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ORIGINAL ARTICLE

Extended follow-up of palbociclib with fulvestrant or letrozole for endocrine-sensitive, hormone receptor-positive/HER2-negative advanced breast cancer in the PARSIFAL trial☆

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Available online 17 June 2025

Background: Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) are the mainstay for hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC). While the approved CDK4/6i have demonstrated significant improvements in progression-free survival (PFS), inconsistencies exist for overall survival (OS) benefits. Here, we report updated efficacy results from PARSIFAL, a randomized phase II study, that evaluated first-line palbociclib with either letrozole or fulvestrant in postmenopausal patients with endocrine-sensitive, HR-positive/HER2-negative ABC.

Patients and methods: PARSIFAL-LONG was an international, multicenter, observational study that extended follow-up for patients included in PARSIFAL. The primary objective evaluated updated OS of palbociclib combined with endocrine therapy (fulvestrant or letrozole). Secondary objectives included updated investigator-assessed PFS and subsequent antineoplastic therapies. Exploratory endpoints included identification of new clinical prognostic markers for OS, specifically PFS duration.

Results: A total of 419 of 486 (86.2%) patients from PARSIFAL were included. Median follow-up was 7.3 years (interquartile range 6.7-7.7 years). At data cut-off (8 January 2024), no differences in efficacy were observed between fulvestrant and letrozole for OS (hazard ratio 1.01, 95% confidence interval [CI], 0.80-1.28, $P = 0.927$) or PFS (hazard ratio 1.06,95% CI, 0.85-1.31, $P = 0.612$). Median OS for the overall PARSIFAL-LONG population was 61.8 months (95% CI 56.5-68.4 months), representing the highest OS reported to date for palbociclib and aligning with outcomes observed for other CDK4/6i in this setting. Median PFS was 32.6 months (95% CI 27.5-38.1 months). A total of 85 (20.3%) patients were defined as early progressors (PFS $\leq$ 12 months). These patients had a shorter median post-progression OS than patients who remained progression free at 12 months (18.7 versus 27.4 months; hazard ratio 0.65, $P = 0.004$).

Conclusions: Extended analysis from PARSIFAL confirmed no difference between fulvestrant and letrozole when combined with palbociclib for patients with endocrine-sensitive, HR-positive/HER2-negative ABC. Efficacy results were consistent with those reported in the pivotal first-line trials involving CDK4/6i. Progression within the first year on CDK4/6i may indicate a poorer prognosis.

Key words: palbociclib, fulvestrant, letrozole, hormone receptor positive/HER2 negative, advanced breast cancer, extended overall survival

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☆Note: Part of the data was previously presented as an oral presentation and at the 2023 San Antonio Breast Cancer Symposium.

INTRODUCTION

Hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer is the most common subtype of breast cancer and accounts for ∼70% of all cases.[1] In the advanced disease setting, it remains uncurable; therefore, improving overall survival (OS) is a primary goal.

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) are the standard of care for first-line treatment of HR-positive/HER2-negative advanced breast cancer (ABC) after demonstrating substantial extension of progression-free survival (PFS) when combined with endocrine therapy.[2-4] However, inconsistencies have been observed in OS between the three approved CDK4/6i, with only ribociclib[5] demonstrating a statistically significant benefit in OS, while abemaciclib[6] and palbociclib[7,8] had only numerical improvements in OS without reaching statistical significance.

Despite the remarkable efficacy of CDK4/6i, most patients will eventually develop resistance to this regimen. Several therapeutic options are available for subsequent therapy, but the optimal treatment remains undetermined.[9] Selecting the best treatment after CDK4/6i is critical and depends on multiple prognostic/predictive biomarkers. Several factors have been identified, such as molecular status (*PIK3CA*, *AKT1*, *PTEN*, *ESR1*, and germline *BRCA1/2*),[10-15] HR and HER2 status dynamics,[16,17] type of disease progression (visceral versus non-visceral), and breast cancer symptoms. Additionally, a recent subgroup analysis from the EMERALD study identified progression on CDK4/6i during the first 12 months as a strong predictor of later endocrine resistance.[18]

Previously, the PARSIFAL study, an open-label, randomized, phase II trial, failed to demonstrate an improvement in PFS of fulvestrant over letrozole when combined with palbociclib as first-line therapy in postmenopausal patients with endocrine-sensitive, HR-positive/HER2-negative ABC.[19] Given that this study included the largest number of patients treated with a palbociclib-based regimen, PARSIFAL-LONG was designed as an observational study that aimed to describe updated PFS and OS results from patients included in PARSIFAL, with a longer follow-up after the completion of the scheduled *study* period. A secondary objective explored the PFS $\leq$12-month threshold as a prognostic factor.

PATIENTS AND METHODS

Study design and participants

PARSIFAL-LONG was an international, observational, multicenter study that assessed the updated efficacy results of patients included in the PARSIFAL trial after the end of this study. The end of study of the PARSIFAL trial, which led to the interruption of follow-up monitoring and data collection, was on 8 January 2018. After the conclusion of the trial, the study drugs continued to be provided to those patients who were benefiting from treatment; however, there was no universal standard follow-up schedule after study completion. The PARSIFAL-LONG data collection was initiated in August 2022, once the PARSIFAL trial database was available for integration with additional long-term follow-up information.

The study design of PARSIFAL (NCT02491983) has been previously reported[19] and is detailed in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.105309. Briefly, PARSIFAL was an international, open-label, randomized, phase II trial conducted at 47 sites in seven countries. Postmenopausal patients with endocrine-sensitive, locally confirmed HR-positive/HER2-negative ABC who have not received prior hormonal or chemotherapy treatment in the metastatic setting and who had a disease-free interval of >12 months after (neo) adjuvant endocrine therapy before developing metastases were randomly assigned in a 1 : 1 ratio to receive either fulvestrant or letrozole plus palbociclib.

The study protocol was approved by ethics review committees and surviving patients were re-consented before participation in PARSIFAL-LONG.

