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Original Article

Palbociclib with Fulvestrant or Letrozole in Endocrine-Sensitive Patients with HR-Positive/HER2-Negative Advanced Breast Cancer: A Detailed Safety Analysis of the Randomized PARSIFAL Trial

Serena Di Cosimo[1,2,3], José Manuel Pérez-García[4,5,6], Meritxell Bellet[7], Florence Dalenc[8], Miguel J. Gil Gil[9], Manuel Ruiz Borrego[10], Joaquín Gavilá[11], Miguel Sampayo-Cordero[12,13], Elena Aguirre[12,13], Peter Schmid[14], Frederik Marmé[15], Joseph Gligorov[16], Andreas Schneeweiss[17], Joan Albanell[18], Pilar Zamora[19], Duncan Wheatley[20], Eduardo Martínez-De Dueñas[21], Vicente Carañana[22], Kepa Amillano[23], Leonardo Mina[12,13], Andrea Malfettone[12,13], Javier Cortés[‡,24,25,26,27], Antonio Llombart-Cussac[*,‡,28,29,30,31]

[1]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
[2]Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain
[3]Medica Scientia Innovation Research (MEDSIR), Ridgewood, NJ, USA
[4]International Breast Cancer Center (IBCC), Quironsalud Group, Barcelona, Spain
[5]Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain
[6]Medica Scientia Innovation Research (MEDSIR), Ridgewood, NJ, USA
[7]Vall d'Hebrón University Hospital, Medical Oncology Department; Vall d'Hebrón Institute of Oncology (VHIO), Barcelona, Spain
[8]Institut Claudius Regaud, IUCT-Oncopole, CRCT, Inserm, Department of Medical Oncology, Toulouse, France
[9]Institut Català d'Oncologia, Breast Cancer Unit and Medical Oncology Department, IDIBELL, L'Hospitalet, Barcelona, Spain
[10]Hospital Universitario Virgen del Rocío, Medical Oncology Department, Seville, Spain
[11]Fundación Instituto Valenciano de Oncología, Medical Oncology Department, Valencia, Spain
[12]Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain
[13]Medica Scientia Innovation Research (MEDSIR), Ridgewood NJ, USA
[14]Barts ECMC, Barts Cancer Institute, Queen Mary University of London, and Barts Hospital NHS Trust, London, UK
[15]Leitung Sektion Translationale Gynäkologische Onkologie Nationales Centrum für Tumorerkrankungen und Universitätsfrauenklinik Heidelberg, Heidelberg, Germany
[16]Hospital Tenon (AP-HP), Medical Oncology Department, Paris, France
[17]Heidelberg University Hospital and German Cancer Research Center, National Center for Tumor Diseases (NCT), Heidelberg, Germany
[18]Hospital del Mar, Medical Oncology, Barcelona, Spain
[19]Medical Oncology Department, Hospital Universitario La Paz, Madrid, Spain
[20]Royal Cornwall Hospitals NHS Trust, Truro, UK
[21]Hospital Provincial Castellón, Servicio de Oncología, Castelló De La Plana, Spain
[22]Hospital Arnau de Vilanova, Valencia, Spain
[23]Hospital Universitari Sant Joan de Reus, Reus, Spain
[24]International Breast Cancer Center (IBCC), Quironsalud Group, Barcelona, Spain
[25]Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain
[26]Medica Scientia Innovation Research (MEDSIR), Ridgewood, NJ, USA
[27]Department of Medicine, Faculty of Biomedical and Health Sciences, Universidad Europea de Madrid, Madrid, Spain
[28]Hospital Arnau de Vilanova, Valencia, Spain
[29]Universidad Catolica de Valencia San Vicente Martir, Valencia, Spain
[30]Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain
[31]Medica Scientia Innovation Research (MEDSIR), Ridgewood, NJ, USA

*Corresponding author: Antonio Llombart-Cussac, MD, PhD, Arnau de Vilanova Hospital, Valencia, Spain. Tel: +34 932 914 135; Email: allombart1@yahoo.com
‡These authors share senior authorship.

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Abstract

Background: Palbociclib has gained a central role in the treatment of hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC). Despite its manageable toxicity profile, venous thromboembolism (VTE) or interstitial lung disease (ILD)/pneumonitis may infrequently occur. Therefore, we provide a comprehensive summary of the safety and tolerability of the combination of endocrine therapy and palbociclib among patients included in the randomized phase 2 PARSIFAL study.

Materials and Methods: Patients with endocrine-sensitive HR+/HER2- ABC and no prior therapy in an advanced setting ($n = 486$) were randomly assigned 1:1 to receive fulvestrant–palbociclib (FP) or letrozole–palbociclib (LP). Laboratory tests and the incidence of adverse events (AEs) were recorded at baseline and day 1 of each cycle. Progression-free survival (PFS) was estimated for patients with and without VTE.

Results: A total of 483 patients were analyzed. Neutropenia, leukopenia, anemia, asthenia, arthralgia, fatigue, and diarrhea were the most frequent AEs in both groups. Febrile neutropenia occurred in 3 (1.2%) patients of the FP group and in 1 (0.4%) patient in the LP group. Six (2.5%; 0.4% grade 3) patients in the FP group and 6 patients (2.5%; 0.4% grade 3) in the LP group experienced ILD/pneumonitis. Pulmonary embolism was reported in 12 (5.0%) patients in the FP group and 6 (2.5%) patients in the LP group. Advanced age at baseline was the only factor significantly associated with an increased risk of pulmonary embolism ($P < .01$).

Conclusion: The PARSIFAL data confirmed the favorable safety profile of both palbociclib regimens. VTE and ILD/pneumonitis were occasionally reported, and their early detection allowed patients to continue treatment effectively without detriment to efficacy.

ClinicalTrials.gov Identifier: NCT02491983; https://clinicaltrials.gov/ct2/show/NCT02491983).

