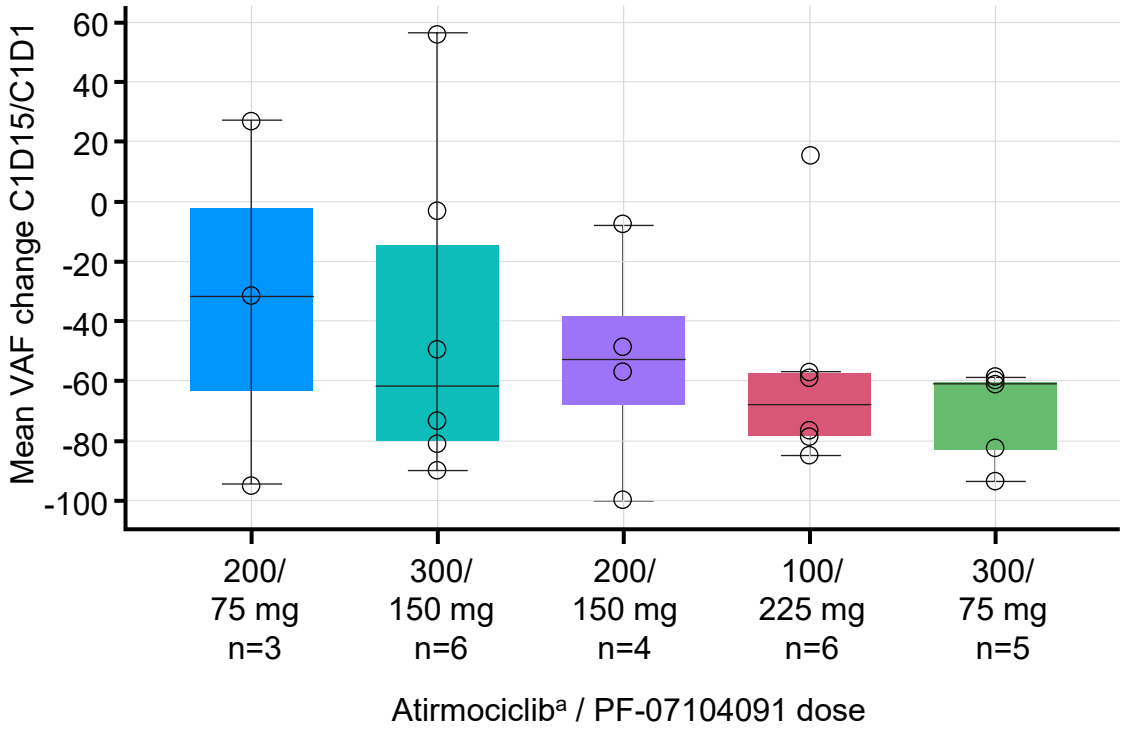




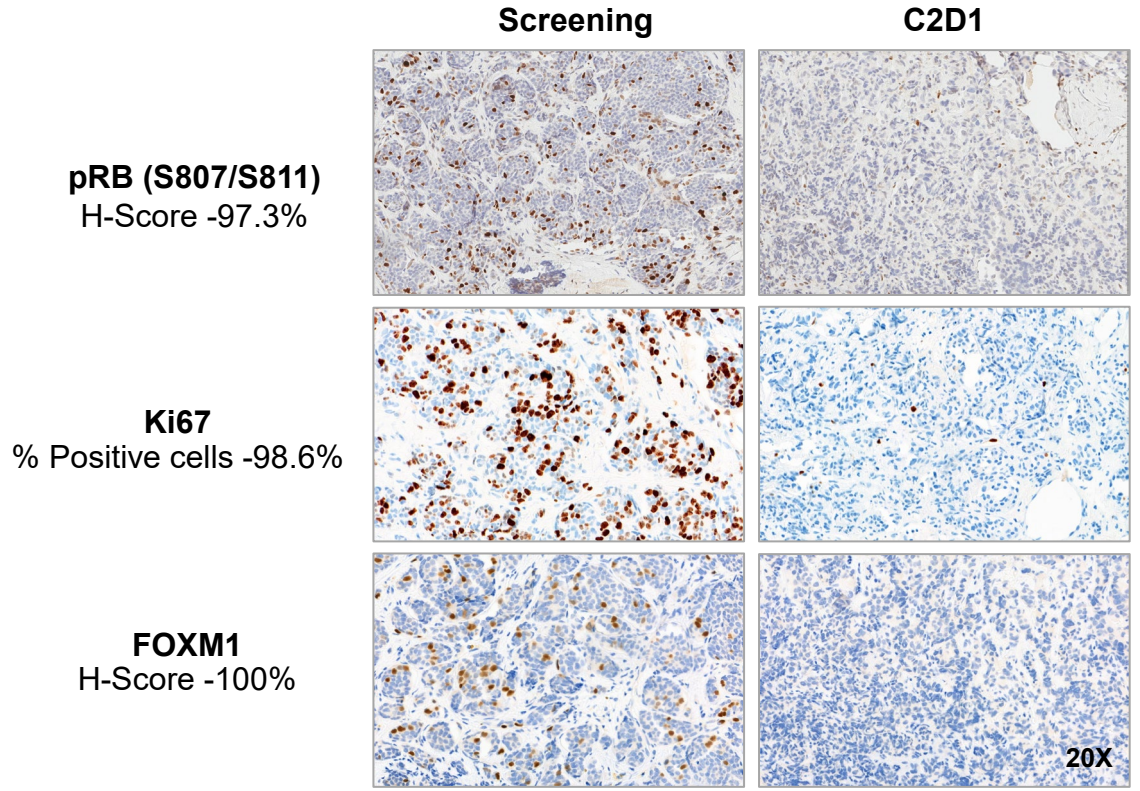
AUC=AUC_{0-10h} for Study C4391001; AUC=AUC_{0-9h} for Study C4161001 and C4391002. [a] Atirmociclib (PF-07220060).
AUC=area under the curve; C_{max}=maximum observed concentration

