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SYNOPSIS

Study Title: A Randomized, Multicenter, Double-Blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women With ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment for Advanced Disease

Study Number: A5481008

Regulatory Agency or Public Disclosure Identifier Number:

ClinicalTrials.gov Identifier: NCT01740427

EudraCT Number: 2012-004601-27

Study Phase: 3

Name of Study Intervention: Palbociclib

Trade Name: Ibrance®

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Version 1.0, 11 October 2022

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

A total of 666 participants were randomized at 186 centers in 17 countries.

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

Publications:

Not Applicable.

Study Period:

Study Initiation Date (First Participant First Visit [FPFV]): 22 February 2013; Interim data cutoff date: 15 November 2021.

This study was neither discontinued nor interrupted.

Rationale:

The study was designed to demonstrate that palbociclib in combination with letrozole provides superior clinical benefit compared to letrozole in combination with placebo in postmenopausal women with estrogen receptor (ER)-positive/human epidermal growth factor

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receptor 2 (HER2)-negative locoregionally recurrent breast cancer or metastatic breast cancer (MBC) who have not received any prior systemic anti-cancer therapies for their advanced disease.

Objectives, Endpoints, and Statistical Methods:

Type	Objective	Endpoint	Presentation of data in this supplemental report
Primary			
Efficacy	To demonstrate that the combination of palbociclib with letrozole is superior to placebo plus letrozole in prolonging PFS in postmenopausal women with ER-positive/HER2-negative ABC who have not received any prior systemic anticancer therapies for their advanced/metastatic disease.	PFS	Not presented.
Secondary			
Efficacy	To compare measures of tumor control duration and OS between the treatment arms.	OS	Updated data are reported in this CSR.
		1-year, 2-year, and 3-year survival probabilities	Updated data are reported in this CSR.
		OR	Not presented.
		DR	Not presented.
		DC/CBR	Not presented.
Safety	To characterize the effects of palbociclib at therapeutic doses in combination with letrozole on QTc interval in this participant population	QTc	Not presented.
	To compare safety and tolerability between the treatment arms.	Type, incidence, severity (as graded by NCI CTCAE v4.0), seriousness and relationship to study medications of AE and any laboratory abnormalities	Not presented.
Biomarker	To characterize alterations in genes, proteins, and RNAs relevant to the cell cycle (eg, CCND1 amplification, CDKN2A deletion), drug targets (eg, CDK 4/6), and tumor sensitivity and/or resistance (eg, Ki67, pRb) in tumor tissues	Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1, CDKN2A), proteins (eg, Ki67, pRb), and RNA expression (eg, CDK4, CDK6)	Not presented.
PK	To determine trough palbociclib plasma concentration in this participant population and explore correlations between exposure and response and/or safety findings	Trough plasma concentration of palbociclib	Not presented.
Health related QoL	To compare health related quality of life between the treatment arms.	EQ-5D Score	Not presented.
		FACT-B	Not presented.

Abbreviations: ABC = advanced breast cancer; AE = adverse event; CBR = clinical benefit rate; CCND1 = cyclin D1; CDK = cyclin-dependent kinase; CDKN2A = cyclin-dependent kinase inhibitor 2A; CSR = clinical stud report; CTCAE = Common Terminology Criteria for Adverse Events; DC = disease control; DR = duration of response; EQ-5D = EuroQol-5D; ER = estrogen receptor; FACT-B = Functional Assessment of Cancer Therapy-Breast; HER2 = human epidermal growth factor receptor 2; NCI = National Cancer Institute; PCD = primary completion date; PFS = progression free survival; QTc = corrected QT interval; OS = overall survival; OR = objective response.

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Statistical methods for endpoints reported in this CSR are summarized below:

- OS was summarized in the intent-to-treat (ITT) population using the Kaplan-Meier methods and displayed graphically where appropriate. The median event time and 2-sided 95% confidence interval (CI) for the median were provided. A stratified (by disease site) log-rank test was used to compare OS between the 2 treatment arms (palbociclib plus letrozole vs placebo plus letrozole) and the hazard ratio (HR) and its 95% CI (subject to the multiplicity adjustment at the final analysis) were estimated.