Endpoints

The primary endpoint was updated OS, defined as the time from randomization until death of any cause. Secondary efficacy endpoints included (i) extended investigator-assessed PFS, defined as the time from randomization until objective tumor progression or death, and (ii) antineoplastic therapies after treatment with palbociclib plus endocrine therapy. Exploratory endpoints included the identification of new prognostic and predictive markers of OS, specifically related to PFS duration.

Statistical analysis

OS and PFS analyses were carried out in the intention-to-treat population, which included all patients according to the group they were randomly assigned in the PARSIFAL trial. Post-trial treatments were assessed in all patients who received a subsequent anticancer therapy.

Originally, the study was designed with the assumption that for 388 patients from the PARSIFAL trial, 195 OS events would provide a 70% power to detect a hazard ratio of 0.7 in favor of fulvestrant plus palbociclib group at two-sided 5% significance. However, the final analysis was planned with all the OS events and patients included until 8 January 2024. Additionally, the PARSIFAL trial did not demonstrate significant difference between treatment groups for its primary objective (PFS); therefore, all *P* values reported are considered descriptive.

OS and PFS analyses were carried out using standard Kaplan–Meier methods. Hazard ratio and 95% confidence intervals (CIs) for the difference between treatment groups in OS and PFS were estimated using the stratified Cox regression model, including type of disease presentation (*de novo* versus recurrent) and the presence of visceral involvement (yes versus no) as stratification factors.

Data analyses were carried out from 9 September to 8 October 2024, using R software for Windows

Table 1. Patient characteristics

	PARSIFAL $n = 486$	PARSIFAL-LONG $n = 419$
Median age (years, range)	63 (25-90)	64 (25-90)
Race, *n* (%)		
Asian	3 (0.6)	3 (0.7)
Black	4 (0.8)	4 (1)
White	461 (94.9)	394 (94)
Unknown	18 (3.7)	18 (4.3)
ECOG performance status, *n* (%)		
0	275 (56.6)	229 (54.7)
1	187 (38.5)	168 (40.1)
2	24 (4.9)	22 (5.3)
Menopausal status, *n* (%)		
Premenopausal[a]	37 (7.6)	32 (7.6)
Postmenopausal	449 (92.4)	387 (92.4)
Duration of palbociclib treatment in months		
Median (min-max)	25.1 (0.5-52.6)	25.3 (0.5-52.6)
Type of HT associated with palbociclib, *n* (%)		
Fulvestrant	243 (50.0)	210 (50.1)
Letrozole	243 (50.0)	209 (49.9)
Type of disease, *n* (%)		
De novo	198 (40.7)	172 (41.1)
Recurrent	288 (59.3)	247 (58.9)
Disease site, *n* (%)		
Visceral	233 (47.9)	195 (46.5)
Non-visceral	253 (52.1)	224 (53.5)
Liver involvement, *n* (%)		
No	400 (82.3)	348 (83.1)
Yes	86 (17.7)	71 (16.9)
Number of disease sites, *n* (%)		
<3	274 (56.4)	237 (56.6)
≥ 3	212 (43.6)	182 (43.4)
Measurable disease, *n* (%)		
No	110 (22.6)	106 (25.3)
Yes	376 (77.4)	313 (74.7)
Adjuvant endocrine therapy, *n* (%)		
No	281 (57.8)	243 (58.0)
Yes	205 (42.2)	176 (42.0)

ECOG, Eastern Cooperative Oncology Group; HT, hormone therapy.
[a]Patients received gonadotropin-releasing hormone agonists.

(The R Foundation, Vienna, Austria) for all statistical analyses, version 4.4.1 released on 14 June 2024.

RESULTS

Patients and post-progression treatments

A total of 419 out of 486 (86.2%) patients were included. This population accounts for all patients from each of the 36 participating centers (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105309). Given that the end of study for PARSIFAL was 8 January 2018, PARSIFAL-LONG was opened as a new study and some of the original sites declined or were unable to participate. However, demographic and baseline disease characteristics were similar between the PARSIFAL-LONG and the overall PARSIFAL intention-to-treat populations (Table 1). The median age was 64 years (range 25-90 years). A total of 229 (54.7%) patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 172 (41.4%) patients were diagnosed with *de novo* ABC, and 176 (42.0%) patients had previously received adjuvant endocrine therapy for early breast cancer. Visceral disease and liver metastases were present in 195 (46.5%) and 71 (16.9%) patients, respectively. At data cut-off (8 January 2024), and a median follow-up of 7.3 years (interquartile range 6.7-7.7 years), 272 (64.9%) and 329 (78.5%) events were reported for OS and PFS, respectively.

A total of 243 (73.9%) among 329 patients with a PFS event received subsequent anticancer treatments after progression on study treatment. Endocrine therapy-based regimens were used in 176 (72.4%) of the 243 patients for first subsequent therapy and in 65 (34.6%) of the 188 patients who received second subsequent therapy. Capecitabine (14.4%) and paclitaxel (4.5%) were the most frequently administered chemotherapy agents for both first and second subsequent therapies; only five (2.1%) and four (1.6%) patients received sacituzumab govitecan and trastuzumab deruxtecan in the course of the disease, respectively (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105309).

Extended follow-up of overall survival

With the extended follow-up, there was no difference in OS (hazard ratio 1.01, 95% CI 0.80-1.28, $P = 0.927$, Figure 1A) between the treatment arms, with a median OS of 65.6 months (95% CI 52.9-73.2 months) for palbociclib with fulvestrant and 61.6 months (95% CI 55.7-66.4 months) for palbociclib with letrozole. There was also no difference observed for PFS (hazard ratio 1.06, 95% CI 0.85-1.31, $P = 0.612$, Figure 1B), with a median PFS of 29.7 months (95% CI 24.2-38.1 months) for palbociclib with fulvestrant and 34.5 months (95% CI 27.5-39.5 months) for palbociclib plus letrozole.

