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SYNOPSIS

Study Title: Phase 1/2a Dose Escalation and Expansion Study Evaluating Safety, Tolerability, Pharmacokinetic, Pharmacodynamics and Anti-Tumor Activity of PF-06873600 as a Single Agent and in Combination With Endocrine Therapy

Study Number: C3661001

Regulatory Agency or Public Disclosure Identifier Number:

US IND Number: 134457

ClinicalTrials.gov ID: NCT03519178

EudraCT Number: 2020-001757-40

Study Phase: 2a

Name of Study Intervention: Ebvaciclib (PF-06873600)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date:

Document Version	Report Date
Final CSR (PCD Date) Version 1.0	28 November 2023

Number of Study Center(s) and Investigator(s):

A total of 153 participants were enrolled and 151 participants were treated at 22 centers in 5 countries in this study.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: None.

Study Period:

Study Initiation Date (First Participant First Visit): 07 March 2018

Primary Completion Date: 05 April 2023

This study was neither discontinued nor interrupted.

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Rationale:

PF-06873600 is an inhibitor of cyclin-dependent kinases (CDK) 2, 4 and 6 that is being investigated in women of any menopausal status and men with hormone receptor positive (HR+) human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer (mBCa) and patients with other tumor types that have potential to have increased Cyclin E expression/CDK2 activity, including locally recurrent/advanced or metastatic triple negative breast cancer (TNBC) (women and men) and women with advanced platinum resistant ovarian cancer.

This was the first-in-patient clinical study of PF-06873600. The study was divided into 2 parts: monotherapy dose escalation (Parts 1A and 1C) and then dose finding with PF-06873600 immediate release (IR) formulation in combination with endocrine therapy (ET) (letrozole and fulvestrant [Ful]) (Part 1B) followed by dose expansion arms in combination with ET (Part 2).

The purpose of this study was to assess the safety and tolerability of PF-06873600, as a single agent (Parts 1A and 1C) and in combination with ET (Part 1B). In addition, the preliminary antitumor activity of PF-06873600 was evaluated in patients with HR+ HER2- mBCa in Part 2 (PF-06873600+Ful, 2A: post cyclin-dependent kinase 4/6 inhibitors [CDK4/6i]; 2C: CDK4/6i naïve/post ET), as well as the further confirmation of safety and tolerability of PF-06873600.

The study was terminated in September 2022 based on a strategic decision following the review of clinical results within the current Pfizer oncology portfolio. This decision was not due to any safety concerns or requests from any regulatory authorities. The safety profile for PF-06873600 remained unchanged.

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Objectives, Endpoints, and Statistical Methods:

Parts 1A and 1C: Single Agent Dose Escalation and Part 1B: Combination Dose Finding

Type	Objective	Endpoints
Primary		
Safety	Parts 1A and 1C: To assess the safety and tolerability of increasing doses of PF-06873600 in patients with: • HR-positive HER2-negative advanced or metastatic breast cancer (mBC) patients (third or fourth line setting). • Locally recurrent/advanced or metastatic triple negative breast cancer. • Advanced platinum resistant epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer • In order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Dose for Expansion (RDE) for PF-06873600 as a single agent (Part 1A and Part 1C only). Part 1B: To assess the safety and tolerability of PF-06873600 at the single agent RDE in combination with letrozole and in combination with fulvestrant (in a de-escalation manner, if indicated) in patients with: • HR-positive HER2-negative advanced or mBC (third or fourth line setting) in order to establish the RDE for PF-06873600 in combination with letrozole and in combination with fulvestrant, respectively.	Parts 1A, Part 1B, and Part 1C: • Dose-Limiting Toxicities (DLTs). • Adverse events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing. • Vital sign abnormalities. • Heart rate corrected QT interval (eg, QTcF).