- The 1-year, 2-year and 3-year survival probabilities were provided with their 95% CIs.

Methodology:

This study is an international, multicenter, randomized (2:1), double-blind, placebo-controlled, parallel-group, Phase 3 clinical study comparing the efficacy and safety of palbociclib in combination with letrozole vs placebo in combination with letrozole in postmenopausal women with ER-positive/HER2-negative ABC.

This sCSR presents an updated analysis of final OS inclusive of supplemental OS data from participants who were previously acknowledged as no longer being followed for survival as of the data cutoff date (15 November 2021).

For Study 1008, the final OS analysis was reported with the data cutoff date of 15 November 2021 in the supplemental CSR dated 24 June 2022. In the final OS analysis, there were 59 (13.3%) participants in the palbociclib plus letrozole arm and 47 (21.2%) participants in the placebo plus letrozole arm who were no longer being followed for survival (withdrew consent or lost to follow-up) at the time of data cutoff and were censored in the final OS analysis, which showed that the median OS was numerically longer in the palbociclib plus letrozole arm vs the placebo plus letrozole arm (53.9 months [95% CI: 49.8, 60.8] and 51.2 months [95% CI: 43.7, 58.9], respectively; HR = 0.956 (95% CI: 0.777, 1.177); 1-sided p-value = 0.3378). These results were not statistically significant.

Considering the impact of this disproportionate censoring between treatment arms could have on the interpretation of OS outcomes, the study team, in consultation with the study steering committee and study investigators, initiated additional efforts to recover survival information, wherever feasible for these participants. Following these efforts, the number of participants for whom complete survival information was not available, was reduced from 106 to 67 (9.2% in the palbociclib plus letrozole arm and 11.7% in the placebo plus letrozole arm); the final OS analysis was repeated using the updated dataset using the same cut-off date as in the previous analysis (15 November 2021). This supplemental OS CSR, with the same data cutoff date of 15 November 2021 as the CSR for OS final analysis, is to report the updated OS analysis, inclusive of the recovered OS data, outcome for study accuracy.

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Number of Participants (planned and analyzed):

At least 650 eligible participants were planned to be randomized 2:1 to receive either palbociclib plus letrozole (at least 433 participants) or placebo plus letrozole (at least 217 participants).

In this study, 666 female participants were randomized (2:1) to the treatment arms: 444 participants to the palbociclib plus letrozole arm and 222 participants to the placebo plus letrozole arm. All randomized participants were treated.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Postmenopausal female participants (≥18 years of age) with confirmed diagnosis of ER-positive/HER2-negative ABC were enrolled in the study.

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

Participants received either palbociclib 125 mg or placebo orally QD for 21 days of every 28-day cycle, followed by 7 days off treatment in combination with letrozole, 2.5 mg, orally QD, continuously. The manufacturing lot numbers for the study intervention(s) that were dispensed in this study were provided in the CSR for OS final analysis.

Duration of Study Intervention:

Participants continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. However, participants may have continued treatment as assigned at randomization beyond the time of progressive disease (PD) at the discretion of the investigator if that was considered to be in the best interest of the participant and as long as no new anti-cancer treatment was initiated.

Summary of Results:

This supplemental OS CSR, with the same data cutoff date of 15 November 2021 as the CSR for final OS analysis, is to report the updated OS analysis, inclusive of the recovered OS data, outcome for study accuracy. Therefore, only updated efficacy results are presented.

Efficacy Results:

OS analysis including additional data on those who were no longer being followed for survival as of the data cutoff date (15 November 2021) are summarized as follows (39 participants with new information at final OS endpoint data timing of a total of 106 participants with prior missing mortality data; total events moves from 405 in first analysis to 435 in analysis reported here) (Table S1):

- The median OS was 53.8 months (95% CI: 49.8, 59.2) in the palbociclib plus letrozole arm and 49.8 months (95% CI: 42.3, 56.4) in the placebo plus letrozole arm. The

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observed HR was 0.921 (95% CI: 0.755, 1.124); stratified 1-sided p-value = 0.2087) (Table S1).

- Forty-one (9.2%) participants in the palbociclib plus letrozole arm and 26 (11.7%) participants in the placebo plus letrozole arm were no longer being followed for survival (withdrew consent or lost to follow-up) and were censored (Table S1).

