Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Trial Randomizing Sites, Principal Investigators, and Patient Numbers			
Site ID	Recruiting Site	Principal Investigator	Total of Patients Randomized per Site
101	Hospital Universitari Vall D'Hebron	Meritxell Bellet	51
202	Institut Universitaire du Cancer Toulouse - Oncopole	Florence Dalenc	39
104	Institut Catala d'Oncologia Bellvitge	Miguel Gil Gil	37
107	Hospital Virgen del Rocío	Manuel Ruiz Borrego	32
502	National Center for Tumor Diseases	Frederik Marmé	21
102	Instituto Valenciano de Oncología	Kino Gávila	20
401	Barts Cancer Institute	Peter Schmid	20
117	Hospital Universitario La Paz	Pilar Zamora	16
406	Royal Cornwall Hospital	Duncan Wheatley	16
118	Hospital de Castellón	Eduardo Martinez-de-Dueñas	14
109	Hospital Joan XXIII	Kepa Amillano	13
302	Istituto Nazionale Tumori Milano	Serena Di Cosimo	13
115	Hospital Universitario Miguel Servet	Antonio Antón	12
907	Saint-Petersburg Scientific Practical Centre of Specialized Kinds of Medical Care	Vladimir Moiseyenko	12
203	Institute Curie	Paul Cottu	10
108	Institut Catala d'Oncologia Girona	Gemma Viñas	9
204	Centre Regionale de Lutte contre le Cancer Paul Strauss. H. de Strasburg	Thierry Petit	9

801	General University Hospital in Prague. Clinic of Oncology	Petra Tesarova	9
906	Oncology Dispensary, Pyatigorsk	Vladimir Vladimirov	9
116	Hospital Clínico Universitario de Santiago	Juan Cueva Bañuelos	8
303	European Institute of Oncology	Marco Colleoni	8
405	Singleton Hospital	Gianfilippo Bertelli	8
113	Hospital de Basurto	Purificación Martínez	7
114	Hospital Clínico Zaragoza	Raquel Andres	7
904	MKNC Moscow Clinical Scientific Center	Tatiana Barannikova	7
105	Hospital del Mar	Sonia Servitja	6
201	APHP Tenon	Joseph Gligorov	6
205	George Pompidou European Hospital	Jacques Medioni	6
306	Senatore Antonio Perrino Hospital	Saverio Cinieri	6
110	Hospital Juan Ramón	Juan Bayo	5
112	Complejo Hospitalario de Cáceres. San Pedro Alcántara	Santiago González	5
802	Olomuc Clinic of Oncololgy	Bohuslav Melichar	5
120	Hospital Arnau de Vilanova Valencia	Vicente Caranyana	4
310	AO Cagliari	Francesco Atzori	4
402	Royal United Hospital	Mark Beresford	4
403	Hospital Nottingham	Steven Chan	4
106	Hospital Central de Asturias	Maria Luque Cabal	3
119	Hospital Quiron-Institut Oncologic Baselga	Jose Perez	3

103	Hospital Universitario Provincial de Córdoba Reina Sofía	Juan de la Haba	3
503	Klinikum Dessau	Joachim Bischoff	3
905	Republci Clinical Oncology Dispensary	Guzel Mukhametsina	3
305	AO San Gerardo	Maria Cazzaniga	2
307	Istituti Spitalieri	Daniele Generali	2
407	The Christie NHS Foundations	Andrew Wardley	2
304	AO Universitaria Policlinico di Modena	Laura Cortesi	1
308	Guglielmo da Saliceto Hospital	Luigi Cavanna	1
309	Ospedale Molinette	Mario Airoldi	1
	Total of Recruiting Sites: 47	*Total randomized patients:*	486