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Type	Objective	Endpoints
Secondary		
Pharmacokinetics (PK)	• To evaluate the single- and multiple- dose PK of PF-06873600 when given as a single agent (Part 1A, and Part 1C), in combination with letrozole, and in combination with fulvestrant (Part 1B).	PK parameters of PF-06873600: • Single Dose (SD) - maximum observed plasma concentration (C_{max}), time for C_{max} (T_{max}), area under the plasma concentration-time profile from time 0 to the time of last quantifiable concentration (AUC_{last}), and as data permitted, area under the plasma concentration-time profile from time 0 extrapolated to infinity (AUC_{inf}), apparent clearance (CL/F), apparent volume of distribution (V_z/F), and terminal half-life ($t_{½}$). • Multiple Dose (MD) (assuming steady state was achieved) - steady state C_{max} ($C_{ss,max}$), time for steady state C_{max} ($T_{ss,max}$), steady state area under the plasma concentration-time profile within 1 dose interval ($AUC_{ss,\tau}$), steady state lowest observed concentration ($C_{ss,min}$), steady state apparent clearance (CL_{ss}/F), and as data permitted, steady state volume of distribution (V_{ss}/F), $t_{½}$, and observed accumulation ratio based on AUC (R_{ac}) ($AUC_{ss,\tau}$/ single-dose area under the plasma concentration-time profile within 1 dose interval [$AUC_{sd,\tau}$]).
Efficacy	• To document any preliminary evidence of anti-tumor activity of PF-06873600.	• Objective Response (OR), as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. • Time-to-event endpoints: eg, Duration of Response (DoR), Progression-Free Survival (PFS), Time to Progression (TTP).
pharmacodynamics (PD)	• To evaluate the PD biomarkers of CDK pathway modulation following treatment with PF-06873600 in tumor.	• Modulation of PD biomarkers (eg, phospho-retinoblastoma protein [pRb], Ki67) of CDK in tumor.
Exploratory*		
PD	• To explore the PD markers of CDK pathway modulation following treatment with PF-06873600 in surrogate tissue (ie, skin) and blood.	• Modulation of PD biomarkers (eg, pRb, Ki67) of CDK in surrogate tissue (ie, skin), and in blood (thymidine kinase 1 [TK1] activity).

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Type	Objective	Endpoints
Biomarker	• To explore biomarkers of sensitivity or resistance to PF-06873600 in tumor tissue (archival and/or de novo tumor tissue).	• Genomic (gene alterations, including mutation and copy number variation) and transcriptomic (ribonucleic acid [RNA] expression and pathway gene signatures) characteristics in baseline and post-treatment tumor biopsies and their relationship to clinical outcome. • Cell cycle and/or target-related protein (eg, cyclin E1) expression in tumor biopsies and their relationship to clinical outcome.
Biomarker	• To explore peripheral blood candidate biomarkers of sensitivity or resistance to PF-06873600.	• Peripheral blood candidate biomarkers consisting of deoxyribonucleic acid (DNA), RNA or proteins that may be related to response or resistance to treatment, including genetic alterations (eg, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha [PIK3CA], estrogen receptor 1 [ESR1] mutations) in circulating tumor DNA, and their relationship to clinical outcome.

*These exploratory evaluations were not included for this terminated study.

Part 2: PF-06873600 Combination Dose Expansion

Type	Objective	Endpoints
Primary		

Efficacy
 	
Safety
	• To evaluate the preliminary antitumor activity and confirm the safety and tolerability of PF-06873600:
	
	In combination (at the RDE from Part 1B) in patients with:
	• HR-positive/HER2-negative advanced or mBC (PF-06873600 + fulvestrant) – (second or third line setting).
	• HR-positive/HER2-negative advanced or mBC (PF-06873600 + a nonsteroidal aromatase inhibitor) (CDK4/6i naive).
	• HR-positive HER2-negative advanced or mBC (PF-06873600+fulvestrant) (CDK4/6i naïve/post ET).
		• Preliminary antitumor activity measure for efficacy included ORR, as assessed using RECIST 1.1.
		• Safety and tolerability:
		  • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03) timing, seriousness and relationship to study therapy.
		  • Lab abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03) and timing.
		  • Vital sign abnormalities.
		  • Heart rate corrected QT interval (eg, QTcF).