- The 1-year and 2-year survival probabilities were numerically higher in the placebo plus letrozole arm, while ≥3-year survival probabilities were numerically higher in palbociclib plus letrozole arm (Table S1).

The Kaplan-Meier plot of OS by treatment arm for the ITT population is presented in Figure S1.

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Table S1. Summary of Overall Survival by Treatment - Intent to Treat Set

	Palbociclib (PD-0332991) + Letrozole (N=444)	**Placebo + Letrozole (N=222)**
	n (%)	**n (%)**
Number of deaths	287 (64.6)	148 (66.7)
Cause of death		
Disease Under Study	242 (54.5)	122 (55.0)
Study Treatment Toxicity	1 (<1.0)	1 (<1.0)
Unknown	21 (4.7)	12 (5.4)
Other	22 (5.0)	13 (5.9)
Missing	1 (<1.0)	0
Number censored	157 (35.4)	74 (33.3)
Reason for censorship		
Subject Remains In Follow-up	116 (26.1)	48 (21.6)
Subject No Longer Being Followed For Survival	41 (9.2)	26 (11.7)
Survival Probability at Month 12 [1] (95% CI [2])	92.7 [89.8, 94.8]	95.0 [91.1, 97.2]
Survival Probability at Month 24 [1] (95% CI [2])	78.0 [73.8, 81.6]	81.3 [75.4, 86.0]
Survival Probability at Month 36 [1] (95% CI [2])	69.0 [64.3, 73.1]	63.8 [56.9, 69.9]
Survival Probability at Month 48 [1] (95% CI [2])	56.4 [51.5, 61.0]	51.2 [44.3, 57.7]
Survival Probability at Month 60 [1] (95% CI [2])	45.2 [40.4, 49.9]	40.7 [33.9, 47.3]
Survival Probability at Month 72 [1] (95% CI [2])	38.4 [33.7, 43.1]	36.0 [29.5, 42.6]
Kaplan-Meier estimates of Time to Event (Month) Quartiles (95% CI) [3]		
25%	28.5 [22.6, 32.7]	27.2 [24.5, 31.5]
50%	53.8 [49.8, 59.2]	49.8 [42.3, 56.4]
75%	99.8 [99.8, .]	. [85.6, .]
Stratified Analysis[6]:		
Hazard Ratio[4]	0.921	
95% CI of Hazard Ratio	0.755-1.124	
P-value [5]	0.208706	
Unstratified Analysis:		
Hazard Ratio[4]	0.921	
95% CI of Hazard Ratio	0.755-1.123	
P-value [5]	0.206700	

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Table S1. Summary of Overall Survival by Treatment - Intent to Treat Set

	Palbociclib (PD-0332991) + Letrozole (N=444)	Placebo + Letrozole (N=222)
	n (%)	n (%)