eTable 2. Selection Criteria

Inclusion Criteria
Patients must meet ALL of the following inclusion criteria to be eligible for enrolment into the study: 1. Postmenopausal women, as defined by any of the following criteria: • Age 60 or over. • Age 45 to 59 years and meets ≥ 1 of the following criteria: ○ Amenorrhea for ≥ 24 months. ○ Amenorrhea for < 24 months and follicle-stimulating hormone within the postmenopausal range (including patients with hysterectomy, prior hormone replacement therapy, or chemotherapy-induced amenorrhea). • Over 18 years of age and bilateral oophorectomy. OR • Premenopausal women provided they are being treated with LHRH analogues for at least 28 days prior to study entry. 2. Eastern Cooperative Oncology Group (ECOG) score lower or equal to 2. 3. Histologically confirmed recurrent ER-positive (estrogen and/or progesterone) HER2-negative locally advanced or metastatic BC patients (Breast cancer that have at least 1% of cells staging positive for ER should be considered ER-positive according to NCCN and ASCO guidelines (1,2)). 4. Patients should not be candidates for a local treatment with a radical intention. 5. No prior hormonal or chemotherapy line in the metastatic setting. 6. Patient must have measurable (according to RECIST 1.1) or non-measurable disease with these exceptions: • Patients with only blastic bone lesions are not eligible. • Patients with only pleural, peritoneal or cardiac effusion, or meningeal carcinomatosis are not eligible. 7. Life expectancy greater or equal to 12 weeks. 8. Adequate organ function: • Hematological: White blood cell (WBC) count >3.0 x 10^9/L, absolute neutrophil count (ANC) >1.5 x 10^9/L, platelet count >75.0 x10^9/L, and hemoglobin >10.0 g/dL (>6.2 mmol/L). • Hepatic: bilirubin < 1.5 times the upper limit of normal (x ULN); alkaline phosphatase (ALP), aspartate transaminase (AST), and alanine transaminase (ALT) <2.5 times ULN. Patients with ALP ≥2.5 times ULN are eligible if ALP abnormalities are unequivocally related to bone lesions (radiological assessments performed within 4 weeks prior to randomization demonstrated bone metastatic disease). • Renal: serum creatinine < 1.5 x ULN. 9. Exhibit patient compliance and geographic proximity that allow for adequate follow-up. 10. Patient has been informed about the nature of study, and has agreed to participate in the study, and signed the Informed Consent form prior to participation in any study-related activities. 11. No other malignancies within the past five years except adequate treated basal cell or squamous cell skin cancer or carcinoma in situ of the cervix. 12. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCICTCAE version 4.0 Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).

13. Patient has been informed about the translational sub-study and has agreed to participate in the collection of blood and tumor tissue samples by signing the Informed Consent form.

Exclusion Criteria

Patients will be excluded from the study if they meet ANY of the following criteria:

1. ER or HER2 unknown disease.
2. HER2 positive disease based on local laboratory results (performed by immunohistochemistry/FISH).
3. Locally advanced breast cancer candidate for a radical treatment.
4. Prior endocrine therapy in the metastatic setting is not allowed. (Neo)/Adjuvant endocrine therapy is allowed only if the disease-free interval between the end of endocrine therapy and the appearance of metastases in higher than 12 months.
5. Patients with rapidly progressive visceral disease or visceral crisis.
6. Have had a major surgery (defined as requiring general anesthesia) or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery or patients that may require major surgery during the course of the study.
7. Patients with an active, bleeding diathesis.
8. Have a serious concomitant systemic disorder (e.g., active infection including HIV, or cardiac disease) incompatible with the study (at the discretion of investigator), previous history of bleeding diathesis, or anti-coagulation treatment (The use of low molecular weight heparin is allowed as soon as it is used as prophylaxis intention).
9. Are unable to swallow tablets.
10. History of malabsorption syndrome or other condition that would interfere with enteral absorption.
11. Chronic daily treatment with corticosteroids with a dose of ≥ 10mg/day methylprednisolone equivalent (excluding inhaled steroids).
12. Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral oedema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated with local therapy (e.g., radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.
13. Known hypersensitivity to letrozole, fulvestrant or any of their excipients, or to any PD-0332991 excipients.
14. QTcF >480 msec on basal assessments, personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP).
15. Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (e.g., hypocalcemia, hypokalemia, hypomagnesemia).