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Type	Objective	Endpoints
Secondary		
Efficacy	• To further explore preliminary antitumor activity of PF-06873600.	• Time-to-event endpoints: eg, DOR, PFS, overall survival (OS) and TTP.
PK	• To further evaluate the PK of PF-06873600 in combination with letrozole, and in combination with fulvestrant at the respective RDE.	PK parameters of PF-06873600, including but not limited to: • SD - C_{max}, T_{max}. • MD (assuming steady state was achieved) - $C_{ss,max}$, $T_{ss,max}$, $C_{ss,min}$ and $R_{ac,}C_{max}$.
PD	• To evaluate PD biomarkers of CDK pathway modulation following treatment with PF-06873600 in combination with fulvestrant or letrozole in tumor.	• Modulation of PD biomarkers (eg, pRb, Ki67) of CDK in tumor.
Exploratory*		
PD	• To explore pharmacodynamic (PD) markers of CDK pathway modulation following treatment with PF-06873600 in combination with fulvestrant or letrozole in surrogate tissue (ie, skin) and blood.	• Modulation of PD biomarkers (pRb, Ki67) of CDK in surrogate tissue (ie, skin), and in blood (TK1 activity).
Biomarker	• To explore biomarkers of sensitivity and/or resistance to PF-06873600 in tumor tissue (archival and de novo tumor tissue).	• Genomic (gene alterations, including mutation and copy number variation) and transcriptomic (RNA expression and pathway gene signatures) characteristics in baseline and post-treatment tumor biopsies and their relationship to clinical outcome. • Cell cycle and/or target-related protein (eg, cyclin E1) expressions in tumor biopsies and their relationship to clinical outcome.
Biomarker	• To explore peripheral blood candidate biomarkers of sensitivity or resistance to PF-06873600.	• Peripheral blood candidate biomarkers consisting of the DNA, RNA or proteins that may be related to response or resistance to treatment, including genetic alterations (eg, PIK3CA, ESR1 mutations) in circulating tumor DNA, and their relationship to clinical outcome.

*These exploratory evaluations were not included for this terminated study.

Methodology:

This was a Phase 1/2a, open-label, multi-center, non-randomized, multiple dose study to evaluate safety, tolerability, PK, and PD of PF-06873600 administered as a single agent and then in combination with ET.

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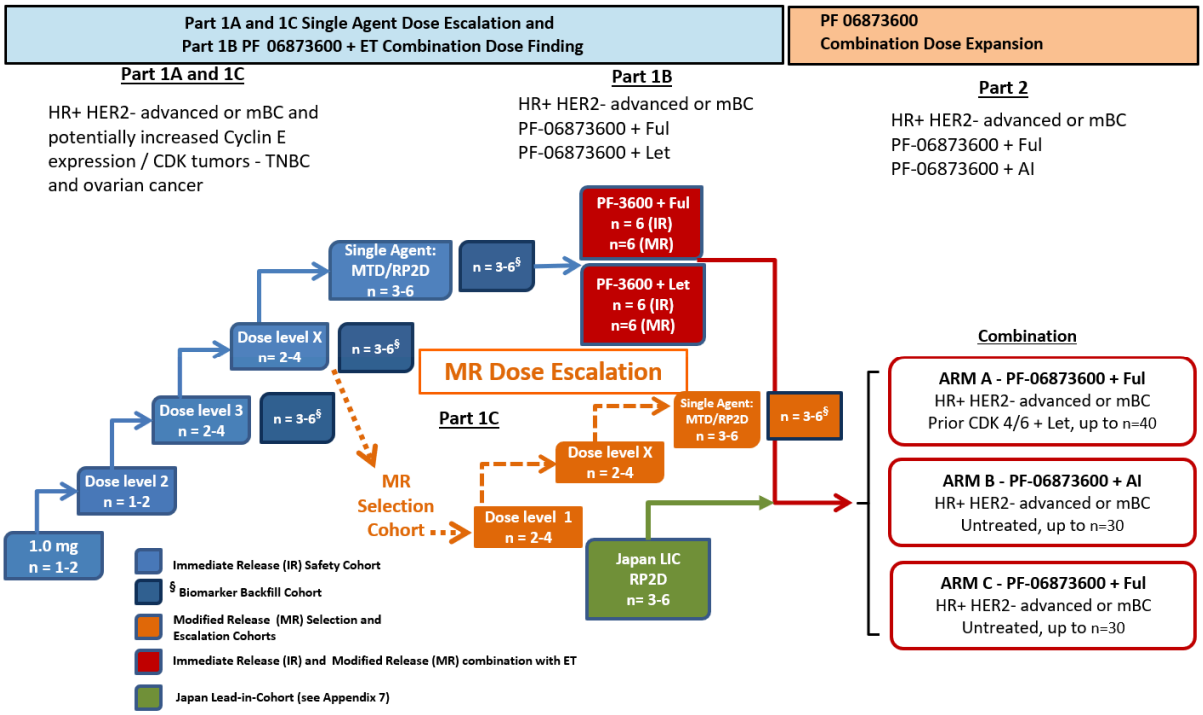
The overall study design was depicted in the schema below (Figure 1).