Key words: palbociclib; endocrine therapy; advanced breast cancer; venous thromboembolism; neutropenia; interstitial lung disease; pneumonitis.

Implications for Practice

Treatment with palbociclib plus either fulvestrant or letrozole is generally well tolerated by patients with advanced breast cancer who are positive for hormone receptors and negative for human epidermal growth factor receptor 2. In the PARSIFAL study, neutropenia grade ≥3 was effectively managed, leading to a very low incidence of febrile neutropenia. Venous thromboembolism was treated with anticoagulants and did not require treatment discontinuation in most cases. Interstitial lung disease/pneumonitis was an uncommon event and was treated with corticosteroids and/or antibiotics. To ensure sustained treatment and optimize the clinical benefit/risk ratio, clinicians should be aware of and implement management strategies for serious and frequent adverse events, including dose adjustments according to local labels.

Introduction

Breast cancer is the most common cancer diagnosed among women worldwide.[1] More than 70% of cases express hormone receptors (HRs), such as estrogen receptors or progesterone receptors, and lack overexpression of human epidermal growth factor receptor 2 (HER2-negative). This has led to the widespread and successful use of endocrine agents as the primary systemic therapy to downregulate HR signaling.[2] The recent advent of cyclin-dependent kinase (CDK) 4/6 inhibitors has largely changed the paradigm for the management of advanced breast cancer (ABC) by prolonging patient survival,[3,4] resulting in an increasing number of women living with metastatic disease. Consequently, there is a growing importance of patient safety in not only the short term but also in the long term. The optimal treatment must take into account the type of drug and the endocrine therapeutic partner, as well as the individual characteristics, the disease burden, and the presence of comorbidities.[2,5]

All CDK4/6 inhibitors exert their antitumor effect by blocking cell-cycle progression through the inhibition of the cyclin D-CDK4/6 complex, which in turn suppresses the activation of the downstream RB-E2F pathway. However, different patterns of side effects have emerged from the pivotal trials investigating the currently approved CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib.[6-8] Studies on the same CDK4/6 inhibitor have reported different prospective efficacy and safety endpoints,[9-11] so it remains difficult to ascertain whether there are substantial differences in the safety profile of a specific type of endocrine therapy until head-to-head comparisons of combinations will be carried out.

Palbociclib was the first agent in this class to be developed and approved in combination with letrozole for endocrine-sensitive or fulvestrant for endocrine-resistant HR-positive/HER2-negative ABC.[12] Non-complicated grades 3-4 neutropenia was the most common adverse event (AE) for palbociclib-containing regimens in all studies, but greater numbers of venous thromboembolism (VTE)[13] and exceptional cases of interstitial lung disease (ILD)/pneumonitis[14] were reported in the palbociclib combination groups.

The PARSIFAL study compared the efficacy and safety of palbociclib with either letrozole or fulvestrant as an initial treatment in postmenopausal women with endocrine-sensitive HR-positive/HER2-negative ABC. After a median follow-up of 32 months, fulvestrant-palbociclib demonstrated no improvement in progression-free survival (PFS) over letrozole-palbociclib, thus strengthening the evidence for the combination of palbociclib with letrozole as the first choice of therapy for ABC.[15] In addition, the study allowed for direct comparison tests to determine whether toxicity profiles differed when combining palbociclib with one type of agent or another for endocrine therapy. We present a comprehensive report on the safety profile of patients included in the PARSIFAL study. Particular emphasis is placed on the adverse events of special interest (AESIs), including VTE and ILD/pneumonitis of the overall safety population.

Materials and Methods

Study Design, Patients, and Procedures

The PARSIFAL study is an international, randomized, open-label clinical trial with 2 parallel arms at 47 sites in 7 countries (ClinicalTrials.gov Identifier: NCT02491983). The methods used in the trial have been described previously.[15] The primary endpoint was investigator-assessed PFS, which was defined as the time from randomization to radiologically confirmed disease progression according to the criteria of the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST) or death during the study. Secondary endpoints

included the safety and tolerability profile of palbociclib with either fulvestrant or letrozole.

All patients provided written informed consent before participation in any study-related activities. Approvals from regulatory authorities and ethics committees were appropriately obtained. The trial was done in accordance with the Declaration of Helsinki and under the principles of good clinical practice[16] and followed the reporting guidelines of the Consolidated Standards of Reporting Trials (CONSORT).[17]

Treatment

Patients were randomized at a 1:1 ratio into 2 groups that received oral palbociclib at 125 mg per day (3 weeks on, 1 week off) plus either intramuscular fulvestrant at 500 mg on days 1, 15, 29, and once monthly thereafter, or oral letrozole at 2.5 mg per day (continuous treatment). A gonadotropin-releasing hormone agonist was administered to the premenopausal or perimenopausal women. Treatment continued until disease progression, unacceptable toxicity, death, or patient withdrawal for any reason occurred. Stratification factors included the type of disease (de novo metastatic or recurrent) and the disease site (visceral or non-visceral).

In the event of adverse reactions, dosing interruptions and dose reduction were allowed for palbociclib but were not applicable to fulvestrant and letrozole per label. Patients were permitted to discontinue palbociclib and continue with endocrine therapy alone. Protocol-required dose modifications for treatment-related toxicities are shown in the Supplementary Methods.

Safety Assessments

AEs were reported from the time at which informed consent was provided until 28 days after the last treatment dose and before initiation of a new anticancer treatment, or until resolution or characterization as chronic/stable, whichever occurred later. Laboratory analyses were performed on days 1 and 14 of the first 2 cycles and on day 1 of subsequent cycles. Physical examinations and vital signs were analyzed on day 1 of every cycle. At every visit, investigators were required to ask patients whether they had had any AEs. Prespecified checklists were not used to ensure that both anticipated and unanticipated events were recorded and to prevent any potential bias in AE reporting.

