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Palbociclib plus letrozole in estrogen receptor-positive advanced/recurrent endometrial cancer: Double-blind placebo-controlled randomized phase II ENGOT-EN3/PALEO trial

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HIGHLIGHTS

- The randomized phase II PALEO trial assessed letrozole ± palbociclib for ER+ advanced/recurrent endometrial cancer.
- Median PFS (primary end point) was 8.3 months with palbociclib–letrozole vs 3.1 months with placebo–letrozole.
- In a landmark analysis at 12 months the PFS hazard ratio was 0.57 (95 % CI, 0.32 to 0.99; $P = .044$).
- Grade ≥ 3 adverse events were more common with palbociclib–letrozole than placebo–letrozole (67 % vs 30 %, respectively).
- Based on these encouraging results, phase III evaluation of letrozole combined with a CDK4/6 inhibitor is planned.

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ABSTRACT

Purpose. The CDK4/6 inhibitor palbociclib inhibits cyclin A, which is overexpressed in endometrial cancer. Combining palbociclib with endocrine therapy improves efficacy in hormone receptor-positive breast cancer. We investigated palbociclib combined with endocrine therapy for estrogen receptor-positive advanced/recurrent endometrial cancer.

Patients and methods. This placebo-controlled double-blind, randomized phase II screening trial (NCT02730429) enrolled women with measurable/evaluable estrogen receptor-positive endometrioid endometrial cancer that was primary metastatic or had relapsed after ≥1 prior systemic therapy. Patients were

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Estrogen receptor-positive
Hormonal therapy
Letrozole
Palbociclib

randomized in a 1:1 ratio, stratified by number of prior chemotherapy lines, measurable versus evaluable non-measurable disease, and prior medroxyprogesterone/megestrol acetate treatment, to receive oral letrozole 2.5 mg on days 1–28 plus either oral palbociclib 125 mg or placebo on days 1–21, repeated every 28 days until disease progression or unacceptable toxicity. The primary end point was investigator-assessed progression-free survival (PFS).

Results. Among 77 patients randomized between February 16, 2017, and December 21, 2018, 73 were treated (36 with palbociclib–letrozole, 37 with placebo–letrozole). Median follow-up was 21.9 (95 % CI, 16.7 to 22.3) months. Median PFS was 8.3 (95 % CI, 4.6 to 11.2) versus 3.1 (95 % CI, 2.7 to 6.8) months, respectively. In a landmark analysis at 12 months the PFS hazard ratio was 0.57 (95 % CI, 0.32 to 0.99; $P = .044$). Grade ≥ 3 adverse events were more common with palbociclib–letrozole (67 %) than placebo–letrozole (30 %), most commonly neutropenia (44 % *v* 0 %, respectively).

Conclusion. These results support a potential role of the palbociclib–letrozole combination as treatment for hormone receptor-positive advanced/recurrent endometrial cancer. Based on these encouraging results, phase III evaluation of letrozole combined with a CDK4/6 inhibitor is planned.

Clinical trial information. NCT02730429

1. Introduction

Patients with advanced endometrial cancer have a dismal prognosis and high unmet needs. Traditionally, systemic treatment has included chemotherapy and hormonal therapy [1–3]. Until recently, treatment decision-making was driven by histologic subtype. Approximately 90 % of endometrioid endometrial cancers are estrogen receptor (ER) positive [4]. For women with slowly progressing hormone receptor-positive endometrial cancer, endocrine therapy (particularly progestogens, including oral medroxyprogesterone acetate [MPA]) is the preferred front-line systemic therapy for metastatic disease, based on benefit/risk profile and convenience [3,5–7]. Aromatase inhibitors, tamoxifen, and fulvestrant may also be considered [7]. In the GOG-3007 non-comparative randomized phase II trial evaluating the mTOR inhibitor everolimus plus letrozole versus hormonal therapy (MPA and tamoxifen) for advanced/persistent/recurrent endometrial cancer, objective response rates (primary end point) were similar in the two treatment arms but progression-free survival (PFS) appeared to be longer with everolimus–letrozole than with hormonal therapy alone, particularly in chemotherapy-naive patients [8].

The present trial was designed before availability of The Cancer Genome Atlas (TCGA) classification or randomized data demonstrating the efficacy of immune checkpoint blockade. At the time there was no standard regimen after failure of platinum-containing chemotherapy, there were no targeted therapies, and cure remained elusive [5,9–11]. Today, there remains a great need for better therapies, particularly non-chemotherapy options offering long-term disease control while avoiding negative impacts on quality of life. In this context, agents targeting cell-cycle checkpoints have attracted interest in endometrial cancer.

The interplay between cyclins and cyclin-dependent kinases (CDKs) drives the mammalian cell cycle; dysregulation of this process is one of the hallmarks of cancer [12,13]. The CDK cyclin A, which is highly expressed in endometrial cancer, is involved in the transition from G1 to S phase and G2 to M phase [14]. CDK4 expression is also increased in endometrioid endometrial cancers and appears to be an early event of neoplastic transformation [15]. The CDK4/6 inhibitor palbociclib is an established treatment for hormone receptor-positive advanced breast cancer, significantly improving PFS when combined with letrozole [16]. Preclinical studies suggest that CDK4/6 inhibition is effective in endometrial cancers, particularly those with cyclin D aberrations [17], and may help to overcome resistance to endocrine therapy associated with cyclin D dependence. Therefore, we initiated the first global randomized trial evaluating the activity of palbociclib combined with letrozole for advanced/recurrent ER-positive endometrial cancer.