Figure 1. Overall Study Schema



Abbreviations: AI = aromatase inhibitor; Let = letrozole; LIC = Lead-in-Cohort; MR = modified release; RP2D = recommended phase 2 dose.

Number of Participants (planned and analyzed):

Planned: Approximately 75 participants were planned to be enrolled in the dose escalation/finding safety cohorts, and an additional 6-12 participants were expected in the biomarker cohorts in Parts 1A and 1C.

In the dose expansion cohorts, approximately 100 participants (40, 30, and 30 in Parts 2A, 2B, and 2C, respectively) were expected to be enrolled in Part 2.

Analyzed: A total of 153 participants were assigned to treatment and 151 (98.7%) were treated in the study.

- In Part 1A, a total of 53 participants were assigned to treatment and 51 were treated.
- In Part 1B, a total of 16 participants were assigned to treatment and treated.
- In Part 1C, a total of 11 participants were assigned to treatment and treated.

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- A total of 45 and 28 participants were assigned to treatment and treated in Part 2A and Part 2C, respectively.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were participants with HR+ HER2- advanced or mBC (histologically or cytologically proven). Participants with TNBC and ovarian cancer were included in Parts 1A and 1C.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

PF-06873600

PF-06873600 was administered orally twice a day (BID) (in 12 ±4 hour intervals) on a continuous basis. Alternative intermittent dosing regimen was explored in part 1A (5 days on/2 days off) and alternative modified release (MR) formulation dosing in Part 1C. A cycle was defined as 28 days, regardless of missed doses or dose delays.

Letrozole

Letrozole was administered orally once daily (QD) continuously together with PF-06873600.

Fulvestrant

Fulvestrant 500 mg was administered intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock.

The manufacturing lot numbers for the study interventions dispensed in this study are provided in Table S1.

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Table S1. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/ Potency	Dosage Form
Fulvestrant (2) Syringe Barrels @ 250mg/5 ml each syringe solution for injection	RE655	20-002296	50 mg/ml	Commercial product*
Fulvestrant (2) Syringe Barrels @ 250mg/5 ml each syringe solution for injection	RJ319	20-AE-00083	50 mg/ml	Commercial product*
Fulvestrant (2) Syringe Barrels @ 250mg/5 ml each syringe solution for injection	RX352	22-AE-00424	50 mg/ml	Commercial product*
Fulvestrant (Faslodex) 250 mg/5 mL solution for Injection pre-filled syringe	RR367	21-AE-00226	50 mg/ml	Commercial product*
Letrozole 2.5mg film-coated tablets	M2003757	20-002297	2.5 mg	Commercial product**
PF-06873600 1 mg Round White to Off-White Tablet	N/A	17-003913	1 mg	Tablet
PF-06873600 10 mg MR Tablet (Long Duration)	19-000301 / 19-001521	19-002793	10 mg	Tablet
PF-06873600 10 mg MR Tablet (Long Duration)	20-DP-00200	20-002447	10 mg	Tablet
PF-06873600 10 mg MR Tablet (Short Duration)	19-000300 / 19-001519	19-002792	10 mg	Tablet
PF-06873600 25 mg Oval White to Off-White Tablet	19-DP-00092	19-004615	25 mg	Tablet
PF-06873600 25 mg Oval White to Off-White Tablet	21-000217	21-DP-00442	25 mg	Tablet
PF-06873600 25 mg Oval White to Off-White Tablet	N/A	17-003915	25 mg	Tablet
PF-06873600 25 mg Oval White to Off-White Tablet	N/A	18-003627	25 mg	Tablet
PF-06873600 40 mg MR Tablet (Long Duration)	19-000425 / 19-001525	19-002795	40 mg	Tablet
PF-06873600 40 mg MR Tablet (Short Duration)	19-000424 / 19-001523	19-002794	40 mg	Tablet
PF-06873600 5 mg Round White to Off-White Tablet	19-DP-00093	19-004614	5 mg	Tablet
PF-06873600 5 mg Round White to Off-White Tablet	20-003985	20-DP-00278	5 mg	Tablet
PF-06873600 5 mg Round White to Off-White Tablet	N/A	17-003914	5 mg	Tablet

*Dosage form was solution for injection.
**Dosage form was tablet.