Given an absence of differences or trends between treatment regimens, both arms were combined for subsequent exploratory analyses. For the whole population, the median OS was 61.8 months (95% CI 56.5-68.4 months, Figure 2A) and median PFS was 32.6 months (95% CI 27.5-38.1 months, Figure 2B).

Impact of progression-free survival duration on overall survival

A total of 85 (20.3%) patients were considered early progressors as they had confirmed disease progression within the first 12 months of palbociclib therapy (PFS $\leq$ 12) months (early progressor subgroup) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105309). There were five (1.2%) patients who were alive but discontinued before the 12 months of treatment without progressive disease and were therefore removed from this analysis. The reasons for discontinuation of those patients were patient decision (2/5), adverse events (ulcerative colitis and dyspnea; 2/5), and physician's decision (1/5). However, all patients were assessed for survival follow-up. The remaining 329 (78.5%) patients were progression free at 12 months (PFS $>$ 12). Among the early progressor subgroup, the number of events for OS at the time of analysis was 79 (92.9%). For the PFS $>$ 12, the number of events for OS and

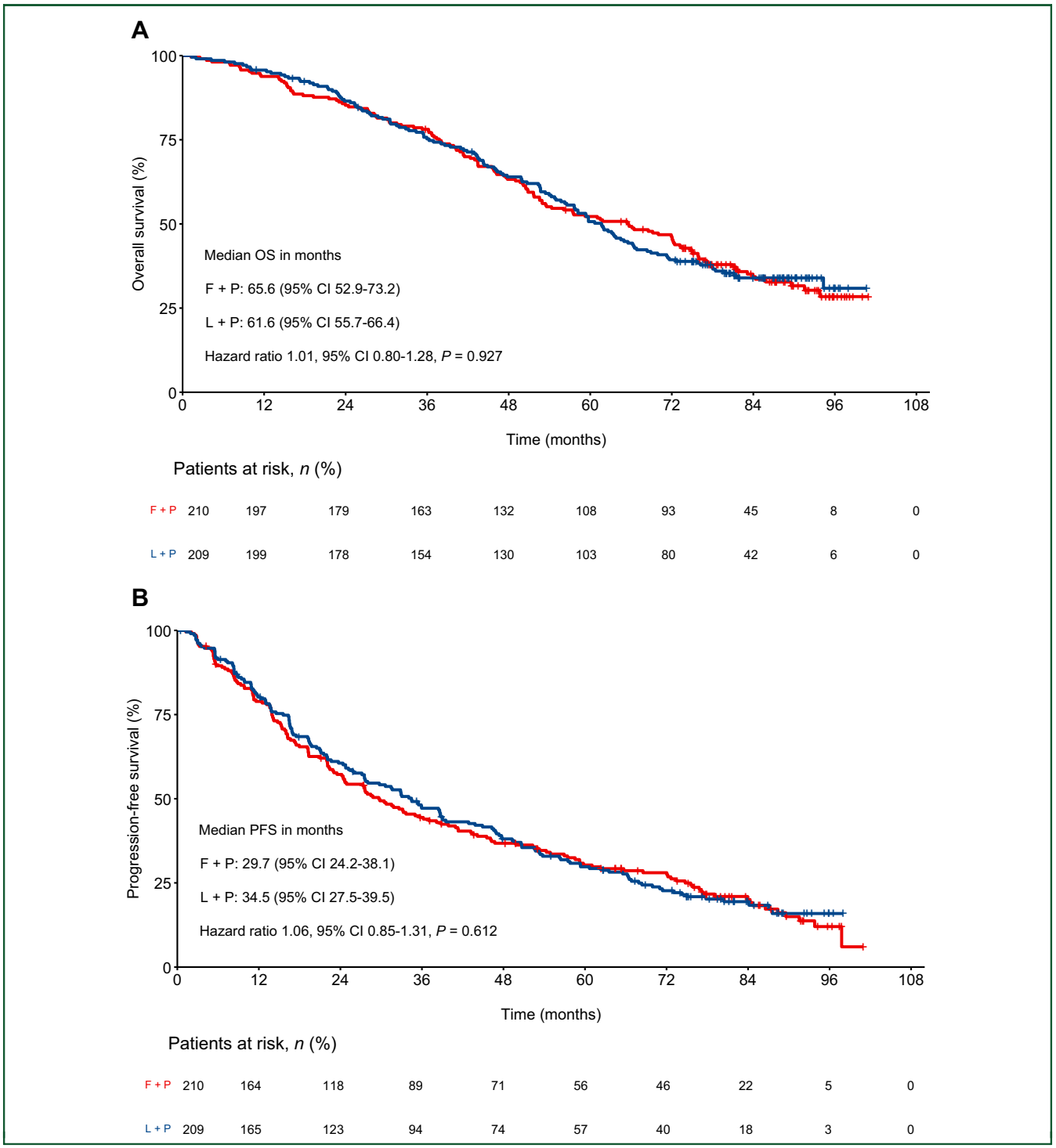

Figure 1. Kaplan–Meier curves of overall survival (A) and progression-free survival (B) by endocrine therapy arm.
CI, confidence interval; F, fulvestrant; L, letrozole; OS, overall survival; P, palbociclib; PFS, progression-free survival.

PFS was 193 (58.7%) and 244 (74.2%), respectively. Median PFS for the early progressor and PFS > 12 subgroups was 7.4 months and 46.1 months, respectively.

Median OS from inclusion for the early progressors was significantly shorter compared with the PFS > 12 (23.4 months versus 72.2 months; hazard ratio 0.19, 95% CI 0.14-0.25, $P < 0.001$) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105309).