AE assessment consisted of the description of the events; their duration, severity, timing, and seriousness; and their relatedness to study treatment as reported by the investigator. At each cycle, AEs were coded by the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0, and AE severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Serious adverse events (SAEs) were defined as death, a life-threatening event, an event that caused or extended long-term hospital care, an event that caused disability or incapacity, or an event that necessitated medical intervention to prevent permanent impairment or damage.

Statistical Analyses

All patients who received at least one dose of study treatment were included in the safety analyses. Frequencies and patterns of the AEs experienced by the patients were reported through descriptive statistics according to the study arm. AE frequency was presented based on the maximum toxicity grade for a patient during the treatment as reported by investigators.

The association between baseline clinical characteristics, pulmonary embolism, and ILD was assessed. Mean differences were compared with the Wilcoxon test. For proportions, the chi-squared or Fisher's exact tests were used. We evaluated the influence of pulmonary embolism on PFS with landmark analyses at 6, 8, and 12 months using the Kaplan–Meier method. Patients whose treatment duration was shorter than the landmark time were excluded. Patients who experienced a pulmonary embolism before the landmark were assigned to the pulmonary embolism group, whereas those who had not experienced pulmonary embolism were assigned to the non–pulmonary embolism group for landmark analysis.

The hazard ratios were estimated using Cox's proportional hazards model. The analysis was based on the Wald test and Breslow method for handling ties. Two-sided p values with a level of significance alpha ≤ 0.05 and 95% CIs were used. P values and CIs obtained from these analyses were interpreted as descriptive. Data analysis was carried out using R software version 4.0.2.

Results

Patient Characteristics

Between July 30, 2015, and January 8, 2018, 486 women were randomly assigned to receive fulvestrant plus palbociclib (n = 243) or letrozole plus palbociclib (n = 243). The safety analyses involved a total of 483 patients who received at least one dose of fulvestrant plus palbociclib (n = 241) or letrozole plus palbociclib (n = 242). Three patients did not start study treatment due to the investigator decision (n = 1), withdrawal of consent (n = 1), and protocol violation (n = 1) (Supplementary Fig. S1). Demographics and baseline characteristics were generally balanced across treatment groups and have been published previously[15] (Supplementary Table S1).

At the final cutoff date for data analysis on January 31, 2020, the median follow-up was 32.3 months (interquartile range (IQR), 24.5–39.7 months), and those who were continuing treatment comprised 29.9% (n = 72) of the patients receiving fulvestrant-palbociclib and 36.4% (n = 88) of the patients receiving letrozole-palbociclib. Treatment discontinuation occurred in 70.1% (n = 169) of patients in the fulvestrant–palbociclib group and 63.6% (n = 154) of patients in the letrozole-palbociclib group. The median treatment durations were 23.9 (IQR, 11.0-33.1) and 25.2 (IQR, 12.9-33.2) months in the fulvestrant–palbociclib group and letrozole–palbociclib group, respectively. The median relative dose intensities were 99.2% (IQR, 97.3%-100%) for fulvestrant and 91.7% (IQR, 76.0-97.6%) for palbociclib in the fulvestrant–palbociclib group; while they were 98.8% (IQR, 96.3%-99.9%) for letrozole and 90.0% (IQR, 77.4%-98.3%) for palbociclib in the letrozole–palbociclib group. AEs leading to treatment discontinuation were reported in 5.4% (n = 13) of patients in the fulvestrant–palbociclib group and 2.1% (n = 5) of patients in the letrozole–palbociclib group (Supplementary Table S2).

Overall Safety Profile

For all cycles, the reported incidence rates of AEs of any grade were 99.6% (n = 240) and 99.2% (n = 240) in patients treated with palbociclib plus fulvestrant and those treated with palbociclib plus letrozole, respectively. Most of these were treatment-related AEs and were usually mild and manageable. Despite the similar incidence between groups, the letrozole-palbociclib group had fewer SAEs, treatment-related

SAEs, and AEs leading to treatment discontinuation than the fulvestrant–palbociclib group (Table 1). The most common AEs in both groups were neutropenia, leukopenia, asthenia, arthralgia, fatigue, and diarrhea (Table 2). Febrile neutropenia had a low incidence in both the fulvestrant (3 patients [1.2%]) and letrozole (1 patient [0.4%)] groups.

Table 1. Incidence of all adverse events.

Variable	Fulvestrant–palbociclib (*n* = 241)	Letrozole–palbociclib (*n* = 242)
AEs	240 (99.6)	240 (99.2)
Grades 3-4 AEs	195 (80.9)	190 (78.5)
Treatment-related AEs	225 (93.4)	230 (95.0)
Treatment-related grades 3-4 AEs	170 (70.5)	169 (69.8)
SAEs	72 (29.9)	51 (21.1)
Treatment-related SAEs	21 (8.7)	7 (2.9)
AEs leading to treatment discontinuation	13 (5.4)	5 (2.1)

Data are presented as *n* (%), unless otherwise specified.
Abbreviations: AE, adverse events; SAE, serious adverse events.

VTE

The cumulative incidence of AESIs over time in both groups is shown in Table 3. There was no significant difference in the occurrence of any grade VTE between groups (5.8% [*n* = 14] in the fulvestrant–palbociclib group versus 4.5% [*n* = 11] in the letrozole–palbociclib group; *P* = .681; Table 3). There were numerically more grades 3–5 events in the fulvestrant than letrozole group (13 [5%] vs. 7 [2.9%]; *P* = .254). One patient with unrelated pulmonary embolism (grade 5) died due to progressive disease in the fulvestrant–palbociclib group. Overall, events of pulmonary embolism occurred in 5.0% (*n* = 12; grades 3-5) of patients in the fulvestrant–palbociclib group and 2.5% (*n* = 6; grades 3-4) of patients in the letrozole–palbociclib group (Table 3). The median time from the first dose of the study drugs to the first episode of pulmonary embolism was 4.1 (IQR, 2.7-10.1) months for the fulvestrant–palbociclib group versus 7.0 (IQR, 2.8-13.2) months for the letrozole-palbociclib group.