Duration of Study Intervention:

Participants would receive PF-06873600 orally BID on a continuous basis in 28-day cycles. Alternative intermittent dosing regimen was explored in Part 1A (5 days on/2 days off) and

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alternative MR formulation dosing in Part 1C. The plan was to continue treatment until progression of disease, uncontrollable toxicity, a decision by the patient or investigator to discontinue treatment or the study is terminated. It is estimated that each participant may remain on treatment for approximately 6-8 cycles, making total study duration approximately 32-36 weeks.

Summary of Results:

Demographic and Other Baseline Characteristics:

Of 151 participants in the safety analysis set, all participants were female, with the majority were White (71.5%). The median age was 59.0 years (range: 28, 84), and the median weight was 70.400 kg (range: 42.50, 134.00). A total of 81 (53.6%) participants had baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 69 (45.7%) baseline ECOG PS 1, and 1 (0.7%) baseline ECOG PS as 2.

Of 151 participants in the safety analysis set in this study, 144 (95.4%) had the diagnosis of breast cancer and (136 [90.1%]) were HR+/HER2-; 5 (3.3%) participants had TNBC. Seven (4.6%) had the diagnosis of ovarian cancer. Cohorts 1B, 2A and 2C included mBCa participants only.

Exposure:

The median duration of PF-06873600 treatment was 58.0 days (range: 5, 1093) in Part 1A; a median of 2.0 cycles (range: 1, 36) were administered.

The median duration of PF-06873600 treatment was 125.5 days (range: 11, 419) in Part 1B; a median of 5.0 cycles (range: 1, 15) were administered.

The median duration of PF-06873600 treatment was 112.0 days (range: 25, 466) in Part 1C; a median of 4.0 cycles (range: 1, 16) were administered.

The median duration of PF-06873600 treatment was 120.0 days (range: 18, 636) in Part 2A; a median of 5.0 cycles (range: 1, 23) were administered.

The median duration of PF-06873600 treatment was 148.5 days (range: 1, 413) in Part 2C; a median of 5.5 cycles (range: 1, 15) were administered.

Efficacy Results:

<u>Primary Efficacy Endpoint – Objective Response Rate in Part 2</u>

A total of 67 participants were evaluable for OR in Part 2. A total of 8 (11.9%) participants achieved PR.

In Part 2A (PF-06873600+Ful, HR+/HER2- mBCa post CDK4/6i), 3 participants achieved OR (all PRs); the ORR was 6.7% (95% confidence interval [CI]: 1.4%, 18.3%).

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In Part 2C (PF-06873600+Ful, HR+/HER2- mBCa CDK4/6i naïve/post ET), 5 participants achieved OR (all PRs); the ORR was 22.7% (95% CI: 7.8%, 45.4%).

Secondary Efficacy Endpoints - Duration of Response

The DoR for 1 confirmed responder in Part 2C was 5.8 months.

The other 7 confirmed responders were censored: 1 participant in Part 2A for start of new anti-cancer therapy, 3 participants (2 in Part 2A and 1 in Part 2C) due to study being terminated by sponsor, and 3 participants in Part 2C for being event free as of the cutoff date.

Secondary Efficacy Endpoints - Progression Free Survival

In Part 2A (PF-06873600+Ful, HR+/HER2- mBCa post CDK4/6i), among 45 participants in full analysis set, 27 had an event of disease progression. The estimated median PFS was 5.6 months (95% CI: 3.9, 7.8).

In Part 2C (PF-06873600+Ful, HR+/HER2- mBCa CDK4/6i naïve), among 28 participants in full analysis set, 8 had an event of disease progression or death. The estimated median PFS was 11.1 months (95% CI: 7.5, not evaluable [NE]).

Secondary Efficacy Endpoints – Objective Response Rate in Part 1

In Part 1A, 1 participant achieved PR, treated at PF-06873600 IR 50 mg BID dose level.

In Part 1B, 1 participant achieved PR, treated with PF-06873600 IR 25 mg BID plus fulvestrant combination.

In Part 1C, 1 participant achieved PR, treated with PF-06873600 IR 25 mg BID after two 20 mg MR lead-in doses.

Safety Results:

Because the frequency of certain medical events may be underestimated by reliance on a single Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT), certain PTs representing a similar medical event were analyzed in aggregate using Customized Query (CQ) and represented throughout this clinical study report (CSR).