[1] Estimated from the Kaplan-Meier curve. [2] Calculated from the product-limit method. [3] Based on the Brookmeyer and Crowley Method.
[4] Assuming Cox proportional hazards, hazard ratio less than 1 indicates reduction in hazard rate in favor of Palbociclib (PD-0332991)+Letrozole.
[5] 1-sided p-value from the log-rank test. [6] Stratified by disease site (visceral vs. non-visceral) per Randomization.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.5b Date of Reporting Dataset Creation: 20SEP2022
Date of Table Generation: 28SEP2022 (15:37)
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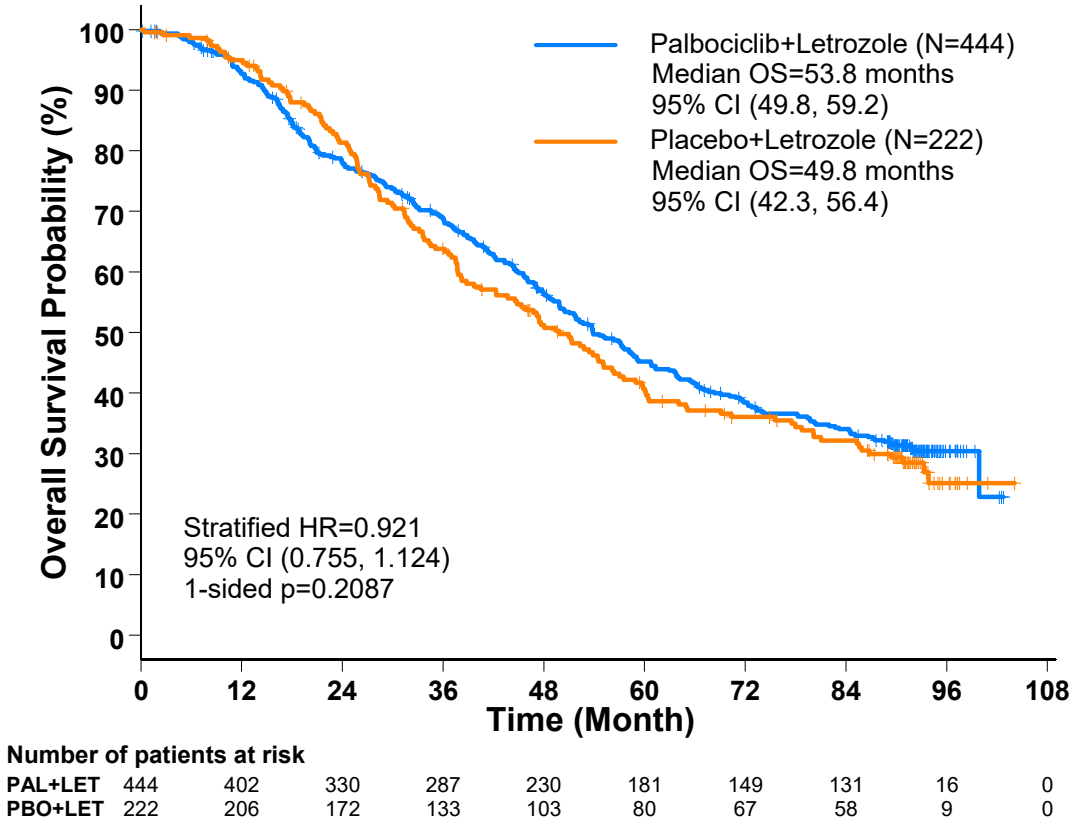
Table 14.2.10.1b is for Pfizer internal use.

Figure S1. Kaplan-Meier Plot of Overall Survival (ITT)



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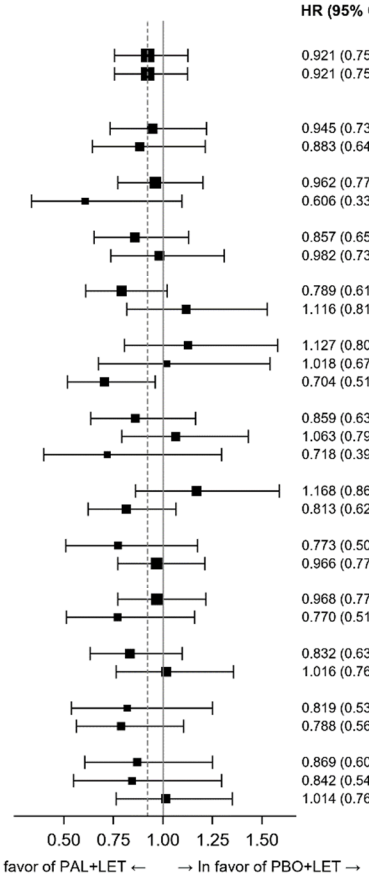
A series of prespecified subgroup analyses were performed for the OS endpoint based on stratification factors and additional baseline characteristics. A forest plot of OS in selected subgroups is presented in Figure S2.