2. Patients and methods

ENGOT-EN3/PALEO (ClinicalTrials.gov, NCT02730429) was a European Network of Gynecological Oncological Trial groups and Gynecological Cancer InterGroup multicenter double-blind placebo-controlled randomized phase II trial sponsored and led by the Nordic Society of Gynecological Oncology Clinical Trials Unit (NSGO-CTU). The trial was conducted in 25 academic centers representing NSGO-CTU (Denmark, Finland, Norway), North-Eastern German Society of Gynecological Oncology (NOGGO; Germany), Grupo Español de Investigación en Cáncer de Ovario (GEICO; Spain), and Multicentre Italian Trial in Ovarian cancer (MITO; Italy) (Appendix) in compliance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Local regulatory and ethics boards in each country approved the protocol and informed consent form. An independent data monitoring committee oversaw the study through regular safety data reviews to ensure patient safety.

Eligible patients had endometrioid endometrial cancer that was ER positive (≥10 % expression by immunohistochemistry) and measurable or evaluable by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients had to have primary stage 4 disease or disease progression after at least one prior systemic therapy. Except for MPA or megestrol acetate, previous endocrine therapies were prohibited. The proportion of patients previously treated with MPA or megestrol acetate was capped at 50 % (39 patients). Prior CDK inhibitor therapy was not permitted. Patients had to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, serum albumin ≥30 g/L, adequate bone marrow, renal, and hepatic function, and life expectancy ≥12 weeks, and be considered fit to receive combination therapy. All patients provided written informed consent before enrollment.

Eligible patients were randomly assigned in a 1:1 ratio using a third-party randomization system (KFE Herlev and Mainz University Pharmacy, Germany), with allocation communicated via fax and e-mail. The three stratification factors were: number of prior chemotherapy lines (0 [primary advanced disease] *v* 1 [first relapse] *v* ≥ 2 [second or later relapse]); disease measurability (measurable *v* evaluable non-measurable per RECIST); and prior MPA/megestrol acetate use (yes *v* no). Palbociclib and placebo capsules were identical and presented in the same packaging to ensure blinding to study medication. Treatment assignment was unknown to the patients, study staff, and sponsor until database lock. Unblinding to choose post-progression anticancer therapy was prohibited.

Patients were randomly assigned to receive oral letrozole 2.5 mg on days 1–28 combined with either oral palbociclib 125 mg or placebo on

days 1–21, with cycles repeated every 28 days until disease progression, unacceptable toxicity, deterioration to ECOG PS ≥3, or consent withdrawal. Post-study therapy was at the investigators' discretion.

In the event of any grade 3 non-hematologic toxicity (except nausea or vomiting), both study drugs were withheld until symptoms resolved to grade ≤ 1. The protocol (available online) provides details of dose adjustments for hematologic toxicity. There were no letrozole dose reductions, but the palbociclib/placebo dose was reduced to 100 mg at the first reduction (nadir absolute neutrophil count values of $<0.5 \times 10$ [9]/L for >7 days or $< 0.1 \times 10$ [9]/L for >5 days; platelets $<25 \times 10$ [9]/L; or febrile neutropenia) and 75 mg at the second. If patients experienced further grade 3/4 toxicity after the second dose reduction, palbociclib was discontinued permanently and letrozole continued alone. Treatment was discontinued permanently for any grade 4 non-hematologic adverse event (AE; except nausea or vomiting) and withheld for any grade 3 non-hematologic toxicity (except nausea or vomiting) until resolved to grade ≤ 1.

Tumors were assessed by computed tomography scan of the chest, abdomen, and pelvis within 14 days preceding randomization and of the abdomen and pelvis every 12 weeks from the start of study therapy. Magnetic resonance imaging or positron emission tomography/computed tomography scanning was permitted, providing the same assessment method and technique were used throughout the trial. Patients completed the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30; version 3.0) and Quality-of-Life Questionnaire Endometrial Cancer Module (QLQ-EN24) at baseline and before treatment administration every 12 weeks, at the end-of-treatment visit, and 3 and 6 months after the end of treatment. AEs were recorded at every cycle until 28 days after the last dose of study therapy, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

The primary end point was investigator-assessed PFS, defined from the date of randomization to the date of progression or death. If a patient was lost to follow-up or withdrew consent, PFS was censored at the last time point when the patient was known to be alive without progression. The planned sample size was 78 patients. Estimation of the assumed PFS was somewhat arbitrary because of the heterogeneous nature of the study population, including all lines of treatment and allowing patients with prior MPA/megestrol acetate treatment. Assuming a median PFS of 5 months (anticipating that 50 % of enrolled patients would have primary stage 4 disease), the trial had 80 % power to detect a target hazard ratio of 0.625 (representing an increase in median PFS from 5 to 8 months) with a one-sided alpha of 15 % after events in 68 patients and accrual over 18 months. During the study follow-up before unblinding, these assumptions were revised because of the lower-than-expected PFS event rate (slowing to one event every 2 months). By February 2020, PFS events had been recorded in 58 patients. At that time, six patients without events had received more than 20 cycles of therapy. As median PFS with placebo–letrozole was shorter than anticipated, probably explained by the lower-than-expected proportion of treatment-naive patients enrolled, the independent data monitoring committee considered it reasonable to perform the primary analysis after 58 rather than 68 events. This would provide 80 % power with a one-sided alpha of 15 % (corresponding to a two-sided 30 % level of significance), assuming a median PFS of 4.8 instead of 5 months in the control arm and study follow-up of 41 months, representing little loss of sensitivity compared with the initial design. Additionally, given these changes and the short median PFS in the control arm, the primary analysis was modified to a landmark analysis at 12 months to capture the treatment effect in the clinically relevant population of patients with PFS events, with less emphasis on the tail of the curve where patients in both treatment groups had long-term disease stabilization.