eTable 3. Criteria for Defining Progression-Free Survival Events and Censoring		
Situation	Date of progression or censoring	Outcome
Progression documented between scheduled visits	Earliest of: • Date of assessment by investigator (if progression is based on clinical criteria) Or • Date of assessment showing new lesion (if progression is based on new lesion) Or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Death before first progressive disease assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions	Censored
Death or progression after more than one missed visit	Date of last radiological assessment of measured lesions.	Censored

eTable 4. Relative Dose Intensity and Drug Discontinuation			
	All patients (n = 486)	Fulvestrant–Palbociclib (n = 243)	Letrozole–Palbociclib (n = 243)
Median relative dose intensity (PCT25–PCT75)		Fulvestrant: 99.2 (97.3–100) Palbociclib: 91.7 (76.0–97.6)	Letrozole: 98.8 (96.3–99.9) Palbociclib: 90.0 (77.4–98.3)
Treatment discontinuation	326 (67.1)	171 (70.4)	155 (63.8)
Disease progression	244 (50.2)	122 (50.2)	122 (50.2)
Withdrawal of consent[a]	32 (6.6)	16 (6.6)	16 (6.6)
Adverse events	18 (3.7)	13 (5.3)	5 (2.1)
Death	10 (2.1)	8 (3.3)	2 (0.8)
Physician's decision[b]	8 (1.6)	5 (2.2)	3 (1.2)
Protocol deviation	7 (1.4)	4 (1.8)	3 (1.2)
Second neoplasm[c]	5 (1.0)	2 (0.9)	3 (1.2)
Lost to follow-up	2 (0.4)	1 (0.4)	1 (0.4)
Safety analysis set	All patients (n = 483)	Fulvestrant–Palbociclib (n = 241)	Letrozole–Palbociclib (n = 242)
Dose reduction for palbociclib	193 (40.0)	85 (35.3)	108 (44.6)
Dose delayed for the combination	241 (49.9)	118 (49.0)	123 (50.8)

Abbreviations: PCT25, percentile 25; PCT75, percentile 75.

Data are n (%), unless otherwise specified.

[a] Twelve of 32 (37.5%) patients withdrew consent during the trial and continued to receive the same regimen in routine clinical care outside it.

[b] One of 8 (12.5%) patients was diagnosed with new primary breast cancer during the trial.

[c] Out of 5 patients, 2 (40%) were diagnosed with endometrial carcinoma, 1 (20%) with lung cancer, 1 (20%) with follicular lymphoma, and 1 (20%) with acute myeloid leukemia during the clinical trial.

eTable 5. Tumor Best Response According to RECIST version 1.1			
	Fulvestrant–Palbociclib (n = 243)	Letrozole–Palbociclib (n = 243)	*P* value
Complete response	11 (4.5)	10 (4.1)	
Partial response	102 (42.0)	112 (46.1)	
Stable disease	59 (24.3)	46 (18.9)	
No complete response/No progressive disease	39 (16.0)	52 (21.4)	
Progressive disease	22 (9.1)	13 (5.3)	
Not evaluable	10 (4.1)	10 (4.1)	
Rate of objective response (95% CI)	46.5% (40.1–53.0)	50.2% (43.7–56.7)	.41
Median duration of response, months (95% CI)	34 (23.3–NE)	30.2 (26.7–NE)	
Rate of clinical benefit (95% CI)	70.8% (64.6–76.4)	69.1% (62.9–74.9)	.69
Median time to progression, months (95% CI)	28.9 (24.6–36.2)	32.8 (26.0–38.6)	.49
Median time to response, months (95% CI)	5.3 (3.7–5.5)	5.2 (2.9–5.5)	
Patients with measurable disease	Fulvestrant–Palbociclib (n = 195)	Letrozole–Palbociclib) (n = 181)	
Rate of objective response (95% CI)	56.4% (49.1–63.5)	65.7% (59.3–72.6)	

Abbreviations: 95% CI, 95% confidence interval; NE, not estimable; RECIST, Response Evaluation Criteria In Solid Tumors.