Figure S2. Forest Plot of Overall Survival by Subgroups (ITT)

ITT and Subgroup	PAL+LET Events/N (%)		PBO+LET Events/N (%)		HR (95% CI)	No Longer being Followed (%) PAL+LET	PBO+LET
All patients (ITT, Stratified)	287/444	(64.6)	148/222	(66.7)	0.921 (0.755, 1.124)	9.2	11.7
All patients (ITT, Unstratified)	287/444	(64.6)	148/222	(66.7)	0.921 (0.755, 1.123)	9.2	11.7
Age							
<65 Years	166/263	(63.1)	92/141	(65.2)	0.945 (0.732, 1.219)	8.0	12.1
≥65 Years	121/181	(66.9)	56/81	(69.1)	0.883 (0.643, 1.213)	11.0	11.1
Race							
White	234/344	(68.0)	118/172	(68.6)	0.962 (0.771, 1.200)	8.1	10.5
Asian	29/65	(44.6)	18/30	(60.0)	0.606 (0.335, 1.094)	15.4	23.3
Disease site							
Visceral	148/214	(69.2)	78/110	(70.9)	0.857 (0.651, 1.128)	7.9	15.5
Non-visceral	139/230	(60.4)	70/112	(62.5)	0.982 (0.736, 1.308)	10.4	8.0
Prior hormonal therapy							
Yes	159/250	(63.6)	91/126	(72.2)	0.789 (0.610, 1.021)	12.0	10.3
No	128/194	(66.0)	57/96	(59.4)	1.116 (0.816, 1.526)	5.7	13.5
Disease free interval							
De Novo Metastases	112/167	(67.1)	49/81	(60.5)	1.127 (0.805, 1.577)	5.4	12.3
≤12 months	72/98	(73.5)	33/48	(68.8)	1.018 (0.674, 1.538)	9.2	16.7
>12 months	103/179	(57.5)	66/93	(71.0)	0.704 (0.517, 0.959)	12.8	8.6
Region							
North America	111/168	(66.1)	68/99	(68.7)	0.859 (0.635, 1.163)	7.7	12.1
Europe	144/212	(67.9)	63/95	(66.3)	1.063 (0.791, 1.430)	9.0	8.4
Asia/Pacific	32/64	(50.0)	17/28	(60.7)	0.718 (0.398, 1.294)	14.1	21.4
ECOG performance status							
0	161/257	(62.6)	55/102	(53.9)	1.168 (0.860, 1.586)	7.8	17.6
1/2	126/187	(67.4)	93/120	(77.5)	0.813 (0.621, 1.064)	11.2	6.7
Bone-only disease							
Yes	63/103	(61.2)	34/48	(70.8)	0.773 (0.509, 1.174)	11.7	6.3
No	224/341	(65.7)	114/174	(65.5)	0.966 (0.771, 1.210)	8.5	13.2
Measurable Disease							
Yes	222/338	(65.7)	112/171	(65.5)	0.968 (0.771, 1.215)	8.6	13.5
No	65/106	(61.3)	36/51	(70.6)	0.770 (0.512, 1.159)	11.3	5.9
Prior chemotherapy							
Yes	140/213	(65.7)	80/109	(73.4)	0.832 (0.632, 1.096)	9.4	8.3
No	147/231	(63.6)	68/113	(60.2)	1.016 (0.762, 1.355)	9.1	15.0
Most recent therapy							
Aromatase inhibitor	59/92	(64.1)	34/45	(75.6)	0.819 (0.537, 1.249)	10.9	2.2
Anti-estrogen	99/154	(64.3)	52/74	(70.3)	0.788 (0.563, 1.103)	13.0	14.9
Number of disease sites							
1	83/138	(60.1)	45/66	(68.2)	0.869 (0.604, 1.249)	10.9	9.1
2	68/117	(58.1)	30/52	(57.7)	0.842 (0.548, 1.294)	11.1	21.2
≥3	136/189	(72.0)	73/104	(70.2)	1.014 (0.763, 1.349)	6.9	8.7



Conclusions:

The analysis of OS does not demonstrate evidence of any OS decrement and the benefit-risk remains positive with delay of progression, delay of chemotherapy as well as manageable toxicities. The additional analysis of OS provides treating physicians and participants with a more accurate representation of the benefit of palbociclib.

- The median OS was numerically longer in the palbociclib plus letrozole arm vs the placebo plus letrozole arm (53.8 months [95% CI: 49.8, 59.2] and 49.8 months [95% CI: 42.3, 56.4], respectively; HR = 0.921 [95% CI: 0.755, 1.124; stratified 1-sided p-value = 0.2087]). These results were not statistically significant.