Table 2. Summary of adverse events of any grade occurring in ≥10% of patients.

Variable	Fulvestrant–palbociclib (*n* = 241)			Letrozole–palbociclib (*n* = 242)		
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Any	240 (99.6)	167 (69.3)	28 (11.6)	240 (99.2)	168 (69.4)	22 (9.1)
Hematologic AEs						
Neutropenia	198 (82.2)	141 (58.5)	18 (7.5)	207 (85.5)	153 (63.2)	12 (5.0)
Leukopenia	60 (24.9)	16 (6.6)	1 (0.4)	61 (25.2)	14 (5.8)	0
Anemia	55 (22.8)	6 (2.5)	0	68 (28.1)	6 (2.5)	0
Thrombocytopenia	49 (20.3)	3 (1.2)	0	39 (16.1)	1 (0.4)	1 (0.4)
Non-hematologic AEs						
Asthenia	90 (37.3)	7 (2.9)	0	87 (36.0)	5 (2.1)	0
Diarrhea	65 (27.0)	4 (1.7)	0	60 (24.8)	3 (1.2)	0
Arthralgia	62 (25.7)	1 (0.4)	0	80 (33.1)	1 (0.4)	0
Fatigue	62 (25.7)	4 (1.7)	0	63 (26.0)	4 (1.7)	0
Back pain	57 (23.7)	7 (2.9)	0	49 (20.2)	1 (0.4)	0
Nausea	57 (23.7)	3 (1.2)	0	45 (18.6)	0	0
Alopecia	56 (23.2)	0	0	61 (25.2)	0	0
Cough	54 (22.4)	0	0	42 (17.4)	0	0
Hot flush	41 (17.0)	0	0	46 (19.0)	0	0
Stomatitis	40 (16.6)	0	0	48 (19.8)	2 (0.8)	0
Pain in extremity	39 (16.2)	1 (0.4)	0	28 (11.6)	2 (0.8)	0
Vomiting	35 (14.5)	2 (0.8)	0	39 (16.1)	2 (0.8)	0
Constipation	34 (14.1)	0	0	40 (16.5)	3 (1.2)	0
Headache	34 (14.1)	0	0	33 (13.6)	3 (1.2)	0
Decreased appetite	34 (14.1)	3 (1.2)	0	33 (13.6)	0	0
Viral upper respiratory tract infection	32 (13.3)	1 (0.4)	0	32 (13.2)	1 (0.4)	0
Dyspnea	33 (13.7)	0	0	29 (12.0)	0	0
Abdominal pain upper	22 (9.1)	0	0	31 (12.8)	3 (1.2)	0
Pruritus	28 (11.6)	0	0	25 (10.3)	1 (0.4)	0
Musculoskeletal pain	27 (11.2)	0	0	23 (9.5)	0	0
Urinary tract infection	23 (9.5)	0	0	26 (10.7)	1 (0.4)	0

Data are presented as *n* (%), unless otherwise specified.
Five patients died due to unrelated AEs, 3 of whom (1.2%) were randomized to fulvestrant–palbociclib and 2 (0.8%) to letrozole–palbociclib.
Abbreviations: AEs, adverse events.

Table 3. Incidence of adverse events of special interest.

AEs	Fulvestrant-palbociclib (n = 241)		Letrozole-palbociclib (n = 242)	
	Any grade	Grade 3-5	Any grade	Grade 3-4
Thromboembolic events	14 (5.8)	13 (5.0)	11 (4.5)	7 (2.9)
Pulmonary embolism [a]	12 (5.0)	12 (5.0)	6 (2.5)	6 (2.5)
Varicose vein	0	0	2 (0.8)	0
Pelvic venous thrombosis	0	0	1 (0.4)	0
Jugular vein thrombosis	1 (0.4)	0	0	0
Ischemic stroke	1 (0.4)	1 (0.4)	0	0
Ischemic cardiomyopathy	0	0	1 (0.4)	0
Cerebrovascular accident	0	0	1 (0.4)	1 (0.4)
ILD/pneumonitis [b]	6 (2.5)	2 (0.8)	6 (2.5)	3 (1.2)

Data are presented as n (%), unless otherwise specified.
[a]One patient in the fulvestrant–palbociclib group died due to unrelated pulmonary embolism.
[b]ILD/pneumonitis included any reported preferred terms that were part of the Standardized MedDRA Query (narrow scope) interstitial lung disease.
Abbreviations: AEs, adverse events; ILD, interstitial lung disease.

The baseline characteristics of patients experiencing pulmonary embolism are reported in Supplementary Table S3. The only factor that correlated with pulmonary embolism was age (median age 69.5 [range, 47.0-84.0] years versus 62.0 [range, 25.0-90.0] years; $P < .01$ in patients with and without the event). Notably, 56% (10 out of 18) of patients with pulmonary embolism were asymptomatic and diagnosed incidentally during a routine computed tomography scan for tumor assessment, while the remaining 44% (8 out of 18 patients) were symptomatic. In addition, in 16.7% (3 out of 18) of patients pulmonary embolism was detected in the context of progressive disease (Fig. 1). There were no significant differences in the number of treatment discontinuations and median time to the first episode among symptomatic and asymptomatic patients who experienced pulmonary embolism (Table 4).

Despite the occurrence of pulmonary embolism, 83.3% (15 of 18) of patients did not interrupt the study treatment. Dose reduction or discontinuation of palbociclib due to pulmonary embolism occurred in 16.7% (n = 3) of patients for each one (Supplementary Table S4). Pulmonary embolism was mainly managed with low-molecular-weight heparins (91.7% [n = 11] of patients in the fulvestrant-palbociclib group versus 100% [n = 6] of patients in the letrozole-palbociclib group). Overall, enaxoparin and tinzapirin were the most frequently prescribed medications. A landmark analysis using 3-time points (6, 8, and 12 months) suggested that the rate of PFS in patients who experienced pulmonary embolism without treatment discontinuation was not statistically different from that of patients without pulmonary embolism (hazard ratio, 1.5, 95% CI, 0.6-3.8, P = .343; Fig. 2).