Secondary end points included objective response rate per RECIST version 1.1, disease control rate (complete or partial response, or stable disease for ≥12 weeks), time to first subsequent therapy/death, time to second progression or death (PFS2), time to second subsequent therapy/death, overall survival (OS), patient-reported outcomes (PROs), safety, and tolerability.

The objective of this randomized phase II screening trial [18] was to obtain preliminary evidence of activity. The primary analysis population for efficacy and safety included all randomized patients who received at least one dose of study treatment. PFS and OS were compared between treatment arms using a multiple Cox regression including the stratification factors as covariates and a stratified log-rank test. If a major deviation from the proportional hazards assumption was observed on visual inspection of the Kaplan–Meier plots, the protocol prespecified that the analysis would be adapted accordingly. Kaplan–Meier estimates are presented with corresponding two-sided 95 % confidence intervals (CIs). PFS2, time to first and second subsequent therapy, and OS were analyzed similarly. The proportions of patients achieving response or

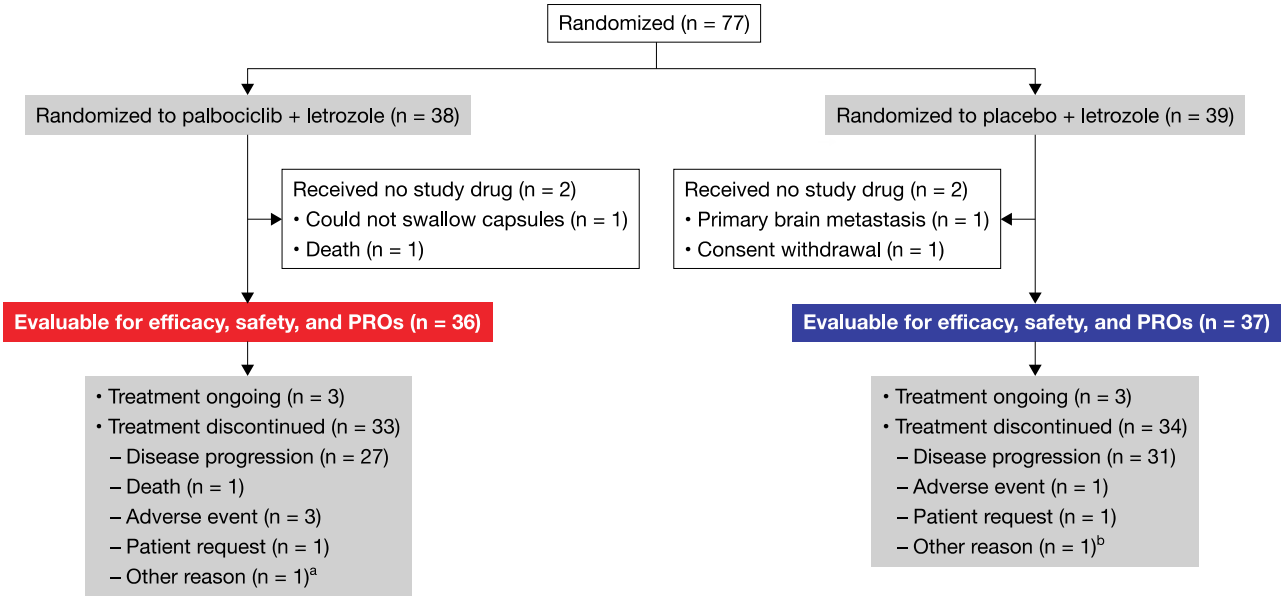


Fig. 1. Patient disposition (data cutoff November 1, 2020). [a]Performance status deteriorated to 3/4. [b]Investigator decision. PRO, patient-reported outcome.

Table 1
Baseline characteristics.

Characteristic, No. of Patients (%)	Palbociclib plus Letrozole ($n = 36$)	Placebo plus Letrozole ($n = 37$)
Median age, years (IQR)	68.5 (63–73)	67 (61–72)
Race, white	36 (100)	37 (100)
Relevant comorbidities		
Previous cancer	1 (3)	3 (8)
Diabetes	6 (17)	3 (8)
Hypertension	19 (53)	18 (49)
Ischemic heart disease	2 (6)	0
ECOG performance status		
0	18 (50)	23 (62)
1	15 (42)	10 (27)
Missing	3 (8)	4 (11)
RECIST status		
Measurable	32 (89)	31 (84)
Non-measurable evaluable	4 (11)	6 (16)
FIGO stage		
I	10 (28)	14 (38)
II	7 (19)	7 (19)
III	9 (25)	7 (19)
IVA	0	2 (5)
IVB	5 (14)	5 (14)
Unknown	5 (14)	2 (5)
Prior vaginal brachytherapy	12 (33)	7 (19)
Prior external beam therapy	13 (36)	15 (41)
Prior megestrol acetate/MPA	4 (11)	7 (19)
Prior chemotherapy setting	30 (83)	29 (78)
Adjuvant	14 (39)	6 (16)
First line	7 (19)	19 (51)
Second line	6 (17)	1 (3)
Third line	0	1 (3)
Other	3 (8)	2 (5)
Missing	6 (17)	8 (22)
Prior adjuvant/first-line chemotherapy		
Prior adjuvant/first-line		
Platinum based	20 (56)	23 (62)
Non-platinum based	1 (3)	1 (3)
Not specified	0	1 (3)
Prior second-line chemotherapy		
Platinum based	5 (14)	1 (3)
Non-platinum based	1 (3)	0
Prior lines of therapy		
0	5 (14)	4 (11)
1	19 (53)	17 (46)
≥2	12 (33)	16 (43)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; MPA, medroxyprogesterone acetate; RECIST, Response Evaluation Criteria in Solid Tumors.

disease control were compared between treatment arms using a Fisher exact test. EORTC QLQ-C30 and QLQ-EN24 were analyzed as described in their corresponding scoring manuals, focusing on global health status/quality of life (GHS/QoL) and symptom scales/items considered particularly relevant to palbociclib.