Data are n (%), unless otherwise specified.

eTable 6. Adverse Events of Special Interest between Arms According to CTCAE version 4.0

	Fulvestrant–Palbociclib (n = 241)			Letrozole–Palbociclib (n = 242)		
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Thromboembolic events	14 (5.8)	11 (4.6)	2 (0.8)	11 (4.5)	7 (2.9)	0
Pulmonary embolism[a]	12 (5.0)	10 (4.2)	2 (0.8)	6 (2.5)	6 (2.5)	0
Varicose vein	0	0	0	2 (0.8)	0	0
Pelvic venous thrombosis	0	0	0	1 (0.4)	0	0
Jugular vein thrombosis	1 (0.4)	0	0	0	0	0
Ischemic stroke	1 (0.4)	1 (0.4)	0	0	0	0
Ischemic cardiomyopathy	0	0	0	1 (0.4)	0	0
Cerebrovascular accident	0	0	0	1 (0.4)	1 (0.4)	0
ILD/pneumonitis[b]	6 (2.5)	2 (0.8)	0	6 (2.5)	3 (1.2)	0

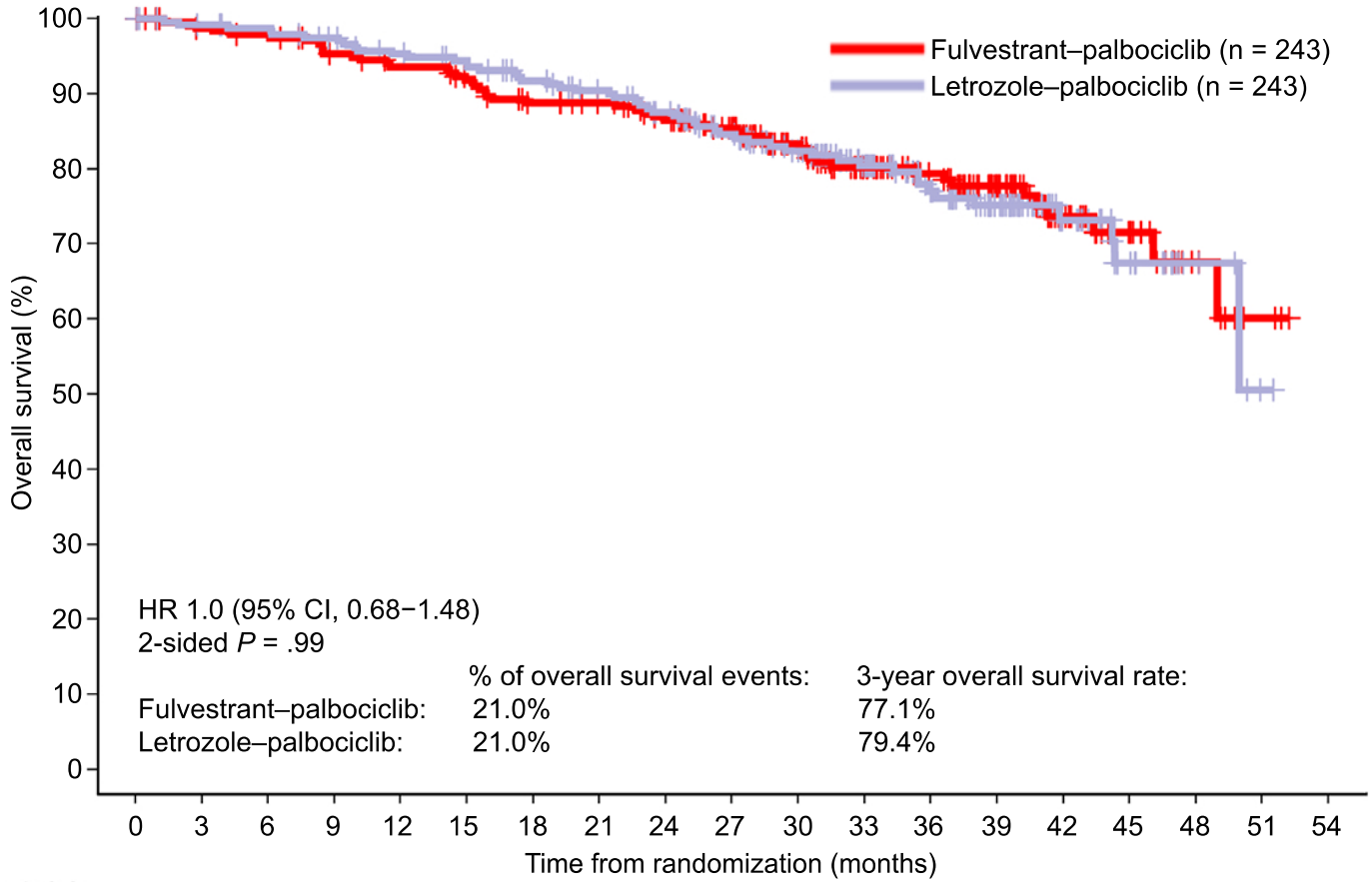
Abbreviations: AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease.