In addition to events of pulmonary embolism, the fulvestrant–palbociclib group had one case of jugular vein thrombosis and one case of ischemic stroke, whereas the letrozole-palbociclib group had 2 cases of varicose vein and one case of pelvic venous thrombosis, ischemic cardiomyopathy, and cerebrovascular accident.

ILD/Pneumonitis

ILD/pneumonitis events were reported in 12 patients in the overall population (6 (50.0%) in the fulvestrant–palbociclib group and 6 (50%) in the letrozole–palbociclib group. Grade 3 ILD/pneumonitis events were reported in 2 patients in the overall population (1 [0.4%] in the fulvestrant–palbociclib group and 1 [0.4%] in the letrozole–palbociclib group; Table 2). The baseline characteristics of patients who developed ILD/pneumonitis are reported in Supplementary Table S5. ILD/pneumonitis occurred more frequently in the elderly (median age 71.5 [range, 57.0-83.0] years versus 62.0 [range, 25.0-90.0] years; $P < 0.01$ in patients with and without the event). The median time from the first dose of the study drugs to the first episode of any grade of ILD/pneumonitis was 6.3 (IQR 4.5-21.7) months for the fulvestrant–palbociclib group versus 16.2 (IQR 11.3-20.0) months for the letrozole–palbociclib group. The median duration of an episode of grade ≥ 2 ILD/pneumonitis was 66.0 (IQR 63.5-66) days for the fulvestrant–palbociclib group versus 64.5 (IQR 63-65.2) days for the letrozole–palbociclib group (Supplementary Table S5). Palbociclib was permanently discontinued in 2 of 2 patients (100.0%) who experienced grade ≥ 3 ILD/pneumonitis, and most of the patients continued in the study with dose adjustments according to the protocol (Supplementary Tables S6 and S7).

Discussion

The optimal management of ABC has changed dramatically with the recent introduction of CDK4/6 inhibitors.[18] Palbociclib, ribociclib, and abemaciclib have achieved survival gains in both endocrine-sensitive or -resistant populations.[19] Despite their similar mechanism of action, there are differences in the type, frequency, and severity of CDK4/6 inhibitors-associated AEs that merit evaluation. In addition, the endocrine partner could modulate the safety and tolerability profile of CDK4/6 inhibitors.[19,20] We assessed the safety profile and specifically the VTE and ILD/pneumonitis of palbociclib in combination with fulvestrant or letrozole in the endocrine-sensitive HR-positive/HER2-negative ABC patients from the PARSIFAL trial. Findings from the current analysis confirmed that grades 3-4 ILD/pneumonitis was sporadic, affecting less than 1% of treated cases with no

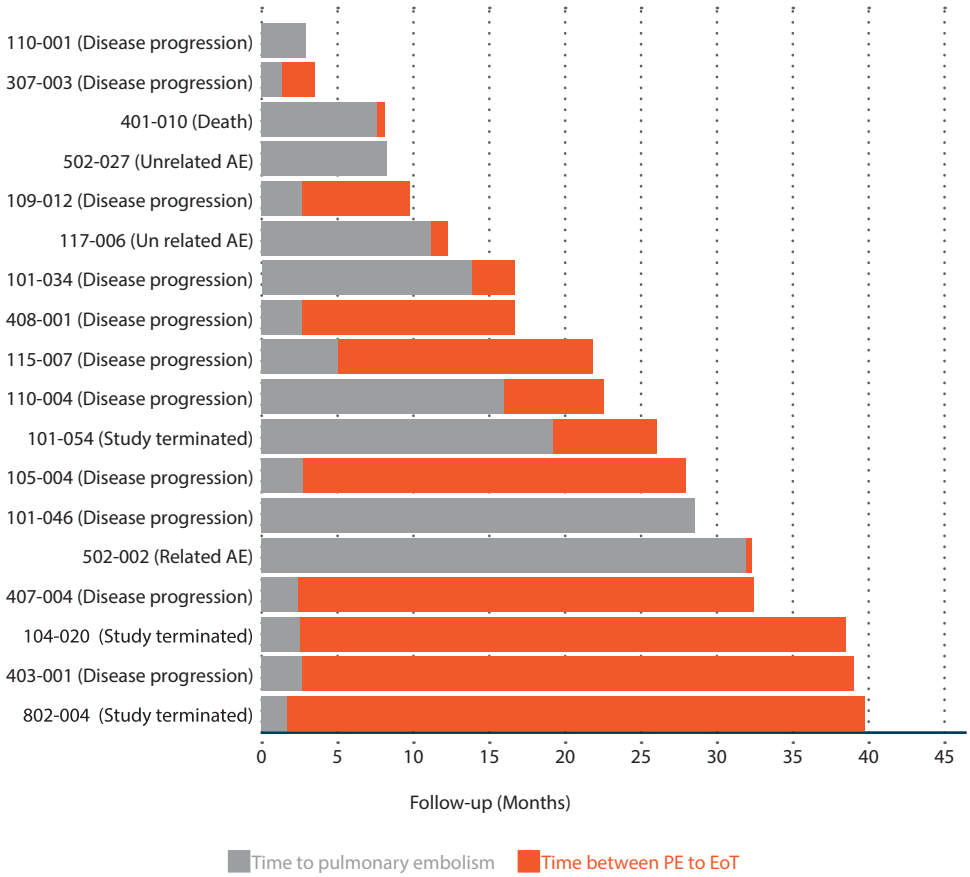

Figure 1. Study follow-up of patients who experienced pulmonary embolism. Asymptomatic grade 3 pulmonary embolism was reported in 10 patients on routine 3-monthly computed tomography scan. In addition, in 5 patients, pulmonary embolism was detected in the context of progressive disease. Abbreviations: AE, adverse event; EoT, end of treatment; PE, pulmonary embolism.