Of the 1385 all-causality treatment-emergent adverse events (TEAEs) reported in 147 (97.4%) participants across all cohorts, 832 events reported in 138 (91.4%) participants were considered to be treatment-related.

The most frequently reported all-causality TEAEs (≥30% of participants) were nausea (62.9%), anaemia (CQ including anaemia, haemoglobin decreased, red blood cell count decreased, haematocrit decreased, normochromic anaemia, normocytic anaemia and normochromic normocytic anaemia) (44.4%), fatigue (CQ including asthenia, fatigue,

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tiredness and malaise) (43.7%), neutropenia (CQ including neutropenia, neutrophil count decreased, neutrophil percentage decreased, cyclic neutropenia, agranulocytosis, granulocytopenia and granulocyte count decreased) (37.7%), and vomiting (35.8%).

The most frequently reported treatment-related TEAEs (≥20% of participants) were nausea (60.9%), anaemia (CQ) (41.1%), fatigue (CQ) (39.7%), neutropenia (CQ) (37.1%), vomiting (33.8%), alopecia (27.8%), leukopenia (CQ including leukopenia and white blood cell count decreased) (24.5%), and headache (21.2%).

A total of 34 (22.5%) participants had all-causality serious adverse events (SAEs) reported. The most frequently reported all-causality SAEs were febrile neutropenia (5 [3.3%] participants), abdominal pain, colitis, and hypotension (each in 3 [2.0%] participants).

A total of 13 (8.6%) participants had treatment-related SAEs reported. The most frequently reported treatment-related SAEs were febrile neutropenia (5 [3.3%] participants) followed by neutropenia (CQ), colitis, and stomatitis (each in 2 [1.3%] participants).

A total of 69 (45.7%) participants had maximum Grade 3-4 all-causality TEAEs, and 54 (35.8%) participants had maximum Grade 3-4 treatment-related TEAEs.

A total of 19 (12.6%) deaths reported as of primary completion date (PCD). Five (3.3%) deaths were reported on treatment (while receiving study treatment or within 28 days after last dose of study treatment or start of new anti-cancer therapy minus 1 day, whichever occurred first). Grade 5 TEAE of cardiac arrest was reported in 2 (1.3%) participants; Grade 5 TEAEs of death, disease progression, gastrointestinal bacterial infection, haemolysis, and respiratory failure were each reported in 1 (0.7%) participant.

A total of 2 (1.3%) participants reported treatment-related Grade 5 TEAEs. Grade 5 treatment-related TEAEs of cardiac arrest and gastrointestinal bacterial infection were each reported in 1 (0.7%) participant.

Dose-Limiting Toxicity

In Part 1A, a total of 6 (9.4%) participants had DLTs reported.

Two participants in PF-06873600 35 mg BID cohort had DLTs:

- One participant had Grade 4 neutrophil count decreased, considered treatment-related.
- One participant had Grade 4 neutrophil count decreased and Grade 4 platelet count decreased, both AEs considered treatment-related.

Four participants in PF-06873600 50 mg BID cohort had DLTs:

- One participant had Grade 4 febrile neutropenia, considered treatment-related.

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- One participant had Grade 3 fatigue, considered treatment-related.
- One participant had Grade 4 febrile neutropenia, Grade 4 thrombocytopenia, Grade 5 cardiac arrest, and Grade 4 multiple organ dysfunction syndrome, all considered treatment-related.
- One participant had Grade 3 febrile neutropenia and Grade 3 colitis, both AEs considered treatment-related.

Clinical Laboratory Evaluation

A total of 13 (8.7%) participants across all cohorts reported Grade 4 neutrophil count decreased, 6 (4.0%) reported Grade 4 white blood cell decreased, 3 (2.0%) reported Grade 4 platelet count decreased, and 1 (0.7%) reported Grade 4 lymphocyte count decreased, all of whom had grade increased compared to baseline.

Except Grade 4 hypophosphatemia reported in 2 (1.4%) participants, Grade 4 blood bilirubin increased, hypercalcemia, hyperkalemia, and lipase increased, were each reported in single participant, all of whom had grade increased compared to baseline.

Vital Signs

For systolic blood pressure, 9 (6.0%) participants had values <90◦mm◦Hg, 15 (10.0%) with increases ≥30◦mm◦Hg, and 26 (17.3%) with decreases ≥30◦mm◦Hg.