At the time of the analysis, 264 patients had confirmed progression on the palbociclib regimen. Post-progression analysis determined that early progressors had a significantly shorter median post-progression OS compared with the PFS > 12 subgroup (18.7 months versus 27.4 months, hazard ratio 0.65, 95% CI 0.48-0.87, $P = 0.004$) (Figure 3). An exploratory analysis among early progressors observed post-progression OS of 17.4 months for patients who

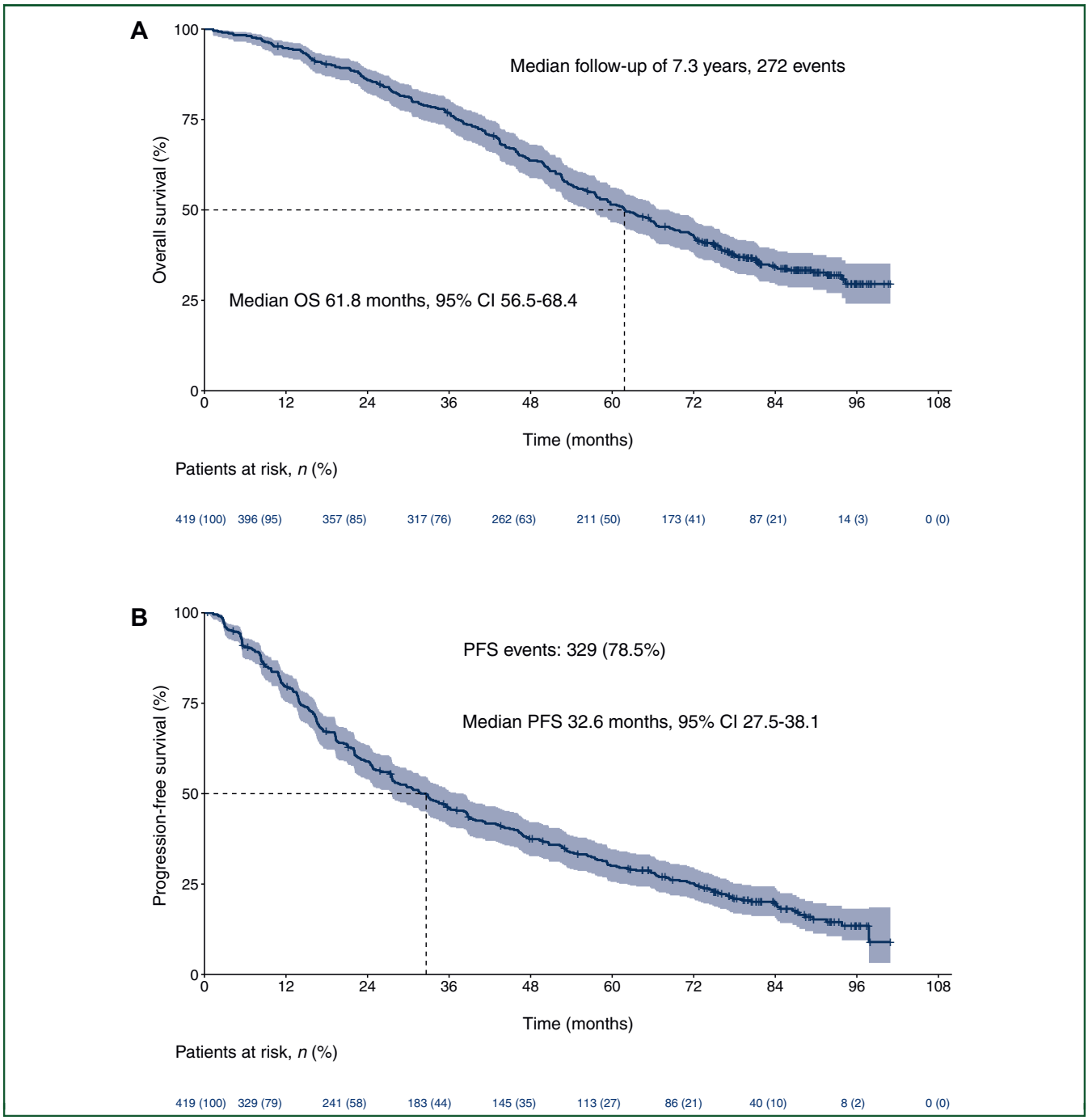

Figure 2. Kaplan–Meier curves of overall survival (A) and progression-free survival (B) in the PARSIFAL-LONG. Median follow-up was calculated using the reverse Kaplan–Meier method.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

progressed within the first 6 months ($n = 37$) and 20.6 months for patients progressing between months 7 and 12 ($n = 42$, $P = 0.671$).

Subgroup analyses of overall survival

Subgroup analysis found no difference between OS in terms of *de novo* metastatic disease ($P = 0.685$) or age ($P = 0.313$). However, ECOG performance status of 0 was associated with a better OS than for ECOG $\geq$1; 74.9 months versus 52.6 months (hazard ratio 0.60, 95% CI 0.47-0.76, $P < 0.0001$). There was a significantly shorter OS when three or more organ sites were affected; 55.7 months versus 68.7 months (hazard ratio 0.77, 95% CI 0.6-0.99, $P = 0.045$). Patients with visceral disease had a significantly shorter median OS compared with patients without visceral disease; 51.7 months versus 70.0 months (hazard ratio 0.67, 95% CI 0.53-0.85, $P = 0.001$). Additionally, patients with liver involvement presented a significantly worse median OS compared with patients without liver metastases; 46.1 months versus 65.6 months (hazard ratio 0.60, 95% CI 0.45-0.81, $P = 0.001$) (Figure 4).