Table 4. Severity, treatment discontinuation, time to the first episode, and median duration of pulmonary embolism in symptomatic and asymptomatic cases.

Characteristics, *n* (%)	Symptomatic (*n* = 8)	Asymptomatic (*n* = 10)	*P* value [a]
Grade			
Grade 3	5 (62.5)	10 (100)	.03
Grade 4	2 (25.5)	–	
Grade 5	1 (12.5)	–	
Treatment discontinuation	2 (33.3)	1 (10.0)	.396
Median time to the diagnosis of an episode, months (IQR)	4.8 (2.3–12.4)	4.1 (2.8–12.2)	.756
Median duration, days (IQR)[b]	7.5 (6.8–16.3)	83 (11.3–180.8)	.079

Data are *n* (%), unless otherwise specified.
[a]The analyses were performed through Wilcoxon exact test for quantitative characteristics and Chi-square or Fisher's exact tests for qualitative characteristics.
[b]Median duration of pulmonary embolism in symptomatic and asymptomatic cases was evaluated until clinical symptomatology resolution or radiological disappearance, respectively. Thus, the duration of symptomatic and asymptomatic thromboembolic events is not comparable.
Abbreviation: IQR, interquartile range.

treatment-related deaths. As fatal cases due to ILD/pneumonitis have occasionally been reported in the post-approval setting of CDK4/6 inhibitors,[19] more investigation is needed to extend our findings to abemaciclib, ribociclib, and real-world settings.[14,21]

VTEs are well-established reported toxicity related to CDK4/6 inhibitors, and thromboembolism rates in palbociclib-based randomized trials range from 0.6 to 5%. A meta-analysis reported a non-significant increase in pulmonary embolism for palbociclib combinations compared with exclusive endocrine therapy (3.2 versus 1.9%, respectively).[13] Nevertheless, the real-world risk appears to be higher than in clinical trials: data reveal that venous events affect nearly 10% of breast-cancer patients receiving palbociclib, a rate that is 5-times greater than that reported in registration trials.[22-24]

A retrospective analysis reported 38 (9%) VTE out of 424 patients treated in clinical practice, of whom 92% received palbociclib.[22] Another study of 64 individuals treated with palbociclib over a 5-month period reported 7 (11%) VTE events.[23] More recently, a single-institution analysis of 266 patients reported 26 (9.8%) VTE events. Interestingly, no increased risk of pulmonary embolism was found when the propensity score corresponding to new users of palbociclib plus fulvestrant was compared to historical users of single-agent fulvestrant.[24]

Most studies with hormone therapy did not explicitly state their methods of ascertaining VTE cases.[25] Therefore, due to this methodological limitation, it is not surprising that the proportion of patients varies widely, irrespective of the type of hormone therapy. Specifically, 2 studies reported VTE in 2.8% and 2.5% of patients receiving fulvestrant compared

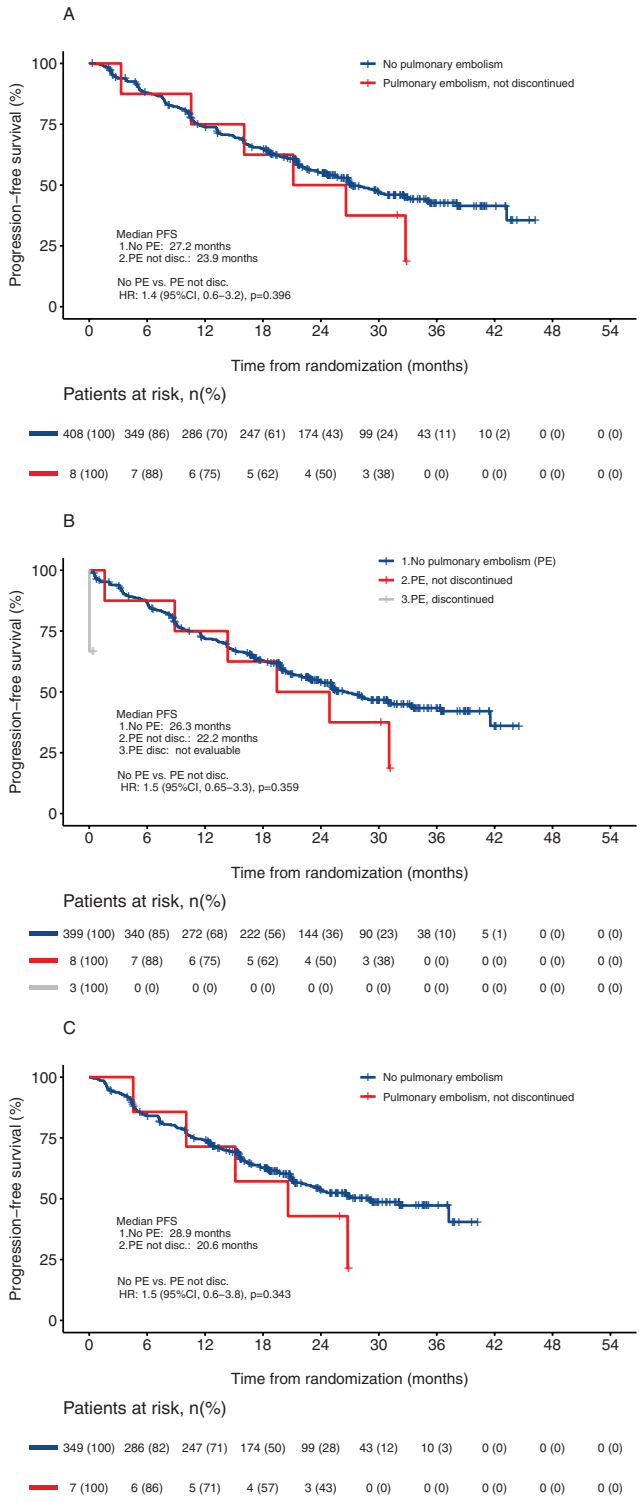

Figure 2. Progression-free survival landmark analysis for patients with pulmonary embolism who did not discontinued study versus patients without pulmonary embolism. **(A)** Landmark at 6 months, **(B)** 8 months, and **(C)** 12 months.

to 1.3% and 5.7% of those on anastrozole, respectively.[20,21] More recently, the FIRST study reported the same event rate of 1% in patients treated with fulvestrant and anastrozole.[26] In the EFECT study, 1.1% of patients in the fulvestrant group and 0.9% in the exemestane group experienced VTEs.[27] The number of patients analyzed and their characteristics may account for the apparent inconsistency of VTE events in the different studies. Furthermore, it should also be considered how AEs were diagnosed, as most of the cases we reported were completely asymptomatic and encountered incidentally during a diagnostic examination performed for tumor assessment.