[a] One patient died due to unrelated pulmonary embolism in fulvestrant–palbociclib arm. Of the pulmonary embolism events, 10 were asymptomatic incidental findings on routine 3-month tumor assessment and 5 were detected in the context of tumor progression.

[b] Interstitial lung disease (ILD)/pneumonitis includes any reported preferred terms that are part of the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query “Interstitial Lung Disease”.

Data are n (%), unless otherwise specified.

eFigure 1. Overall Survival

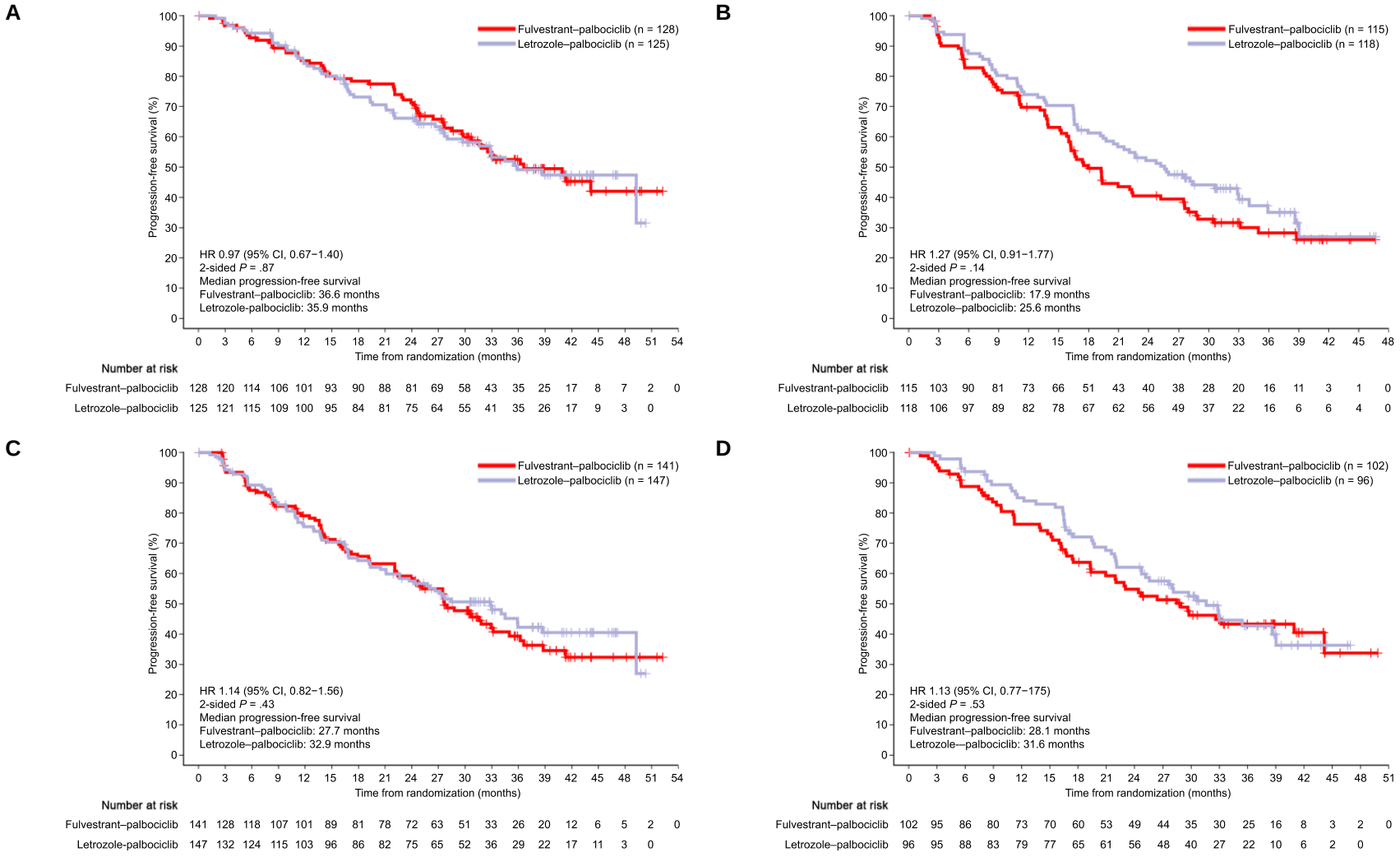


Number at risk

Fulvestrant-Palbociclib	243	235	232	222	216	209	198	193	182	167	141	114	96	71	44	24	10	3	0
Letrozole-Palbociclib	243	236	233	227	219	214	204	194	184	165	141	116	87	64	35	20	6	1	0

Abbreviations: 95% CI, 95% of confidence interval; HR, hazard ratio; OS, overall survival.

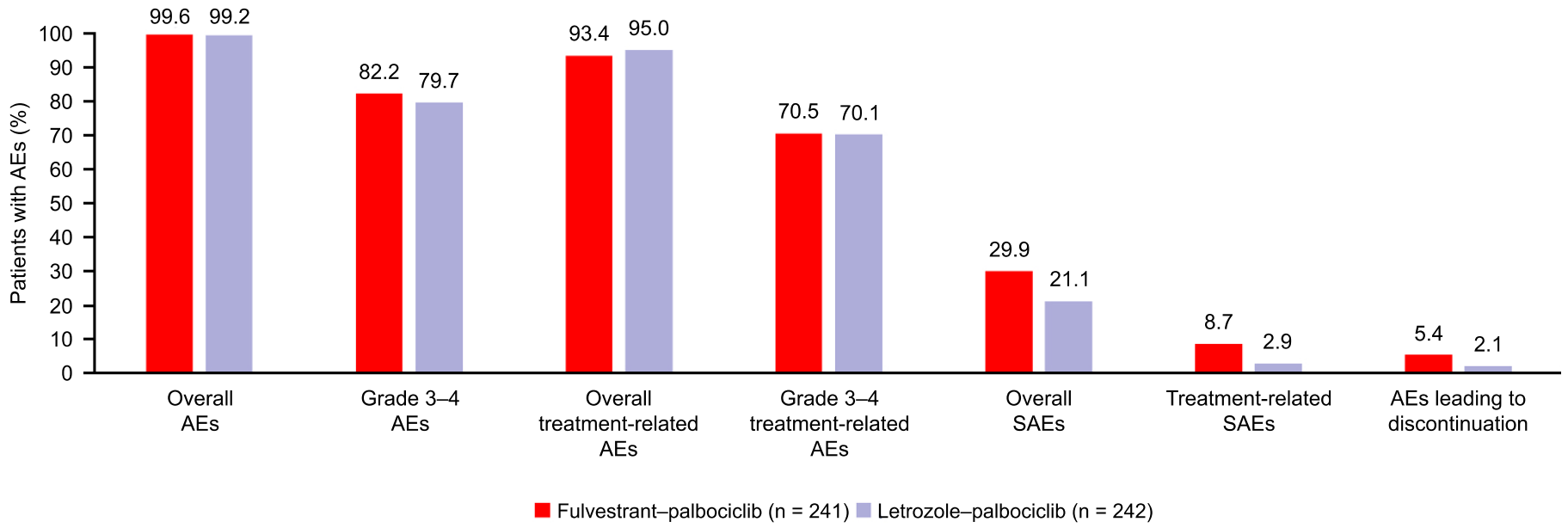
eFigure 2. Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Patients Without (A) and with (B) Visceral Disease, and With Recurrent (C) and *de novo* (D) Metastatic Disease in the Intent-To-Treat Population



Abbreviations: CI, confidence interval; HR, hazard ratio.

The *P* values for treatment-by-visceral involvement (eFigure 1 A and B) and treatment-by-type of disease (eFigure 1 C and D) interaction tests were .28 and .98, respectively. It was tested by a Cox model for PFS with a treatment-by-factor interaction term set at 2-sided 0.1 alpha level. The likelihood ratio was the statistical test used.

eFigure 3. Summary of All Adverse Events After Randomization According to CTCAE version 4.0



Abbreviations: AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; SAEs, serious adverse events.

eMethods

1.1. Protocol-Specified Outcomes and Measurements

Tumor response was assessed for all patients, unless they withdraw from the study for any reason not attributable to PD confirmed radiologically or clinically as per RECIST version 1.1 and who did not receive an acceptable complete assessment of the disease. The measurable and non-measurable disease were documented at screening and re-assessed at every tumor assessment thereafter.