All subgroup and PRO analyses were exploratory. There was no adjustment for multiple testing. Statistical analyses were done using Stata version 15.0.

3. Results

Between February 16, 2017, and December 21, 2018, 77 patients were enrolled and randomized (38 to palbociclib–letrozole, 39 to placebo–letrozole). Two patients in each arm received no study drug, thus the evaluable populations for efficacy, safety, and PROs included 36 patients in the palbociclib–letrozole arm and 37 in the placebo–letrozole arm (Fig. 1). Baseline characteristics were well balanced between the treatment arms (Table 1). Comorbidities were relatively frequent and one-third of patients had received ≥2 prior lines of therapy.

At the data cutoff for the primary analysis (May 15, 2020; median follow-up 21.9 [95 % CI, 16.7 to 22.3] months), 28 (78 %) of 36 patients treated with palbociclib–letrozole and 31 (84 %) of 37 treated with placebo–letrozole group had experienced disease progression or died. Median PFS was 8.3 (95 % CI, 4.6 to 11.2) months with palbociclib–letrozole versus 3.1 (95 % CI, 2.7 to 6.8) months with placebo–letrozole. In the landmark analysis at 12 months the hazard ratio was 0.57 (95 % CI, 0.32 to 0.99; $P = .044$) (Fig. 2A). Subgroup analyses of PFS according to stratification factors are shown in Fig. 2B.

At 26 weeks, 21 of 33 evaluable patients (64 %, 95 % CI, 45 to 80 %) treated with palbociclib–letrozole achieved disease control compared with 14 of 37 (38 %, 95 % CI, 22 to 55 %) treated with placebo–letrozole. Overall response rates were 9 % (95 % CI, 2 to 24 %) with palbociclib–letrozole and 16 % (95 % CI, 6 to 32 %) with placebo–letrozole.

At the time of the primary PFS analysis, OS results were immature. The final analysis was performed after study closure (data cutoff November 1, 2020) to provide more mature results. By this date, 34 deaths (47 %) had been recorded. The 1-year OS rates were 71 % with palbociclib–letrozole and 78 % with placebo–letrozole; 2-year OS rates were 49 % and 48 %, respectively. The OS hazard ratio was 1.15 (95 % CI, 0.58 to 2.26). An exploratory analysis showed a PFS hazard ratio of 0.71 (95 % CI 0.43–1.19; Fig. 2C). Results for secondary efficacy end points are summarized in Fig. 3.

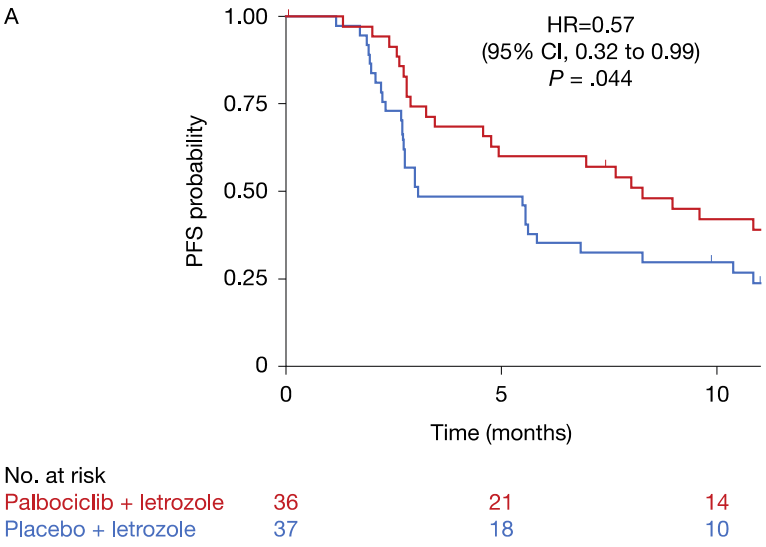
Compliance with PRO assessment was 97 % in the palbociclib–letrozole group and 95 % in the placebo–letrozole group at the first assessment, but fell below 50 % after the fourth assessment timepoint. At baseline, mean QLQ-C30 GHS/QoL was similar in the two groups, at 63.8 (standard deviation [SD] 24.3) in the palbociclib–letrozole group versus 61.0 (SD 23.2) in the placebo–letrozole group. GHS/QoL remained stable over time and showed no difference between treatment arms (Appendix Fig. 1 A). There was also no difference between treatment arms in QLQ-EN24 gastrointestinal symptoms (Appendix Fig. 1B) or other relevant scales (data not shown).