Unique to the PARSIFAL analysis, we had the chance to analyze data according to the type of endocrine therapy received as well as patient and tumor characteristics. We noted an increased number of pulmonary embolism events in the fulvestrant group compared to the letrozole group. With caution due to low numbers, we can hypothesize that the type of endocrine therapy (ie, selective estrogen receptor degraders versus aromatase inhibitors) may play a specific role in the pathophysiology of cancer-associated thrombosis either alone or in association with CDK4/6 inhibitors.[28] Finally, older age, Eastern Cooperative Oncology Group performance status 2, visceral disease, and prior use of antithrombotic agents may be baseline characteristics to consider for these patients in view of the lack of other specific risk factors.

VTE represents an AESI associated with abemaciclib and are recognized with a specific warning on the label. A recent pooled analysis of the MONARCH 2 and MONARCH 3 trials found that any grade of VTE, including pulmonary embolism and deep vein thrombosis, occurred in 4.8% and 6.1% of abemaciclib-treated patients, respectively (versus 0.9% and 0.6% in the control groups).[29] Similarly, clear imbalances emerged in the updated overall survival analyses of the MONALEESA-3 and MONALEESA-7 trials on ribociclib. In one study, 23 (4.8%; 2.3% grades 3-4) pulmonary embolism events occurred in the interventional group versus 2 such events (0.8%; none of grades 3-4) in the control group.[11] Furthermore, 9 (2.7%; 1.5% grades 3-4) pulmonary embolism events occurred in the interventional group versus 3 such events (0.9%; 0.6% grades 3-4) in the control group in the other study.[30]

As VTE events are negative prognostic factors across various types of malignancies, including breast cancer,[31,32] we finally examined the outcome of patients experiencing pulmonary embolism. Our findings are discordant with prior data reporting increased mortality (by 70%) and cancer therapy disruption (up to 40%) in patients suffering a VTE.[32] However, symptomatic cases comprised only 44% of our total population, suggesting that early detection of asymptomatic events optimizes patient management and prognosis. This aspect is intriguing for the clinical development of CDK4/6 inhibitors in an adjuvant setting. The studies available to date either do not report pulmonary embolism[33] or report it in only 1% of cases.[34] This low incidence may be ascribed to individual early-stage breast cancer patient characteristics (eg, young age, few comorbidities) and/or absence of disseminated disease, which is a risk factor for VTE per se. However, asymptomatic cases may have been completely overlooked because imaging, including computed tomography, is a common practice for patients with metastatic breast cancer but not for early-stage disease. The lack of incidentally diagnosed cases could lead to an underdiagnosis of asymptomatic pulmonary embolism, and the short- and long-term consequences deserve additional studies.

Conclusion

The advent of palbociclib has yielded important clinical results, leading to a complete paradigm shift in the setting of

HR-positive/HER2-negative ABC. This substantial progress has improved survival for months to years, meaning the safety profile is a growing determinant of outcome. A major drawback of its clinical use is the occurrence of AEs. Appropriate recognition of VTE is paramount due to their substantial contribution to long-term morbidity in people living with or surviving cancer. In this respect, our study shows that proper AE identification and management have allowed most of the PARSIFAL patient population to effectively continue treatment without any significant detrimental outcomes.

