IBCSG 59-19 / BIG 18-02

POLAR

A phase III open-label, multicenter, randomized trial of adjuvant palbociclib in combination with endocrine therapy versus endocrine therapy alone for patients with hormone receptor positive / HER2-negative resected isolated locoregional recurrence of breast cancer

Palbociclib for HR positive / HER2-negative Isolated Locoregional Recurrence of Breast Cancer (POLAR)

EU CT number:	**2024-510776-20**
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Sponsor:	**ETOP IBCSG Partners Foundation**

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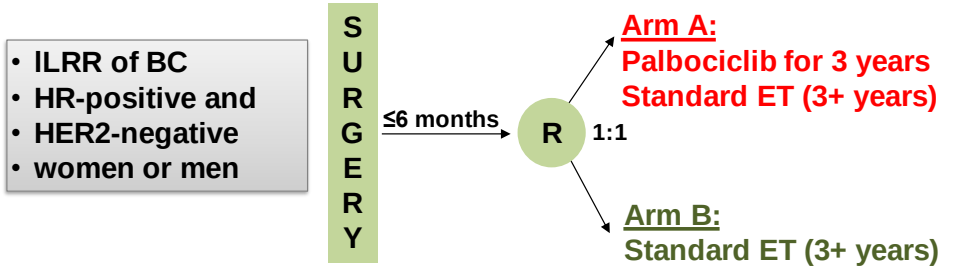
Amendment 2

Protocol Version 3.0

14 January 2025

1. Protocol summary

Title	**A phase III open-label, multicenter, randomized trial of adjuvant palbociclib in combination with endocrine therapy versus endocrine therapy alone for patients with hormone receptor positive / HER2-negative resected isolated locoregional recurrence of breast cancer** **Palbociclib for HR positive / HER2-negative Isolated Locoregional Recurrence of Breast Cancer (POLAR)**
Clinical Phase	Randomized Phase III
Patient population	Female or male patients with histologically confirmed HR-positive, HER2-negative resected isolated locoregional recurrence (ILRR) of breast cancer.
Trial Design	 Palbociclib 125 mg/day orally for 21 days, followed by 7 days rest for 3 years Standard endocrine therapy (as per local practice) –May consist of AI, fulvestrant or SERM, ±LHRH analog if premenopausal or male –Can have already started at time of randomization –Protocol endocrine therapy duration is **at least 3 years** from randomization –Patients are encouraged to continue ET beyond 3 years, according to Investigator's decision Surgery –Randomization must take place within 6 months from the complete gross excision of the isolated locoregional recurrence.
Treatment	Patients will be randomized in a 1:1 ratio to: **Arm A** • Palbociclib 125 mg/day orally for 21 days, followed by 7 days rest for 3 years from randomization. • Standard endocrine therapy for at least 3 years from randomization **Arm B** • Standard endocrine therapy for at least 3 years from randomization → Randomization must take place within 6 months from the complete gross excision of the locoregional recurrence.

	→ Radiotherapy (if given) for the ipsilateral locoregional recurrence must be completed more than 2 weeks prior to randomization.
Background and Rationale	Local or regional recurrence of breast cancer after mastectomy or lumpectomy indicates a poor prognosis, and accompanies or precedes distant metastasis in a high proportion of patients. Patients with isolated locoregional recurrences (ILRR), without evidence of distant metastasis hold a substantial risk of developing subsequent distant metastasis, with 5-year survival probabilities ranging between 45% and 80% after locoregional recurrence [1,2]. These outcomes show the powerful negative prognostic importance of ILRR events and the need for treatments beyond surgical removal of the ILRR. Adjuvant chemotherapy and endocrine therapies reduce the risk of relapse and death in patients with primary breast cancer. However, few data are available to inform the recommendation of systemic treatment for locoregional recurrence. The Swiss Group for Clinical Cancer Research randomized Trial SAKK 23/82 showed an increase in disease-free survival with the use of tamoxifen after locoregional recurrence in hormone-responsive patients who had undergone a mastectomy [3]. The IBCSG carried out the CALOR trial, Chemotherapy as Adjuvant for Locally Recurrent breast cancer (IBCSG 27-02 / BIG 1-02 / NSABP B-37), in collaboration with the Breast International Group (BIG) and the National Surgical Adjuvant Breast and Bowel Project (NSABP), to establish whether chemotherapy improves the outcome of patients with ILRR [4]. The CALOR trial accrued 162 patients from 54 hospitals, 85 patients were randomly assigned to receive chemotherapy and 77 to no chemotherapy. In total, 110 patients had HR+ ILRR. Overall, at a median follow-up of 4.9 years, 5-year disease-free survival (DFS) was 69% (95% CI 56–79) in the chemotherapy group compared with 57% (44–67) in the no chemotherapy group (HR 0.59 [95% CI 0.35–0.99]; p=0.046). Overall survival (OS) was also significantly longer in the chemotherapy group: 5-year OS 88% (95% CI 77–94) vs.. 76% (63–85) with HR 0.41 (95% CI 0.19–0.89; p=0.024). Patients assigned to chemotherapy for ER-negative ILRR tumors had a greater chance of DFS than did those assigned to no chemotherapy (HR 0.32 [95% CI 0.14–0.73]; 5-year DFS was 67% (95% CI 44–82) in the chemotherapy group vs. 35% (18–53) in the no chemotherapy group. In patients with ER-positive ILRR, the corresponding DFS HR was 0.94 (95% CI 0.47–1.89), and 5-year DFS was 70% (53–81) in the chemotherapy group versus 69% (53–81) in the no chemotherapy group. An updated, final analysis of CALOR after median follow-up of about 9 years was published in the Journal of Clinical Oncology