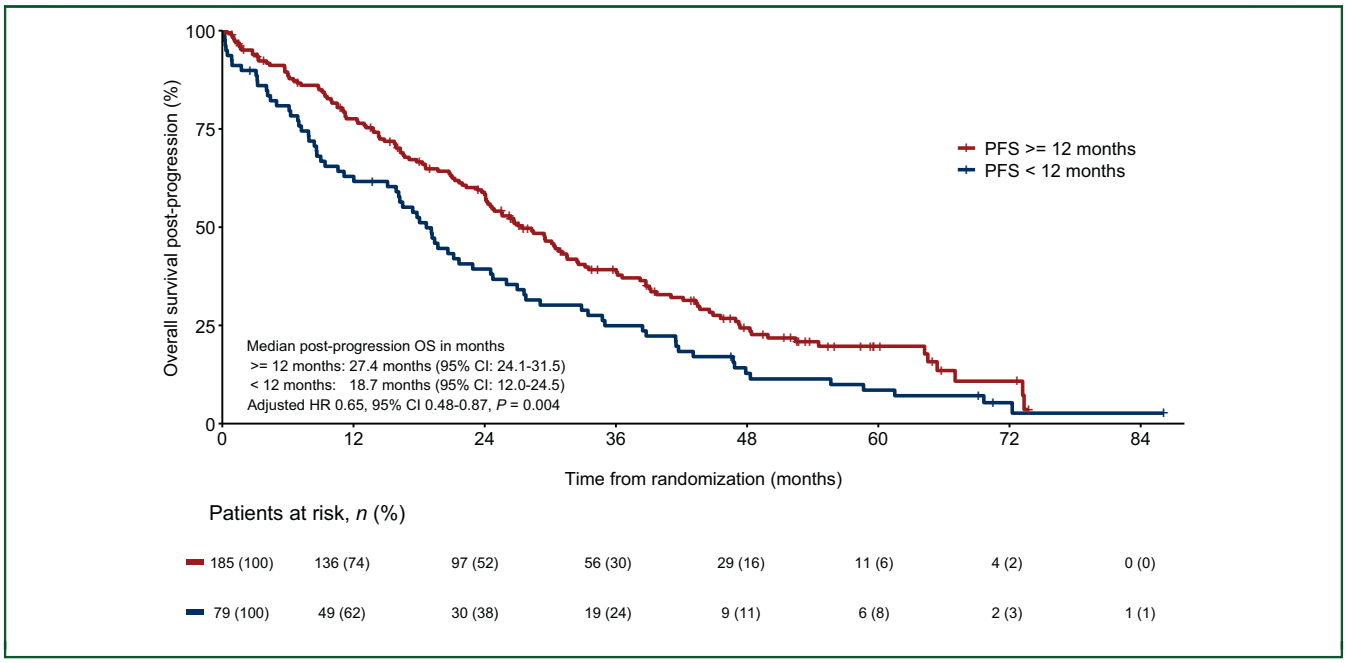

Figure 3. Kaplan–Meier curves of post-progression OS by PFS duration.
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

DISCUSSION

PARSIFAL-LONG has demonstrated the long-term efficacy of first-line treatment with palbociclib in combination with endocrine therapy (letrozole or fulvestrant) in postmenopausal patients with endocrine-sensitive, HR-positive/HER2-negative ABC. Additionally, it reinforced the results of the final analysis of the randomized phase II PARSIFAL study, which demonstrated no differences between fulvestrant and letrozole when combined with palbociclib.

The addition of palbociclib, ribociclib, or abemaciclib to first-line endocrine therapy has dramatically improved outcomes for patients with endocrine-sensitive ABC, as shown in three large randomized phase III studies.[4,20,21] The three trials provided similar improvements in the primary objective of PFS for the CDK4/6i combinations versus endocrine therapy with hazard ratios ranging between 0.54 and 0.58.

In our analysis, median PFS in both arms was in the range of 32.0 months. These results are in line with MONALEESA-2 (25.3 months),[5] MONARCH 3 (28.2 months),[6] and PALOMA-2 (27.6 months)[8] studies, and reflect a population with very similar characteristics. The proportion of patients who were endocrine naive (40%) or had visceral disease (47%) in our study was similar to PALOMA-2 (38% and 48%), MONALEESA-2 (34% and 56%), or MONARCH-3 (41% and 53%) studies, respectively. At the time of this analysis, 90 patients (21.5%) remained progression free, reflecting that a significant number of patients achieve very long disease control on first-line palbociclib regimens.

Concerning OS benefit, ribociclib was the only drug to demonstrate a statistically significant gain in the first-line registration trial.[5] Abemaciclib did not achieve a statistically significant improvement although the median differences in OS were very similar to the ones obtained for ribociclib.[6] In contrast, no OS benefit or trend was observed for the palbociclib study.[7,8] Several aspects have been considered for this OS discrepancies between CDK4/6i when the benefits in PFS were almost identical.[22] The impact of CDK4/6i on OS has been explored with real-world evidence from large retrospective studies.[23-25] P-Reality X concluded that the addition of palbociclib to an aromatase inhibitor improved OS compared with patients treated exclusively with aromatase inhibitors in the first-line setting.[24] Recently, an analysis of real-world data in the German OPAL prospective registry platform including 605 patients showed similar PFS and OS trends for palbociclib with endocrine therapy compared with ribociclib and endocrine therapy when adjusted for a wide range of potential confounding variables.[26]

While there are limitations with indirect comparisons between studies, it should be noted that the median OS achieved in the PARSIFAL-LONG study was 61.8 months, which is in line with the median OS reported in the MONALEESA-2 (63.9 months)[5] or MONARCH 3 (66.8 months)[6] trials. This median OS is also superior to that reported in the PALOMA-2 study (53.9 months).[3] However, it is important to mention that an imbalance in the number of patients with unknown survival status between the treatment arms could have influenced OS results in PALOMA-2. In addition, ~20% of patients included in that study were not endocrine sensitive, a patient population that was formally excluded in PARSIFAL and MONARCH 3 trials, which could also negatively impact OS data.