Atirmociclib (PF-07220060) in combination with PF-07104091 led to modulation of PD biomarkers

Early decrease in ctDNA levels at C1D15



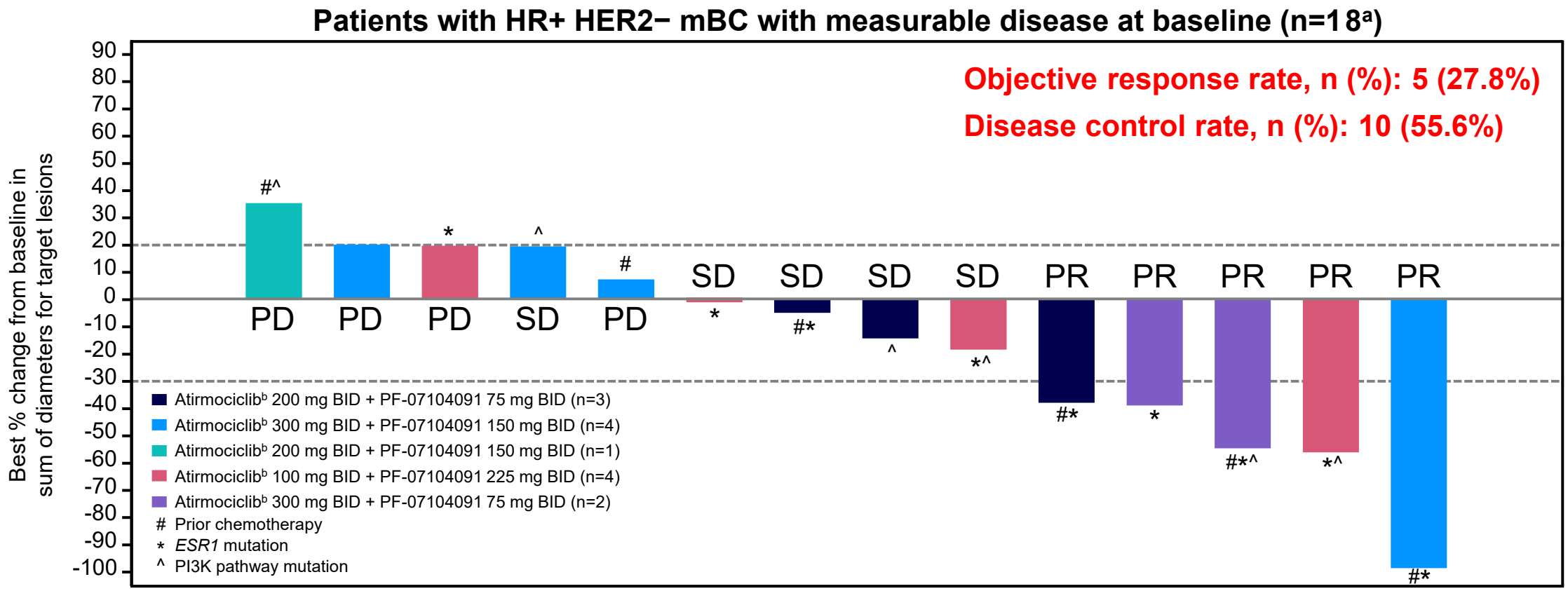
Inhibition of PD biomarker expression in tumor biopsy