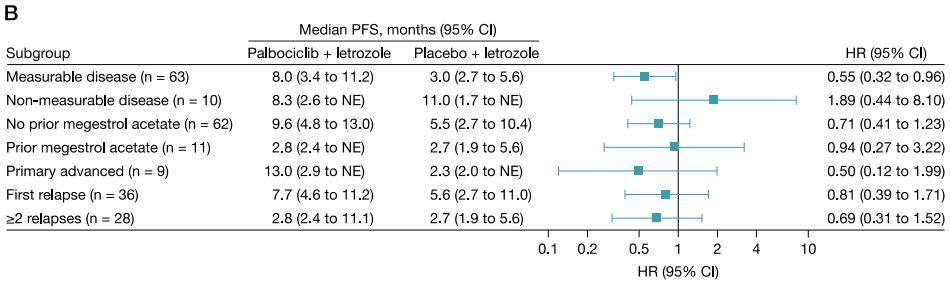
By the final data cutoff date, all but six patients (three in each arm) had discontinued treatment, primarily because of disease progression (Fig. 1). Table 2 summarizes treatment exposure. Grade 3/4 AEs were more common with palbociclib–letrozole (67 %) than placebo–letrozole (30 %). There were no grade 5 AEs. Palbociclib-containing therapy was associated with higher incidences of all-grade hematologic AEs (neutropenia, leucopenia, and anemia) and of grade ≥ 3 neutropenia, leucopenia, anemia, hypertension, and pneumonia (Table 3). The incidences of other AEs were similar in the two treatment arms. AEs led to discontinuation of all treatment in three patients (8 %) in the palbociclib–letrozole group and none in the placebo–letrozole group.

Treatment after progression on study therapy showed some imbalances between treatment groups: in particular, immunotherapy was administered as first subsequent therapy more often in the placebo–letrozole than the palbociclib–letrozole arm (19 % *v* 6 %, respectively), and more patients in the placebo–letrozole arm received chemotherapy in the second subsequent line (16 % *v* 3 %, respectively) (Appendix Table A2).

4. Discussion

This is the first randomized trial to evaluate the activity of a CDK4/6 inhibitor in combination with an aromatase inhibitor in patients with advanced/recurrent ER-positive endometrial cancer. Compared with placebo–letrozole, the palbociclib–letrozole combination demonstrated a statistically significant (at the one-sided 15 % level) and clinically meaningful PFS improvement, meeting the primary objective and demonstrating preliminary evidence of activity. Notably, the treatment effect in patients at second or later relapse appeared similar to that in patients at first relapse.





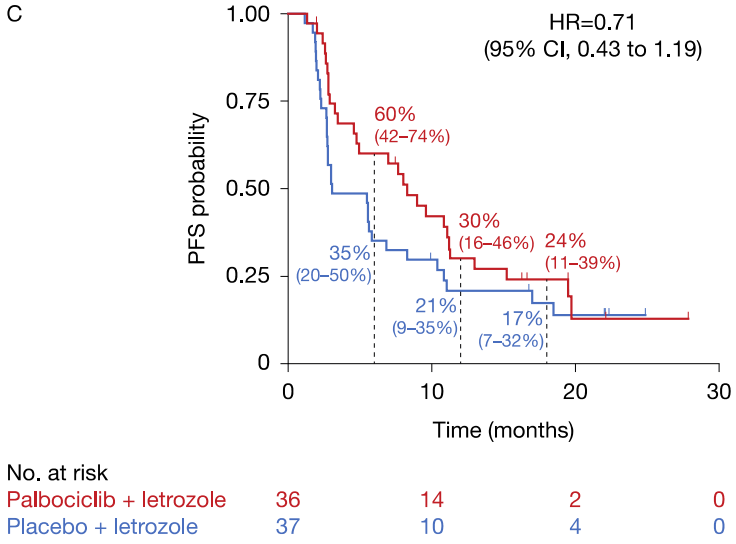


Fig. 2. Progression-free survival (landmark analysis at 12 months). (A) Intent-to-treat population (primary end point). (B) Subgroup analyses of PFS according to stratification factors. (C) Updated analysis of PFS (data cutoff November 1, 2020). CI, confidence interval; HR, hazard ratio; NE, not evaluable; PFS, progression-free survival.