In PARSIFAL-LONG, we also explored the impact of time to progression on first-line CDK4/6i-based endocrine therapy on OS. Several studies had identified a 12-month threshold as a potential predictor of resistance to subsequent endocrine therapies. Sub-analysis from the phase III EMERALD study

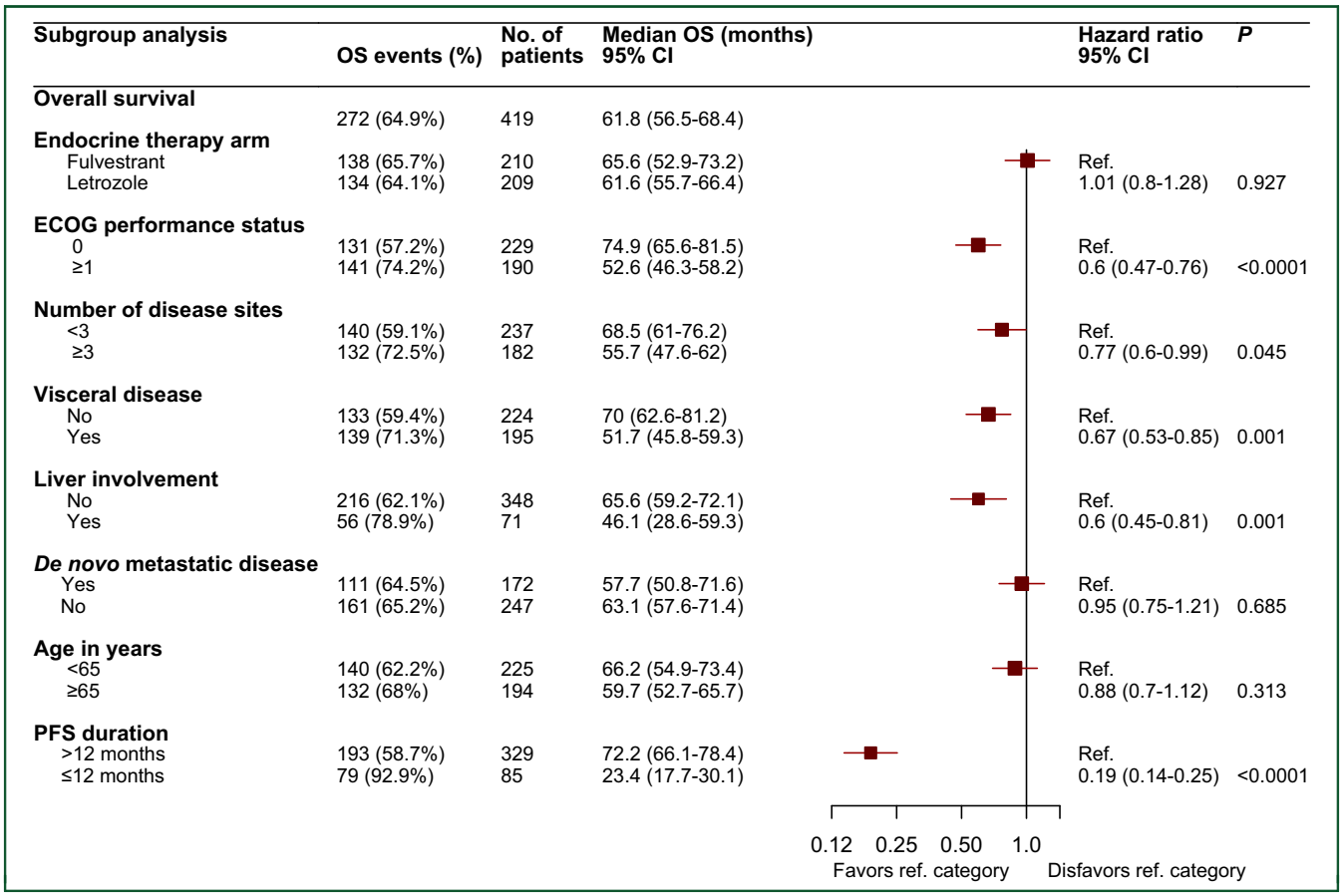

Figure 4. Subgroup analysis for OS.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; ref., reference.

identified that the population with a clinically relevant benefit from elacestrant as second-line therapy for *ESR1*-mutated HR-positive/HER2-negative ABC was limited to those patients who progressed after 12 months on the first-line CDK4/6i treatment.[18] In the METALLICA study, exploring the combination of alpelisib with fulvestrant and metformin as second-line therapy for patients with phosphoinositide 3-kinase pathway-altered endocrine-sensitive ABC progressing on a first-line CDK4/6i, a similar signal was identified.[27,28] Patients who progressed within 12 months on the prior CDK4/6i regimen achieved a median PFS of 2.9 months compared with 11.1 months for patients who were previously on CDK4/6i therapy for $>$ 12 months ($P = 0.002$). Around 20% of patients included in PARSIFAL-LONG had a median PFS $\leq$ 12 months (early progressors). Not surprisingly, this subgroup of patients presented a shorter median OS from the time of inclusion in the study (23.4 months) compared with patients who were progression free at 12 months (72.2 months).

At the time of the final analysis, with a median follow-up of 7.3 years, we confirmed 264 events of progression without death (63%). The post-progression OS was strongly related to the median PFS achieved on the first-line palbociclib regimen. Interestingly, no significant OS differences were observed for patients progressing within 6 months when compared with those who progressed between 7 and 12 months. In fact, the median OS of 18 months for patients progressing within the first year of palbociclib is reminiscent of the median OS for metastatic triple-negative breast cancer patients. In the past, the 6-month period was being considered as the reasonable threshold for subsequent endocrine therapies, introducing the concept of primary endocrine resistance that remains in clinical guidelines.[29] However, our data, which are in line with different subanalysis from second-line trials, suggest that 12 months should be considered as the new criteria for clinical benefit under CDK4/6i regimens to select optimal candidates for subsequent endocrine treatments.