	in April 2018 [5], which confirmed chemotherapy benefitted patients with resected ER-negative ILRR and did not support the use of chemotherapy for ER-positive ILRR. CALOR results strongly suggest that tailoring treatment according to the disease characteristics of the recurrent lesion, in this case ILRR, provides a better indication of the possible responsiveness to treatment than does relying on the characteristics of the primary tumor. In particular, the different outcomes based on receipt of chemotherapy according to ER status were more striking when we examined cohorts according to ER status in the ILRR than according to ER status in the primary tumor. CDK4 and 6 control transition from the G1 to the S phase of the cell cycle by binding to D type cyclins. A primary target of CDK action is the retinoblastoma susceptibility gene product (Rb), which mediates G1 arrest through sequestration of transcriptional factors of the E2F family. Phosphorylation of Rb (pRb) by active cyclin-CDK complexes leads to release of E2F transcription factors and transcription of requisite genes for S-phase entry. CDK4/6 inhibitors, by inhibiting Rb phosphorylation, induce a cell cycle arrest in Rb proficient cancer cells [6]. CDK4/6 pathway activation is a well-known mechanism of resistance to endocrine therapy [7], indeed CDK4/6 inhibitors have shown activity in cellular models of acquired resistance to endocrine therapies [8]. Palbociclib has been granted FDA approval in the U.S. for the treatment of HR-positive/HER2-negative advanced breast cancer in combination with the hormonal treatments letrozole and fulvestrant given the unprecedented results in terms of efficacy of two pivotal clinical trials (PALOMA-2 and PALOMA-3) [9,10]. Palbociclib and other CDK4/6 inhibitors have also shown a good toxicity profile and therefore are ideal candidates for combination with hormonal therapy. Given the demonstrated activity and safety of palbociclib in the first-line treatment of metastatic HR-positive/HER2-negative breast cancer, there is interest in whether the benefits of CDK4/6 inhibition may translate into the adjuvant setting. The purpose of the ongoing PALLAS study (NCT02513394) is to determine whether the addition of 2-years of palbociclib to adjuvant endocrine therapy will improve outcomes over endocrine therapy alone for HR-positive/HER2-negative early breast cancer. Patients randomized in the PALLAS study have stage II or III early breast cancer and may receive either palbociclib at a dose of 125 mg orally once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for a total duration of 2 years, in addition to standard adjuvant endocrine therapy

for a duration of at least 5 years (Arm A) or standard adjuvant endocrine therapy for a duration of at least 5 years (Arm B).

The reason for prolonged duration of palbociclib in the adjuvant setting (2 years) comes from the evidence of preclinical studies where cell senescence was investigated as an appealing mechanism of cell death and was indeed observed in vitro after exposure of breast cancer cells and tumors to a combination of endocrine therapy and palbociclib [7]. Moreover, in vitro data showed that, after removing palbociclib and/or the anti-ER agent, the cells can eventually re- start to divide. Considering the synergistic mechanism of action with anti-hormonal agents and synergistic signaling through the same CDK4/6 dependent mechanism, it is likely that the anti-proliferative mechanism of action will require longer treatment for optimal antitumor effect. It is therefore hypothesized that the longer patients receive combined treatment with palbociclib and an antiestrogen, the more likely they may derive prolonged clinical benefit.

Based on the results of the CALOR trial and on strong evidence of activity of the combination of CDK4/6 inhibitors and endocrine therapy, we hypothesize that the CDK4/6 inhibitor palbociclib in combination with endocrine therapy may be active as adjuvant therapy in patients with HR-positive/HER2-negative resected isolated locoregional recurrence of breast cancer.

References:

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Primary Objective and Endpoint	To determine whether treatment with 3 years of palbociclib plus standard endocrine therapy for at least 3 years prolongs invasive disease-free survival (iDFS) compared to treatment with standard endocrine therapy alone for at least 3 years in patients with hormone receptor positive, HER2-negative resected isolated locoregional recurrence (ILRR) of breast cancer. The primary endpoint iDFS is defined as duration of time from randomization until first appearance of invasive local, regional, or distant recurrence (including invasive ipsilateral breast tumor recurrence), invasive contralateral breast cancer, a second (non-breast) invasive cancer, or death from any cause.
Secondary Objectives and Endpoints	To assess tolerability of 3 years of palbociclib in combination with standard endocrine therapy compared to standard endocrine therapy alone, as measured by adverse events. To assess whether treatment with 3 years of palbociclib plus standard endocrine therapy for at least 3 years prolongs other measures of efficacy as compared to treatment with standard endocrine therapy alone for at least 3 years in this patient population. The secondary endpoints are: • Adverse events, according to CTCAE version 5 • Breast cancer-free interval (BCFI) • Distant recurrence-free interval (DRFI) • Overall survival (OS)
Sample size and trial duration	The trial will randomize a total of 400 patients. Patients will be enrolled at approximately 35 sites in 5 countries. Enrollment is expected to occur over a period of 3.5 years, assuming accrual of 2 patients/month during months 0-6 as Groups and Centers activate the trial, 6 patients/month during months 6-12, and 12 patients/month thereafter. The targeted number of iDFS events for the primary analysis are expected approximately 1.5 years after the inclusion of the last patient, and a final, updated analysis is planned after approximately 4 years after the inclusion of the last patient.