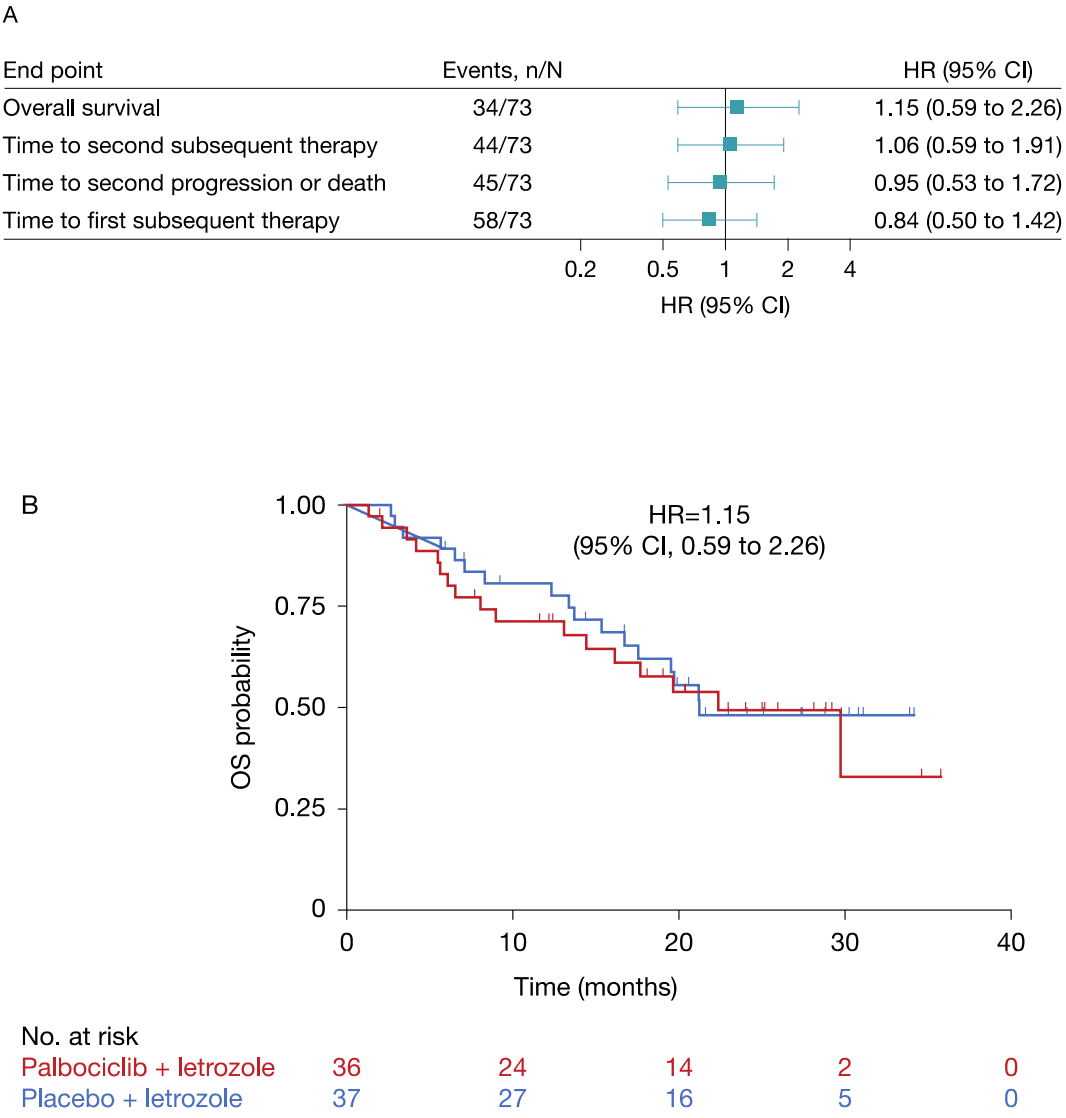


Fig. 3. Secondary efficacy end points (data cutoff November 1, 2020). A) Overview of all secondary efficacy end points. B) Overall survival. CI, confidence interval; HR, hazard ratio.

Table 2
Summary of treatment exposure (Data Cutoff November 1, 2020).

No. of Patients (%)	Palbociclib plus Letrozole (n = 36)	Placebo plus Letrozole (n = 37)
Number of cycles of letrozole interrupted		
0	32 (89)	31 (84)
1	3 (8)	6 (16)
2	1 (3)	0
Number of cycles of palbociclib/placebo interrupted		
0	26 (72)	31 (84)
1	7 (19)	6 (16)
2	1 (3)	0
≥3	2 (6)	0
Number of palbociclib/placebo dose reductions		
None	23 (64)	36 (97)
Reduction to 100 mg	13 (36)	1 (3)
Reduction to 75 mg	6 (17)	0
Treatment discontinuations		
Palbociclib/placebo	9 (25)	5 (14)
Letrozole	7 (19)	4 (11)

Table 3
Most common adverse events (any grade in >20 % of patients, grade ≥ 3 in >5 % of patients; data cutoff November 1, 2020).

No. of Patients (%)	Palbociclib plus Letrozole (n = 36)		Placebo plus Letrozole (n = 37)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any	32 (89)	24 (67)	28 (76)	11 (30)
Neutropenia	24 (67)	16 (44)	1 (3)	0
Pain	14 (39)	3 (8)	13 (35)	4 (11)
Anemia	13 (36)	3 (8)	2 (5)	1 (3)
Leucopenia	9 (25)	2 (6)	0	0
Nausea	8 (22)	1 (3)	11 (30)	0
Constipation	8 (22)	0	9 (24)	0
Asthenia	8 (22)	1 (3)	6 (16)	0
Diarrhea	7 (19)	0	9 (24)	0
Fatigue	5 (14)	0	10 (27)	2 (5)
Hypertension	5 (14)	2 (6)	1 (3)	0
Pneumonia	5 (14)	2 (6)	0	0
Arthralgia	4 (11)	1 (3)	9 (24)	1 (3)
Pulmonary embolism	0	0	2 (5)	2 (5)

Interestingly, the PFS benefit did not appear to translate to an OS benefit, with the 95 % CI for the hazard ratio crossing 1. Although there was minimal crossover to palbociclib in the placebo–letrozole arm, the observed imbalance in post-study therapy, in particular higher use of immunotherapy as first subsequent therapy in placebo–letrozole arm, is a likely explanation for the lack of OS improvement with palbociclib.

These results provide proof-of-concept for the combination and demonstrate activity versus standard-of-care therapy in this setting. In PALEO and previous randomized phase II trials [8,11] median PFS with endocrine therapy alone was a disappointing 2 to 4 months. The median PFS exceeding 8 months with palbociclib–letrozole compares favorably with a median PFS of 1 to 4 months reported in phase II trials of MPA, tamoxifen and other selective ER modulators, aromatase inhibitors, and selective ER degraders [19,20], although cross-trial comparisons are particularly difficult given the mixed patient population enrolled in the PALEO trial. More recently, two small phase II studies of abemaciclib combined with letrozole or fulvestrant have demonstrated median PFS of approximately 9 months [21,22], further supporting the role of endocrine plus CDK4/6 inhibitor combinations.