There were several limitations to the PARSIFAL-LONG study, which include its retrospective nature which could result in inaccurate data capture, with incomplete or missing data. Nevertheless, this data source limitation should not influence OS results. Moreover, unlike in clinical trials, disease progression after the end of the PARSIFAL study was not assessed according to a pre-defined schedule which could impact PFS results of PARSIFAL-LONG. Additionally, some of the sites involved in the trial declined to participate in this observational study. Despite this circumstance, demographic and baseline disease characteristics were comparable between the PARSIFAL-LONG and the overall PARSIFAL intention-to-treat populations and it is improbable that our results would have significantly changed with the inclusion of more patients.

In conclusion, extended follow-up analysis from the PARSIFAL trial demonstrated the remarkable antitumor activity of palbociclib-based regimens and confirmed no difference between fulvestrant and letrozole when combined with palbociclib in patients with endocrine-sensitive, HR-positive/HER2-negative ABC. Median PFS and OS results were consistent with those reported in other first-line trials involving different CDK4/6i. Finally, progression within the first year of first-line CDK4/6i-based regimen should be considered as a clinical predictor of endocrine resistance and poor prognosis and may be translated as a reasonable criterion for future trials exploring endocrine therapies or other strategies like antibody—drug conjugates.

ACKNOWLEDGEMENTS

We thank the patients who kindly participated in our study and their families. We thank all study teams of participating sites and the trial unit staff at Medica Scientia Innovation Research, Pfizer Inc, and AstraZeneca.

FUNDING

This work was supported by Pfizer S.L.U (Madrid, Spain) (no grant number). Fulvestrant was provided by AstraZeneca.

ROLE OF THE FUNDER

The study was conceived and designed by Medica Scientia Innovation Research in collaboration with Pfizer Inc, which funded the study and provided palbociclib. Medica Scientia Innovation Research, as legal sponsor of the study, is responsible for compliance with all clinical and regulatory procedures and adherence to the study protocol. Medica Scientia Innovation Research was responsible for the collection, management, analysis, and interpretation of the data, and for writing the report. All authors had full access to the data used to prepare the manuscript and participated in writing, editing, and/or critically reviewing the manuscript. The funder of the study had no role in data collection, management, data analysis, data interpretation, writing of the report, or decision to submit the manuscript for publication. All coauthors took responsibility for the final version of the paper, vouching for the accuracy and completeness of the reported data and adherence to the study protocol.

DISCLOSURE

ALC reports research support from Roche, Agendia, Lilly, Pfizer, Novartis, Merck Sharp & Dohme, Gilead, Daiichi Sankyo; consulting/advisor fees from Lilly, Roche, Pfizer, Novartis; speaker's bureaus for Lilly, AstraZeneca, Merck Sharp & Dohme, Pfizer, Novartis; travel support from Roche, Pfizer, AstraZeneca, Steamline Therapeutics, Merck Sharp & Dohme; patents (Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés.US 2019/0338368 A1. Licensed); stock or other ownership in MAJ3 Capital & Initia-Research. JMPG reports employee at MEDSIR; advisory role at Lilly, Roche, Eisai, Daichii Sankyo, AstraZeneca, Seattle Genetics, Gilead; travel expenses from Roche. MB reports consulting fees from Esteve; honoraria from Pfizer, AstraZeneca, and Mearini-Stemline; payment for expert testimony from Novartis, Lilly, Pfizer, Stemline-Menarini, and Roche; travel fees from Roche, Pfizer, Novartis, and Stemline-Menarini; advisory board fees from Lilly, Novartis, Pfizer, Stemline-Menarini, and Roche. FD reports honoraria from Novartis and AstraZeneca; travel fees from Daiichi Sankyo, AstraZeneca, Gilead Sciences, and Novartis; advisory board fees from AstraZeneca, Menarini, Gilead Sciences, and Roche. MGG reports consulting fees from Esteve; honoraria from Pfizer, AstraZeneca, and Daiichi Sankyo; travel funding from Roche, AstraZeneca, Pfizer, and Novartis; and advisory board fees from AstraZeneca, Menarini, and Gilead. MRB reports speaker grants from Novatis, Lilly, AstraZeneca, Daiichi, Gilead; advisory board fees from AstraZeneca, Daiichi, Novartis; and travel funding from Roche. JG reports scientific advisory board fees from Novartis, AstraZeneca, Daiichi Sankyo, and Gilead; consulting training fees from Roche, Novartis, Seagen, Pfizer, AstraZeneca, Daiichi Sankyo; honoraria from Roche, Novartis, Seagen, Pfizer, AstraZeneca, and Daiichi Sankyo. PS reports consulting/honorarium from AstraZeneca, Bayer, Boehringer Ingelhiem, Merck, Novartis, Pfizer, Puma, Roche, Eisai, and Celgene; grant/institutional funding from Astellas, AstraZeneca, Genetech, Novartis, Oncogenex, Roche, Medivation, and Merck. DW reports personal fees from Pfizer, Roche, Novartis, AstraZeneca, and MSD. SDC reports receiving an institutional grant (IG 20774) from the Fondazione Associazione Italiana per la Ricerca sul Cancro (AIRC); funding from the Cancer Can.Heal European EU4Health Programme (101080009—European Commission) and from the Ministry of Health for the project PNRR-POC-2023-12378113; serving as an '*ad hoc*' medical monitor for Medica Scientia Innovation Research (MEDSIR), Barcelona (Spain); as well as support for attending meetings and/or travel from Daiichi Sankyo, and participation in an advisory board for Pfizer. PC reports receiving honoraria from Pfizer, Roche, Lilly, Daiichi Sankyo, AstraZeneca, Gilead Sciences, Novartis, and NanoString Technologies; consulting fees from Pfizer and Lilly; travel fees from Roche, Pfizer, and Lilly. ES, MF, MSC report MEDSIR employment. JC reports consulting/advisor for Roche, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Lilly, Merck Sharp & Dohme, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, Expres2ion Biotechnologies, Jazz Pharmaceuticals, Abbvie, BridgeBio, Biontech, Biocon, Circle Pharma, Delcath Systems, Inc., Hexagon Bio; honoraria from Roche, Novartis, Eisai, Pfizer, Lilly, Merck Sharp & Dohme, Daiichi Sankyo, AstraZeneca, Gilead, Steamline Therapeutics; research funding to the institution from Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer healthcare, Eisai, F. Hoffman-La Roche, Guardant Health, Merck Sharp & Dohme, Pfizer, Piqur Therapeutics, Iqvia, Queen Mary University of London; stock for MAJ3 Capital, Leuko (relative); travel and accommodation expenses from Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, Gilead, Merck

Sharp & Dohme, Steamline Therapeutics; patents (Pharmaceutical Combinations of a phosphoinositide 3-kinase Inhibitor and a Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. Issued; Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés.US 2019/ 0338368 A1. Licensed). All other authors have declared no conflicts of interest.