Disease assessment was carried out preferably by computerized tomography (CT) or magnetic resonance imaging (MRI) since these methods are the best currently available and reproducible techniques to measure lesions selected for response assessment. In the event a positron emission tomography (PET)/CT scan was used for tumor assessments, CT portion of PET/CT is usually of lower quality, and was not used instead of dedicated diagnostic CT.

Tumor assessments at baseline included an assessment of all known and/or suspected lesions/sites of the disease. Based on the baseline evaluation, target and non-target lesions were defined according to RECIST version 1.1 as the reference for comparison at each subsequent tumor assessment. The same radiographic procedure employed at screening was used throughout the study (i.e., the use of the same contrast protocol for CT scans).

At baseline, all patients were assessed as follows:

- Assessment of thorax, abdomen, and pelvis.
- Bone scan:

○ If bone involvement was demonstrated with the basal bone scan, it was confirmed by either X-ray, or CT scan (with bone window) or MRI at baseline and every 24 weeks (± 7 days), unless clinically or biochemically suspected bone progression.

○ If no bone involvement was demonstrated, then it was no necessary to repeat the bone assessment unless clinically or biochemically suspected bone progression.

○ If an isotope-based bone scan was performed >28 days but ≤60 days prior to the first study treatment the bone scan did not need to be repeated.

Clinical disease assessments were performed every 8 weeks (± 3 days) from the date of randomization up to 12 months of study treatment start. Thereafter, disease assessments were performed every 12 weeks (± 7 days) until the end of the study treatment. Each assessment was performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments resulted in the inability to determine disease status for that time point.

Response assessments were carried out by the investigator, based on physical examinations, CT or MRI scans, and bone scans using RECIST version 1.1.

Bone scan was used only to identify presence of bone lesions and if bone lesions were present, confirmation and accurate measurement was done with CT or MRI. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI was considered as measurable lesions if the soft tissue component met the definition of measurability. Blastic bone lesions were non-measurable.

If a bone scan cannot be performed during the study because of the unavailability of the Tc-99m isotope, the investigator could have chosen an alternative imaging modality.

At the investigator's discretion, CT scans, MRI scans, and/or bone scans could have been obtained at any time when clinically indicated or if PD was suspected.

- **Progression-Free Survival (PFS)**

PFS was defined as the time from the date of randomization to the date of the first documentation of objective progressive disease or death due to any cause in absence of documented progressive disease. Participants lacking an evaluation of tumor response after randomization had their PFS time censored on the date of randomization with the duration of a day. The length of PFS was calculated according to the following formula:

PFS time (months) = [progression/death date (censor date) – randomization date + 1] / 30.4

Progression was defined according to clinical criteria as a 20% increase in the sum of diameters of target lesions by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and the sum must also demonstrate an absolute increase of at least 5 mm or unequivocal progression of existing non-target lesions or the appearance of new lesions (**eTable 6**).

- **Tumor Best Response**

Tumor best response was defined in terms of complete response, partial response, stable disease, and progressive disease based on RECIST version 1.1 as follows:

- Complete response: Complete disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have had reduction <10 mm in short axis.
- Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Stable disease: Neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for disease progression, taking as reference the smallest sum diameters while on study.
- Disease progression: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum diameters while on study. The development of new, previously undetected lesions is also considered progression.

- **Overall Response Rate (ORR)**

ORR was defined as the proportion of the patients in the analysis set with and without measurable disease at baseline who had a best overall response of complete response or partial response based on RECIST version 1.1 as follows:

- Complete response: Complete disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have had reduction <10 mm in short axis.
- Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- **Clinical Benefit Rate (CBR)**

CBR was defined as the proportion of the patients in the analysis set with and without measurable disease at baseline who had a complete response, partial response, and stable disease for at least 24 weeks based on RECIST version 1.1 as follows:

- Complete response: Complete disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have had reduction <10 mm in short axis.
- Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Stable disease: Neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for disease progression, taking as reference the smallest sum diameters while on study.