The safety profile of palbociclib–letrozole was as predicted from experience in breast cancer [23], with no new signals. The most common AE was neutropenia (grade 3/4 in 44 % of patients treated with palbociclib–letrozole *v* 0 % with placebo–letrozole). In breast cancer, hematologic toxicities with palbociclib tend to appear in early cycles and rarely lead to treatment discontinuation [23–25]. In our trial, 13 patients required dose reductions; adjusting the dosing regimen may reduce the incidence of dose-limiting hematologic toxicity in future trials. However, there was high treatment adherence and PROs showed no relevant negative impact of palbociclib on gastrointestinal symptoms, which might be expected to worsen with palbociclib. Overall, PROs showed no detrimental effect from the combination that would counter any potential efficacy benefit, but in the treatment (versus maintenance) setting, where the goal is symptom relief, the lack of beneficial effect on PRO improvement could be considered a negative outcome.

The main limitations of this randomized phase II trial include the relatively small sample size, resulting in underpowered subgroups, and the heterogeneity of the patient population (except that all patients were white). This reflects the population presenting in clinical practice but brings challenges to assumptions when designing the trial and caveats when trying to consider the results alongside historical trials. The comparator may have underperformed in this extensively pretreated population, but investigators enrolling patients into the trial apparently deemed the control regimen suitable. Furthermore, some patients had very long-term disease control, indicated by the long tail of the PFS curves despite selecting patients with positive biomarker status. The 10 % cutoff for ER positivity may be challenged, but unlike breast cancer, there is no global consensus on the cutoff and in clinical practice and prospective trials (e.g., PARAGON) in ER-positive endometrial cancer, a 10 % cutoff is frequently used [26–30]. Recent work supports a 10 % cutoff, showing greater discrimination than with a 1 % cutoff [28]. In addition, some may question the choice of CDK4/6 inhibitor given the totality of data in breast cancer suggesting differences between drugs within this class. However, when the PALEO trial was initiated, the CDK4/6 inhibitor with the most robust evidence in combination with letrozole and at the most advanced stage of clinical development was palbociclib. With hindsight, a different CDK4/6 inhibitor may have been preferable; indeed, further evaluation of this strategy will explore a different regimen.

Since designing PALEO, the diagnosis of endometrial cancer has evolved. Nowadays, molecular classification (requiring three immunohistochemical and one molecular test) is recommended [7], but was unavailable for the patients enrolled in PALEO, representing a limitation of our analyses. Four molecular subgroups with distinct clinical prognoses are recognized. Knowledge of the specific molecular subtype may influence treatment decisions and introduce the possibility of immunotherapy agents. In the second-line setting, options include dostarlimab or pembrolizumab in patients with microsatellite instability-high or mismatch repair deficient endometrial cancer [31,32] or the combination of pembrolizumab and lenvatinib [33]. Most recently, combining dostarlimab with a platinum–paclitaxel doublet has shown benefit regardless of mismatch repair status [34,35]. In the first-line setting, phase III trials have confirmed the considerable benefit of adding an immune checkpoint inhibitor to a carboplatin–paclitaxel doublet for primary advanced/recurrent disease, although benefit is modest in the mismatch repair-proficient/microsatellite-stable setting, especially in tumors with no specific molecular profile (NSMP) [34–40]. Consequently, patients with NSMP subtype have unmet needs and may represent the molecular subgroup in which hormonal therapy with or without a CDK4/6 inhibitor could have the greatest impact in patients with ER-positive disease. The totality of the data may also suggest that in patients with aromatase inhibitor-naïve highly hormone-dependent disease, a sequential strategy of single-agent aromatase inhibitor followed by combined aromatase inhibitor and CDK4/6 blockade, as used in advanced breast cancer, may be a reasonable strategy. However, the PALEO trial was not designed to explore sequential therapy.

In conclusion, we observed encouraging activity with palbociclib–letrozole in patients with advanced/recurrent ER-positive endometrial cancer. An ongoing open-label randomized two-arm trial (NCT03008408) in the US is evaluating a CDK4/6 inhibitor (ribociclib rather than palbociclib), everolimus, and letrozole triplet therapy in patients with advanced/recurrent endometrial carcinoma. This trial, although only marginally larger than the PALEO trial, may provide supporting evidence for the role of CDK4/6 inhibitors in this setting. Nevertheless, there is a clear need for phase III validation of our results accounting for the recent advances in endometrial cancer management including molecular characterization.

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Prior presentation

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CRediT authorship contribution statement

Mansoor R. Mirza: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Line Bjørge:** Writing – review & editing, Resources. **Frederik Marmé:** Writing – review & editing, Resources. **René DePont Christensen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Marta Gil-Martin:** Writing – review & editing, Resources. **Annika Auranen:** Writing – review & editing, Resources. **Beyhan Ataseven:** Writing – review & editing, Resources. **Maria Jesús Rubio:** Writing – review & editing, Resources. **Vanda Salutari:** Writing – review & editing, Resources. **Adam A. Luczak:** Writing – review & editing, Resources. **Ingo B. Runnebaum:** Writing – review & editing, Resources. **Andrés Redondo:** Writing – review & editing, Resources. **Kristina Lindemann:** Writing – review & editing, Resources. **Fabian Trillsch:** Writing – review & editing, Resources. **M. Pilar Barretina Ginesta:** Writing – review & editing, Resources. **Henrik Roed:** Writing – review & editing, Resources. **Jean-Emmanuel Kurtz:** Writing – review & editing, Methodology. **Karen S. Petersson:** Writing – review & editing, Project administration. **Gitte-Bettina Nyvang:** Writing – review

& editing, Resources. **Jalid Sehouli:** Writing – review & editing, Resources.