DATA SHARING

Data collected within this study will be made available to researchers after contacting the corresponding author and upon revision and approval based on scientific merit by the PARSIFAL-LONG trial management group (which includes a qualified statistician) of a detailed proposal for their use. The data required for the approved, specified purposes, the trial protocol, and the statistical analysis plan will be provided after the completion of a data sharing agreement that will be set up by the study sponsor, beginning 1 month and ending 5 years after article publication. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Estimate timeframe for response will be within 30 days. Please address requests for data to the corresponding author.

REFERENCES

1. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer stat facts: female breast cancer subtypes. Available at https//seer.cancer.gov/statfacts/html/breast-subtypes.html. Accessed June 10, 2024.
2. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol*. 2018;29:1541-1547.
3. Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat*. 2019;174:719-729.
4. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer*. 2019;5:5.
5. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med*. 2022;386:942-950.
6. Goetz MP, Toi M, Huober J, et al. Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2- advanced breast cancer: final overall survival results of MONARCH 3. *Ann Oncol*. 2024;35(8):718-727.
7. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379:1926-1936.
8. Slamon DJ, Diéras V, Rugo HS, et al. Overall survival with palbociclib plus letrozole in advanced breast cancer. *J Clin Oncol*. 2024;42:994-1000.
9. Scheidemann ER, Shajahan-Haq AN. Resistance to CDK4/6 inhibitors in estrogen receptor-positive breast cancer. *Int J Mol Sci*. 2021;22:12292.
10. Andre F, Mills D, Taran T. Alpelisib for PIK3CA-mutated advanced breast cancer. Reply. *N Engl J Med*. 2019;381:687.
11. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in hormone receptor–positive advanced breast cancer. *N Engl J Med*. 2023;388:2058-2070.
12. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. *N Engl J Med*. 2012;366:520-529.
13. Bidard F-C, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol*. 2022;40(28):3246-3256.
14. Robson M, Im S-A, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377:523-533.
15. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med*. 2018;379:753-763.
16. Miglietta F, Griguolo G, Bottosso M, et al. Evolution of HER2-low expression from primary to recurrent breast cancer. *NPJ Breast Cancer*. 2021;7:137.
17. Tarantino P, Gandini S, Nicolò E, et al. Evolution of low HER2 expression between early and advanced-stage breast cancer. *Eur J Cancer*. 2022;163:35-43.
18. Bardia A, O'Shaughnessy J, Bidard F-C, et al. Abstract PS17-02: Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with ESR1 mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial. *Cancer Res*. 2024;84:PS17-02.
19. Llombart-Cussac A, Pérez-García JM, Bellet M, et al. Fulvestrant-palbociclib vs letrozole-palbociclib as initial therapy for endocrine-sensitive, hormone receptor–positive, ERBB2-negative advanced breast cancer: a randomized clinical trial. *JAMA Oncol*. 2021;7:1791-1799.
20. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375:1925-1936.
21. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med*. 2016;375:1738-1748.
22. Grinshpun A, Tolaney SM, Burstein HJ, Jeselsohn R, Mayer EL. The dilemma of selecting a first line CDK4/6 inhibitor for hormone receptor-positive/HER2-negative metastatic breast cancer. *NPJ Breast Cancer*. 2023;9:15.
23. DeMichele A, Cristofanilli M, Brufsky A, et al. Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2− metastatic breast cancer in US real-world clinical practice. *Breast Cancer Res*. 2021;23:37.
24. Rugo HS, Brufsky A, Liu X, et al. Real-world study of overall survival with palbociclib plus aromatase inhibitor in HR+/HER2− metastatic breast cancer. *NPJ Breast Cancer*. 2022;8:114.
25. Palmieri C, Musson A, Harper-Wynne C, et al. A real-world study of the first use of palbociclib for the treatment of advanced breast cancer within the UK National Health Service as part of the novel Ibrance® Patient Program. *Br J Cancer*. 2023;129:852-860.
26. Thill M, Zahn M-O, Welt A, et al. Abstract PO1-04-12: Palbociclib versus ribociclib in first-line treatment of patients with hormone-receptor positive HER2 negative advanced breast cancer – real world outcome data from the German registry platform OPAL. *Cancer Res*. 2024;84:PO1-04-12-PO1-04-12.
27. Llombart-Cussac A, Pérez-Garcia JM, Ruiz Borrego M, et al. Preventing alpelisib-related hyperglycaemia in HR+/HER2−/PIK3CA-mutated advanced breast cancer using metformin (METALLICA): a multicentre, open-label, single-arm, phase 2 trial. *EClinicalMedicine*. 2024;71:102520.
28. Llombart Cussac A, Perez Garcia J, Borrego M, et al. 220P Impact of time to progression (TTP) on CDK4/6 inhibitor (CDK4/6i) therapy on progression-free survival (PFS) in HR+/HER2-/PIK3CA-mutated advanced breast cancer (aBC) patients (pts) treated with alpelisib plus endocrine therapy (ALP+ET): an exploratory analysis of the METALLICA trial. *ESMO Open*. 2024;9:103242.
29. Cardoso F, Paluch-Shimon S, Schumacher-Wulf E, et al. 6th and 7th International consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). *Breast*. 2024;76:103756.