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Conflict of Interest

Serena Di Cosimo: Novartis, Pierre-Fabre, IQVIA (fees for medical education), Fondazione Associazione Italiana Ricerca contro il Cancro (RF, [AIRC institutional grant IG 20774]), Medica Scientia Innovation Research (C/A, medical advisor); **José Manuel Pérez-García:** Lilly, Roche, Eisai, Daiichi Sankyo, AstraZeneca, Seattle Genetics (C/A), Roche (travel compensation), Medica Scientia Innovation Research (E); **Meritxell Bellet:** Pfizer, Novartis, Lilly (C/A, H, speaker's bureau), Pfizer, Roche (travel compensation); **Miguel J. Gil-Gil:** Pfizer, Novartis, Eisai (H), Khern, Daiichi, Pfizer, Roche (travel compensation), Daiichi, Agendia, Genomic Health (C/A); **Manuel Ruíz-Borrego:** Novartis, Pfizer, Merck Sharp & Dohme Corp (C/A), Pfizer, Novartis, Roche, Lilly, AstraZeneca (speaker's bureau); **Joaquín Gavilá:** Pfizer, Novartis, Lilly, Merck Sharp & Dohme Corp. (C/A), Pfizer, Novartis, Lilly, Roche (H), Roche (travel compensation), Novartis, Pfizer (speaker's bureau); **Miguel Sampayo-Cordero:** Medica Scientia Innovation Research, Syntax for Science, Roche (RF, travel compensation, speaker's bureau), Medica Scientia Innovation Research, Syntax for Science, Nestlé (C/A, H), Medica Scientia Innovation Research (E); **Elena Aguirre:** Merck Sharp & Dohme Corp, AstraZeneca, Pfizer, Roche (C/A); **Peter Schmid:** Pfizer, AstraZeneca, Novartis, Roche, Merck, Boehringer Ingelheim, Bayer, Eisai, Celgene, Puma (C/A), Pfizer, AstraZeneca, Novartis, Roche, Merck, Boehringer Ingelheim (H), Roche, Genentech, Oncogenex, Novartis (RF [institutional grants]); **Frederik Marmé:** Roche/Genentech, Novartis, AstraZeneca, Eisai, Tesaro, Clovis, Merck Sharp & Dohme Corp Oncology, Vaccibody (RF [institutional]), Roche, Pfizer, Novartis, PharmaMar, AstraZeneca (travel compensation), and serving as a consultant to Tesaro, Pfizer, Novartis, GenomicHealth, CureVac, Amgen, Celgene, Eisai, Janssen-Cilag (C/A), AstraZeneca, Roche, Vaccibody, ImmunoMedics (C/A [institutional]), Roche/Genentech, Novartis, Pfizer, AstraZeneca, Tesaro, Clovis Oncology, Eisai, Celgene, Genomic Health, PharmaMar, Amgen, CureVac, Merck Sharp & Dohme Corp Oncology, Janssen-Cilag, ImmunoMedics (H, to the institution); **Joseph Gligorov:** Daiichi, Eisai, Genomic Health, Immunomedics, Ipsen, Macrogenics, Merck Sharp & Dohme Corp, Mylan, Novartis, Onxeo, Pfizer, Roche (C/A), Eisai, Genomic Health, Ipsen, Merck Sharp & Dohme Corp, Mylan, Novartis, Pfizer, Roche (speaker's bureau), Eisai, Genomic Health, Roche (RF), Eisai, Genomic Health, Merck Sharp & Dohme Corp, Mylan, Novartis, Pfizer, Roche (travel compensation); **Andreas Schneeweiss:** Celgene, Roche, AbbVie, Molecular Partner (RF), Roche, Celgene, Pfizer, AstraZeneca, Novartis, Merck Sharp & Dohme Corp, Tesaro, Lilly (H), Roche, AstraZeneca (ET), Celgene, Roche (travel compensation); **Joan Albanell:** Pfizer, Roche, Amgen, Merck Sharp & Dohme Corp, Lilly (C/A), Medica Scientia Innovation Research, Roche, Seattle Genetics (RF), Roche, Pfizer (speaker's bureau), Roche, Pfizer, Amgen, Merck Sharp & Dohme Corp, Lilly (travel compensation), Biocartis (royalties), patents for EGFRmut licensed to Biocartis, for InBiomotion (IP); **Pilar Zamora:** Roche (RF), Roche, Pfizer (travel compensation); **Duncan Wheatley:** Pfizer, Roche, Lilly (C/A), Pfizer, Roche, Daiichii Sankyo, Novartis, Lilly (H), Roche (travel compensation), Lilly, Pfizer, Novartis (speaker's bureau), AstraZeneca (personal fees for work on advisory board); **Eduardo Martínez-De Dueñas:** Pfizer, Novartis (C/A), Pfizer (H), Roche (travel compensation); **Leonardo Mina:** Medica Scientia Innovation Research (E); **Andrea Malfettone:** Medica Scientia Innovation Research (E); **Javier Cortés:** Roche, Celgene, Cellestia, AstraZeneca, Biothera Pharmaceutical, Merus, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Servier, Merck Sharp & Dohme, GlaxoSmithKline, Leuko, Bioasis, Clovis Oncology (C/A), Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer Healthcare, Eisai, Hoffmann-La Roche, Guardant Health, Merck Sharp & Dohme, Pfizer, Piqur Therapeutics, Puma C, Queen Mary University of London (RF), Roche, Novartis, Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, Merck Sharp & Dohme, Daiichi Sankyo (H), Medica Scientia Innovation Research (IP); **Antonio Llombart-Cussac:** Lilly, Roche, Pfizer, Novartis, Pierre-Fabre, Genomic Health, GlaxoSmithKline (C/A), Lilly, AstraZeneca, Merck Sharp & Dohme Corp (speaker's bureau), Roche, Foundation Medicine, Pierre-Fabre, Agendia (RF), Medica Scientia Innovation Research, Initia-Research (IP), Eisai, Celgene, Lilly, Pfizer, Roche, Novartis, Merck Sharp & Dohme Corp. (leadership role), Roche, Lilly, Novartis, Pfizer, AstraZeneca (travel compensation). **Florence Dalenc, Vicente Carañana,** and **Kepa Amillano** indicated no financial relationships.

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Author Contributions

Conception/design: J.C., A.L.-C. Obtained funding: J.C., A.L.-C. Administrative, technical, or material support: A.M. Provision of study material or patients: S.D.-C., J.M.P.-G., M.B., F.D., M.J.G.G., M.R.-B., J.G., P.S., F.M., J.G., A.S.,

J.A., P.Z., D.W., E.M-D.D., V.C., K.A. Collection and/or assembly of data: All authors. Data analysis and interpretation: All authors. Statistical analysis: M.S.-C. Manuscript writing: All authors. Final approval of manuscript: All authors. Javier Cortés and Antonio Llombart-Cussac had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Meeting Presentations

Part of the data was presented at the following meetings: American Society of Clinical Oncology (ASCO) Virtual Meeting 2020 (May 29–June 2, 2020, "1007P—PARSIFAL: A randomized, multicenter, open-label, phase II trial to evaluate palbociclib in combination with fulvestrant or letrozole in endocrine-sensitive patients with estrogen receptor (ER)[+]/HER2[-] metastatic breast cancer", Abstract Oral Session ID 312547) and San Antonio Breast Cancer Symposium (SABCS) 2020 (December 8–11, 2020, "#1699, Palbociclib (P) in combination with fulvestrant (F) or letrozole (L) in endocrine-sensitive patients (pts) with hormone receptor (HR)[+]/HER2[-] metastatic breast cancer (MBC): detailed safety analysis from a multicenter, randomized, open-label, phase II trial (PARSIFAL)", Abstract Poster Session ID 1699).

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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