Declaration of competing interest

MRM reports leadership roles and stock for Karyopharm Therapeutics and Sera Prognostics; honoraria from Roche, AstraZeneca, Genmab/Seattle Genetics, GSK, Merck, Mersana, Takeda, Zai Lab, Geneos, and Allarity Therapeutics; consulting/advisory roles for AstraZeneca, Genmab, Karopharm Therapeutics, Pfizer, and GSK; research funding (to institution) from AstraZeneca, Boehringer Ingelheim, Pfizer, Tesaro, Clovis Oncology, Ultimovacs, Apexigen, and GSK; grants and personal fees from Tesaro, AstraZeneca, Pfizer, and Clovis Oncology; travel/accommodation/expenses from AstraZeneca, Karyopharm Therapeutics, Pfizer, Roche, Tesaro, and SeraCare; and other relationships with ENGOT, GCIG, and ESGO. LB reports speaker's bureau participation for GSK and MSD and research funding from AstraZeneca. FM reports honoraria from Roche/Genentech, Novartis, Pfizer, AstraZeneca, Clovis Oncology, Eisai, Genomic Health, PharmaMar, Amgen, MSD Oncology, Seagen, Myriad Genetics, Pierre Fabre, GSK, Agendia, Lilly, Gilead, Daiichi Sankyo, and Immunomedics; consulting/advisory roles for Pfizer, Genomic Health, CureVac, Amgen, Eisai, GSK, Gilead, Seagen, Clovis Oncology, AstraZeneca, Roche, Vaccibody, and Immunomedics; research funding from Roche/Genentech, Novartis, AstraZeneca, Tesaro, Clovis Oncology, MSD Oncology, Vaccibody, Gilead, and GSK; and travel/accommodation/expenses from Roche, Pfizer, AstraZeneca, and Gilead Sciences. RdPC reports employment and stock ownership from Y-mAbs Therapeutics and consulting/advisory role for Karyopharm. MGM reports consulting/advisory roles for AstraZeneca; speakers' bureau for GSK and MSD Oncology; and travel/accommodation/expenses from AstraZeneca, GSK, and MSD Oncology. AA reports consulting/advisory roles and travel/accommodation/expenses from GSK and MSD. BA reports honoraria from Roche, AstraZeneca, MSD, GSK, Eisai Europe, Novartis, Lilly, and Pfizer; consulting/advisory roles for Roche, MSD, Sanofi Aventis GmbH, GSK, and Eisai Europe; and travel/accommodation/expenses from Roche, AstraZeneca, GSK, Lilly, and Daiichi Sankyo/AstraZeneca. VS reports honoraria from AstraZeneca, MSD Oncology, GSK, PharmaMar, and Novocure; consulting/advisory roles for AstraZeneca and Novocure; and travel/accommodation/expenses from GSK and PharmaMar. AR reports consulting/advisory roles for AstraZeneca, GSK, Boehringer Ingelheim, MSD, and Pharma&; speakers' bureau for AstraZeneca, GSK, MSD, and Pharma&; and travel/accommodation/expenses from AstraZeneca. KL reports honoraria from AstraZeneca; consulting/advisory roles for Eisai, MSD, GSK, and Nycode; research funding (inst) from GSK; and is Deputy Medical Director of NSGO-CTU. FT reports research funding and personal fees from AstraZeneca, Clovis, Eisai, ImmunoGen, MSD, SAGA diagnostics, and Tesaro/GSK. MPBG reports consulting/advisory roles for AstraZeneca, GSK, MSD Oncology, Eisai Europe, Clovis Oncology, PharmaMar, and Pharma&; speakers' bureau for AstraZeneca Spain, GSK, Eisai Europe, and MSD Oncology; and travel/accommodation/expenses from AstraZeneca, GSK, and MSD Oncology. JEK reports employment (immediate family member) with MSD; consulting/advisory roles for AstraZeneca, MSD, and GSK; and travel/accommodation from AstraZeneca, Eisai, PharmaMar, and GSK. JS reports honoraria from AstraZeneca, Eisai, Clovis Oncology, Olympus Medical Systems, Johnson & Johnson, PharmaMar, Pfizer, Teva, Tesaro, MSD Oncology, GSK, and Bayer; consulting/advisory roles for AstraZeneca, Clovis Oncology, PharmaMar, Merck, Pfizer, Tesaro, MSD Oncology, Lilly, Novocure, Johnson & Johnson, Roche Diagnostics, NGRESS-Health, Riemser, Sobi, GSK, Novartis, and Alkermes; research funding (inst) from AstraZeneca, Clovis Oncology, Merck, Bayer, PharmaMar, Pfizer, Tesaro, MSD Oncology, and Roche; travel/accommodation/expenses from AstraZeneca, Clovis Oncology, PharmaMar, Roche Pharma AG, Tesaro, MSD Oncology, and Olympus. No other potential conflicts of interest were reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.12.003.

Data availability

No mechanism is yet in place to allow sharing of individual deidentified patient data. Requests sent to Mansoor Raza Mirza, Medical Director, NSGO, Department of Oncology, Rigshospitalet, Copenhagen University Hospital, DK2100 Copenhagen, Denmark, or Mansoor.Raza.Mirza@regionh.dk will be considered on a case-by-case basis.

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