Palbociclib in Combination with Fulvestrant or Letrozole in Endocrine-Sensitive Patients with HR+/HER2- Metastatic Breast Cancer: Detailed Safety Analysis from a Multicenter, Randomized, Open-Label, Phase II Trial (PARSIFAL)

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INTRODUCTION

- Breast cancer is the most commonly occurring cancer in women and the second most common cancer overall. The hormone receptor-positive (HR+)/Human Epidermal Growth Factor Receptor 2-negative (HER2-) population is the largest subgroup amongst postmenopausal women with metastatic disease representing approximately 65% of cases.
- Cyclin-dependent kinases 4 and 6 inhibitors (CDK4/6i) -palbociclib (P), ribociclib, and abemaciclib- are now the standard of care for HR+/HER2- metastatic breast cancer (MBC). In the PALOMA-1 and -2, P plus letrozole (L) significantly prolonged progression-free survival (PFS) when compared to L alone in postmenopausal women with HR+/HER2- MBC [1,2], and in the PALOMA-3, the combination of P and fulvestrant (F) was associated with significant improvements in PFS compared with F plus placebo [3].
- Although venous thromboembolic events have been reported in registrational trials [4,5], a systematic review and meta-analysis of randomized controlled trials showed a high rate of these adverse events (AEs) in HR+/HER2- MBC patients treated with combined CDKi plus endocrine therapy [6]. In addition, rare but severe cases of interstitial lung disease (ILD)/pneumonitis have been observed during post-approval use of all CDK4/6i [7].
- PARSIFAL is an open-label, randomized, controlled, multicenter phase II study assessing the efficacy and safety of the combination P+F vs. P+L in terms of PFS in women with HR+/HER2-MBC.

OBJECTIVE

- To analyze the toxicity profile of patients included in the PARSIFAL study, with particular emphasis given to AEs of special interest of the overall safety population.

METHODS

Patients and Study Design

Figure 1. Study design of the PARSIFAL trial

Key inclusion criteria:

1. ER/PR+/HER2- MBC
2. No prior therapy for advanced disease
3. Postmenopausal or premenopausal*
4. Endocrine sensitive criteria:
   - Relapse >12 months from the end of endocrine therapy; or
   - Endocrine naïve

N = 486

Fulvestrant
500mg IM, on Days 1, 14, 29 & monthly thereafter
+
Palbociclib
125mg PO, once daily, 3 weeks on, 1 week off

Letrozole
2.5mg PO, once daily, continuously
+
Palbociclib
125mg PO, once daily, 3 weeks on, 1 week off

Stratification factors:

- Visceral involvement (No /Yes)
- *"de novo"*/recurrent

Treatment until progressive disease per investigator or intolerable toxicity

*If pre-menopausal, an ovarian suppression method was required.
ER: Estrogen receptor; HER2: Human Epidermal Growth Factor Receptor 2; IM: Intramuscular; MBC: Metastatic breast cancer; PO: Oral administration; PR: Progesterone receptor.

Safety Assessments

- Safety assessments included blood analysis and collection of vital signs at screening, day 1 of each cycle, and end of treatment/withdrawal.
- Grade 3 and 4 AEs and serious adverse events (SAEs) were assessed to determine the safety and tolerability of the different drug combinations as per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03.

Trial Registration: NCT02491983 on July 8th, 2015. First patient included: July 30th, 2015.

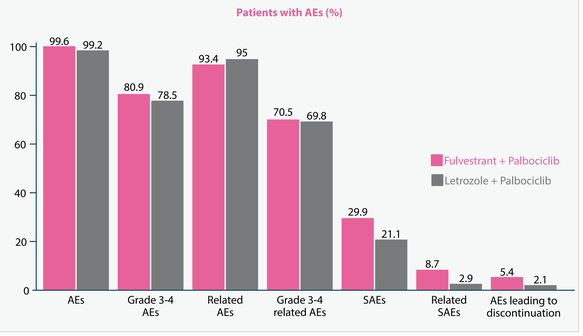
RESULTS

Safety and Tolerability

- Neutropenia, leukopenia, anemia, asthenia, arthralgia, fatigue, and diarrhea were the most frequent AEs in both treatment arms.
- Febrile neutropenia was reported in 1.2% (3 patients) and 0.4% (1 patient) in the FP and LP arms, respectively.
- A total of five patients died due to unrelated AEs: of them three patients (1.2%) in the FP arm and two patients (0.8%) in the LP arm.