○ **Duration of Response (DOR)**

DOR was defined as the time from first documented complete response or partial response until disease progression or death from any cause, based on local investigator's assessment according to RECIST version 1.1.

○ **Time to Progression (TTP)**

TTP was defined as the time from the date of randomization to the date of the first documentation of objective progressive disease. Progression was defined according to clinical criteria as a 20% increase in the sum of diameters of target lesions by RECIST version 1.1 and the sum must also demonstrate an absolute increase of at least 5 mm or unequivocal progression of existing non-target lesions or the appearance of new lesions. Patients alive or died without disease progression were censored at the date of last disease evaluation.

○ **Time to Response (TTR)**

TTR was defined as the time from the date of randomization to the date of the first documentation of objective tumor response for patients who had a best overall response of complete response or partial response based on RECIST version 1.1 as follows:

- Complete response: Complete disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have had reduction <10 mm in short axis.
- Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- **Overall Survival (OS)**

OS was defined as the time from randomization to death due to any cause. Patients without documented death at the time of the final analysis were censored at the date of the last follow-up.

1.2. Relative Dose Intensity (RDI)

The extent of drug exposure was defined with RDI. It was calculated based on the following algorithms, where the “a” to “f” parameters were calculated in each cycle and the “A” to “L” parameters were calculated for each patient as follows:

Cycles parameters:

a) “Actual Cycle Duration” was the treatment duration for a cycle as reported in the electronic case report form. It was the length of time in days between the start dates of actual cycle and next one. At the last cycle, Actual Cycle Duration was the difference between the start date and stop date of treatment.

b) “Actual Cycle Dose Days” was the number of days with dose administration in the cycle, considering the interruptions.

c) “Actual Total Dose per Cycle” was the total dose a patient took in a cycle, considering interruptions and reductions.

d) “Intended Daily Dose per Cycle” was equal to 125 mg/day palbociclib, 2.5 mg/day letrozole, and 500 mg fulvestrant on days 1, 15, 29, and once monthly thereafter.

e) “Intended Cycle Duration” was equal to 28 days, except for the last cycle that was the minimum of 28 and “Actual Cycle Duration”.

f) “Intended Cycle Dose Days for Palbociclib” was equal to 21 days, except for the last cycle that was the minimum of 21 and “Actual Cycle Duration”.

“Intended Cycle Dose Days for Letrozole” was equal to 28 days, except for the last cycle that was the minimum of 28 and “Actual Cycle Duration”.

“Intended Cycle Dose Days for Fulvestrant” was equal to 2 days at cycle 1, and 1 day for all other cycles, except for the last cycle that was the minimum of 2 and “Actual Cycle Duration” at cycle 1, and the minimum of 1 and “Actual Cycle Duration” for all other cycles.

Patient’s parameters:

A) “Total Number of Cycles”.

B) “Treatment Duration” = Sum over all cycles of (a).

C) “Days on drug” = Sum over all cycles of (b).

D) “Total Actual Total Dose” = Sum over all cycles of (c).

E) “Mean Intended Daily Dose” = Mean over all cycles of (d).

F) “Total Intended Duration” = Sum over all cycles of (e).

G) “Total Intended Dose Days” = Sum over all cycles of (f).

H) “Intended Total Dose” = G × E

I) “Actual Average Daily Dose on Dose Days” = D / C

J) “Ratio For Dose Interruption” = C / G

K) “Ratio For Cycle Duration” = F / B

L) “Actual Average Daily Dose Intensity” = I × J × K

Formula to calculate RDI:

RDI = Actual Average Daily Dose Intensity (L) / Mean Intended Daily Dose (E) × 100

eTable 7. Committee Members
Steering Committee
Scientific Global Study Coordinator
Antonio Llombart-Cussac
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Sponsor Medical Monitor
José Manuel Pérez-García
International Clinical Experts
Joan Albanell Mestres Joseph Gligorov Serena Di Cosimo Peter Schmid Andreas Schneeweiss
Translational Study Coordinator
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Alicia García
Protocol Authors
José Manuel Pérez-García
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Javier Cortés Miguel Sampayo-Cordero Andrea Malfettone
Statistician
Miguel Sampayo-Cordero