For diastolic blood pressure, 7 (4.7%) participants had values <50◦mm◦Hg, 15 (10.0%) with increases ≥20◦mm◦Hg, and 24 (16.0%) with decreases ≥20◦mm◦Hg.

For heart rate, 1 (0.7%) participant had value <40 bpm, and 6 (4.0%) participants had values >120 bpm.

Electrocardiograms

For PR interval, 1 (0.7%) participant had change from baseline ≥25% and baseline value >200 msec, and 1 (0.7%) with change from baseline ≥50% and baseline value ≤200 msec.

For QRS interval, 1 (0.7%) participant had change from baseline ≥25% and baseline value >100 msec, and 1 (0.7%) with change from baseline ≥50% and baseline value ≤100 msec.

For QTcF, 44 (29.1) participants had values ≥450 - ≤480 msec, 3 (2.0%) with values ≥481 - ≤500 msec, 2 (1.3%) with values ≥501 msec, 24 (15.9%) with change from baseline >30 - ≤60 msec, and 4 (2.6%) with change from baseline >60 msec.

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Pharmacokinetic Results:

Following oral administration of the IR formulation, PF-06873600 was rapidly absorbed, with median T_{max} values of 1 to 4 hours after the first dose. The geometric mean PK parameters of PF-06873600, including C_{max}, C_{min}, and AUC, in general, increased with dose up to at least 35 mg BID. There was minimal accumulation following repeated BID dosing, with geometric mean R_{ac} ranging from 0.7 to 1.3. The arithmetic mean $t_{½}$ ranged from 2 to 3 hours. PF-06873600 exposure exhibited moderate to high inter-participant variability. At 25 mg BID, the geometric mean coefficient of variation percentage (CV%) values were 58% and 56% for single dose AUC_{inf} and C_{max}, respectively. After multiple dosing at 25 mg BID, the geometric mean CV% values were 45%, 43% and 119% for AUC_{tau}, C_{max} and C_{min}, respectively.

The plasma exposures of PF-06873600 were largely comparable between monotherapy and combination therapy with fulvestrant or letrozole.

Pharmacodynamic Results:

Following PF-06873600 IR 25 mg BID monotherapy in Part 1A, the median change in Ki67 positive cells was -11.67%, and the median change in pRb H-score was -16.49.

Following PF-06873600 IR 25 mg BID / fulvestrant combination treatment in Part 1B and Part 2A, the median change in Ki67 positive cells was -35.90%, and the median change in pRb H-score was -31.88.

Conclusions:

PF-06873600 has been evaluated at doses from 1 mg to 50 mg BID during the dose escalation part (Part 1). PF-06873600 exposures were generally increased with dose up to at least 35 mg BID with moderate to high inter-participant variability. Based on Part 1A and Part 1B safety and PK data, 25 mg BID (IR formulation) was chosen as the recommended dose for monotherapy and in combination with ET (letrozole and fulvestrant). Most frequently reported all grades TEAE, as well as most frequently observed Grade 3-4 TEAE, SAE, DLT and AE leading to dose reduction and discontinuation, were neutropenia and gastrointestinal AEs.

PF-06873600 demonstrated modest anti-tumor activity as monotherapy: 1 PR was observed at PF-06873600 IR 50 mg BID dose level (Part 1A), and 1 PR in MR selection cohort MR 20 mg/IR 25 mg BID (Part 1C).

In dose expansion cohorts, PF-06873600 demonstrated early signs of efficacy in combination with fulvestrant: 3 PRs were observed (ORR of 6.7% [95% CI: 1.4%, 18.3%]) in Part 2A (PF-06873600+Ful, HR+/HER2- mBCa post CDK4/6i), and 5 PRs were observed (ORR of 22.7% [95% CI: 7.8%, 45.4%]) in Part 2C (PF-06873600+Ful, HR+/HER2- mBCa CDK4/6i naïve/post ET).

In conclusion, PF-06873600 demonstrated overall favorable benefit risk profile consistent with CDK4/6 inhibitors class of drugs, as well as some clinical activity in mBC HR+/HER2-

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mBC. Nevertheless, the totality of the PK, safety, and efficacy data do not support the transformational profile needed to justify further clinical development along a path to registration.

The Phase 1 study C3661001 was terminated by Sponsor based on a business strategic decision.