HR+ HER2- BC patient treated with atirmociclib[a] 200 mg + PF-07104091 150 mg

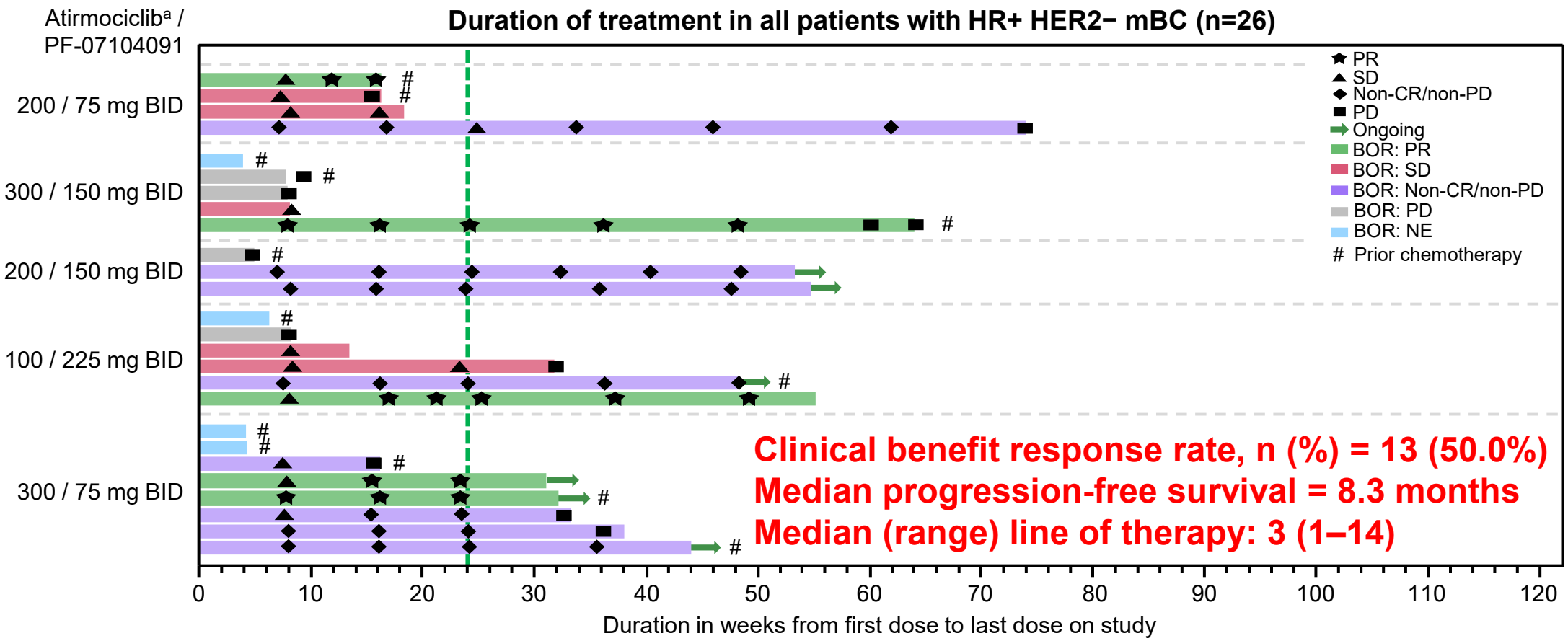
[a] Atirmociclib (PF-07220060). Doses are twice daily. ctDNA was analyzed using Guardant360.
C=cycle; D=day; ctDNA=circulating tumor DNA; PD=pharmacodynamic; VAF=variant allele frequency

Promising antitumor activity was seen in heavily pretreated metastatic breast cancer patients treated with CDK4/6i



[a] 4 patients had non-evaluable responses and are not shown. [b] Atirmociclib (PF-07220060). All patients received prior CDK4/6i. PI3K pathway genes include *PIK3CA*, *AKT1* and *PTEN*. Mutations include alterations in elacestrant, alpelisib and capivasertib CDx tests. Objective response rate includes CR and PR. Disease control rate includes CR, PR, SD, and non-CR/non-PD.
CR=complete response; PR=partial response; PD=progressive disease; SD=stable disease

Promising duration of treatment observed in heavily pretreated metastatic breast cancer patients treated with CDK4/6i



[a] Atirmociclib (PF-07220060).
BOR=best overall response

First-in-class CDK4i atirmociclib (PF-07220060) and CDK2i (PF-07104091) combination shows promising anti-tumor activity in CDK4/6i-treated metastatic breast cancer patients

- The combination of atirmociclib (PF-07220060) and PF-07104091 had a manageable safety profile at the two RDEs selected
- Antitumor activity (ORR 27.8%) was observed with this combination in heavily pretreated metastatic breast cancer patients with prior CDK4/6i, including patients with *ESR1* mutations
- Dose expansions of this combination plus endocrine therapy are ongoing for CDK4/6i-treated or CDK4/6i-naïve patients with metastatic breast cancer

ORR=objective response rate

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