Incidence Rate of Adverse Events

Figure 2. Percentage of patients with AEs



AE: Adverse Events; SAE: Serious Adverse Events

Table 1. Incidence of AEs of special interest (Safety analysis)

	Fulvestrant + Palbociclib (N=241)		Letrozole + Palbociclib (N=242)	
Patients with AEs, n(%)	Any grade	Grade 3-4	Any grade	Grade 3-4
Thromboembolic events	14 (5.8)	13 (5)	11 (4.5)	7 (2.9)
Pulmonary embolism*	12 (5.0)	12 (5.0)	6 (2.5)	6 (2.5)
Varicose vein	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Pelvic venous thrombosis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Jugular vein thrombosis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic stroke	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Ischaemic cardiomyopathy	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.04)
ILD/pneumonitis**	6 (2.5)	2 (0.8)	6 (2.5)	3 (1.2)

* One patient died due to unrelated pulmonary embolism in fulvestrant plus palbociclib arm.
** ILD/pneumonitis includes any reported preferred terms that are part of the Standardized MedDRA Query (narrow scope) Interstitial Lung Disease .
AEs: Adverse Events; ILD: Interstitial lung disease.

Patients' Baseline Characteristics by Pulmonary Embolism

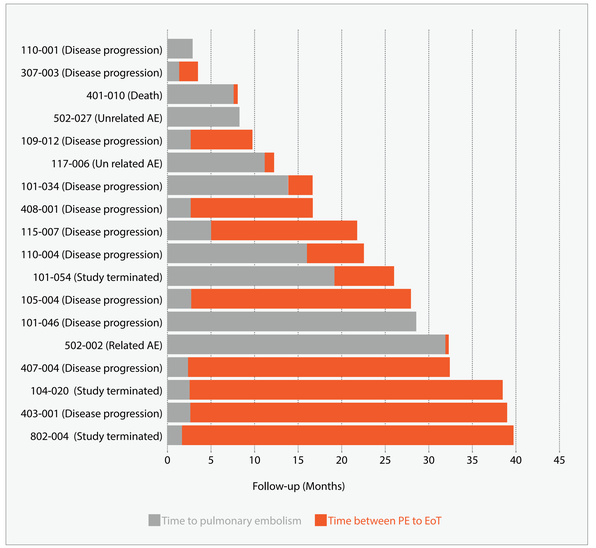
Table 2. Comparison of baseline characteristics between patients with and without pulmonary embolism

Characteristics, n (%)		All patients	Pulmonary embolism		P- value*
			No	Yes	
Age, median (range)		63 (25-90)	62 (25-90)	69.5 (47-84)	<0.01
ECOG PS score	0-1	462 (95.1)	446 (95.3)	16 (88.9)	0.221
	2	24 (4.9)	22 (4.7)	2 (11.1)	
Premenopausal status	No	449 (92.4)	432 (92.3)	17 (94.4)	0.737
	Yes	37 (7.6)	36 (7.7)	1 (5.6)	
De novo disease	No	288 (59.3)	279 (59.6)	9 (50)	0.415
	Yes	198 (40.7)	189 (40.4)	9 (50)	
Visceral disease	No	253 (52.1)	245 (52.4)	8 (44.4)	0.51
	Yes	233 (47.9)	223 (47.6)	10 (55.6)	
Organs involved	<3	274 (56.4)	261 (55.8)	13 (72.2)	0.167
	≥3	212 (43.6)	207 (44.2)	5 (27.8)	
Measurable disease	No	110 (22.6)	106 (22.6)	4 (22.2)	0.966
	Yes	376 (77.4)	362 (77.4)	14 (77.8)	
Chemotherapy					
	Neoadjuvant	46 (9.5)	46 (9.8)	0 (0)	0.162
	Adjuvant	144 (29.6)	140 (29.9)	4 (22.2)	0 483
Endocrine therapy					
Tamoxifen	Tamoxifen	177 (36.4)	171 (36.5)	6 (33.3)	0.782
AIs	AIs	115 (23.7)	112 (23.9)	3 (16.7)	0.477
Previous AT	No	430 (88.5)	414 (88.5)	16 (88.9)	0.53
	Yes	34 (7)	32 (6.8)	2 (11.1) **	

* The analyses were based on Wilcoxon exact test for quantitative characteristics and Chi-square or Fisher exact test for qualitative characteristics.
** The antithrombotic medication was based on Adiro.
AIs: Aromatase inhibitors; AT: antithrombotic; ECOG PS: Eastern Cooperative Oncology Group, Performance Status.

Patients with Pulmonary Embolism

Figure 3. Study follow-up and reasons for end of treatment in patients with pulmonary embolism



Asymptomatic grade 3 pulmonary embolism was reported in 10 patients on routine 3-monthly CT scan. In addition, in five patients, pulmonary embolism was detected in the context of progressive disease.
AE: Adverse event; EoT: End of treatment; PE: Pulmonary embolism.

CONCLUSIONS

- First-line treatment with FP and LP for HR+/HER2- MBC in the PARSIFAL study confirmed the favorable safety profile, with neutropenia representing the most common AE.
- Although rare, ILD/pneumonitis occurred in 2.5% of patients.
- Venous thromboembolic event and pulmonary embolism incidence rates were consistent with age-specific analyses from PALOMA trials and breast cancer population.
- Early detection of these AEs may assist in optimizing their management.

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Conflicts of interest: https://www.medsir.org/parsifal