	Individual patients' trial participation is anticipated until 4 years after inclusion of the last patient. The expected range of participation is therefore 4 to 7.5 years.
Inclusion Criteria	• Histologically confirmed invasive breast cancer, defined as first proven ipsilateral local and/or regional recurrence of a primary invasive breast cancer in at least one of the sites below: – Breast – Chest wall including mastectomy scar and/or skin – Axillary or internal mammary lymph nodes • Completion of locoregional therapy: – Completion of gross excision of recurrence within 6 months prior to randomization – Completion of radiotherapy (if given) more than 2 weeks prior to randomization • Negative or microscopically involved margins • Female or male aged 18 years or older • ECOG performance status 0 or 1 • Recurrent tumor must be hormone receptor positive: ER+ and/or PgR+ ≥1% by IHC • Recurrent tumor must be HER2-negative (0, 1+, 2+ by IHC and/or ISH/FISH not amplified) Tumor with HER2 status 2+ by IHC must also be negative (not amplified) by ISH/FISH • Normal hematological, renal, and liver function • The patient agrees to make tumor (diagnostic core biopsy or surgical specimen of ILRR) available for submission for central pathology review • Patients must either be planned to initiate, or have already started, endocrine therapy for ipsilateral isolated locoregional recurrence • Written Informed Consent (IC) prior to randomization
Exclusion Criteria	• Recurrence of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules) not surgically removable • Evidence of distant metastasis as based on conventional staging examinations (physical, chest X-ray or CT, abdominal ultrasound or CT, bone scintigraphy or FDG-PET-CT). • Bilateral synchronous or metachronous invasive breast cancer (in situ

	carcinoma of the contralateral breast is allowed) • Inflammatory breast cancer • Patients with a history of malignancy, other than invasive breast cancer, with the following exceptions: – Patients diagnosed, treated and disease-free for at least 5 years and deemed by the investigator to be at low risk for recurrence of that malignancy are eligible – Patients with the following malignancies are eligible, even if diagnosed and treated within the past 5 years: ductal carcinoma in situ of the breast; cervical cancer in situ; thyroid cancer in situ; non-metastatic, non-melanomatous skin cancers • Previous treatment with palbociclib or any other CDK 4/6 inhibitors • Previous or planned chemotherapy or planned radiotherapy for the ipsilateral isolated locoregional recurrence (radiotherapy is allowed, but must be completed more than 2 weeks prior to randomization) • Concurrent disease or condition that would make the patient inappropriate for study participation or any serious medical disorder that would interfere with the patient's safety • Contraindications or known hypersensitivity to the palbociclib or excipients • History of extensive disseminated/bilateral or known presence of interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, obliterative bronchiolitis, and pulmonary fibrosis. History of prior radiation pneumonitis is not an exclusion criterion. • Pregnant or lactating women; lactation has to stop before randomization
Assessments	• Treatment visits: – Arm A: every month for 3 months, followed by every 3 months for 3 years – Arm B: every 3 months for 3 years • Blood test every 3 months during the protocol treatment phase Arm A: complete blood count every 2 weeks during cycles 1 and 2, followed by every month while taking palbociclib • Adverse events (CTCAE v5) will be recorded at every treatment visit • All Serious Adverse Events must be notified to ETOP IBCSG Partners Foundation within 24 hours

	• End of treatment visit within 28-60 calendar days after the end of the protocol treatment phase • Follow-up visits: every 6 months
Documentation	Electronic Case Report Forms (eCRFs) must be completed in DFexplore
Randomization and Stratification	Randomization will be in a 1:1 ratio to: **Arm A:** Palbociclib for 3 years plus standard endocrine therapy for at least 3 years **Arm B**: Standard endocrine therapy for at least 3 years Stratification will be performed according to: • Gender and menopausal status (postmenopausal woman vs. premenopausal woman or man) • Planned endocrine therapy for the ipsilateral isolated locoregional recurrence (fulvestrant vs.. oral AI or SERM) Dynamic institution balancing will be used in order to balance randomized assignments within institutions.
Statistical considerations	The trial will enroll 400 patients, who will be stratified and randomized to palbociclib plus standard endocrine therapy (ET), or standard ET alone. Palbociclib plus ET is hypothesized to be superior to ET alone. The assumed accrual rates over approximately 3.5 years are summarized above. The primary objective will determine whether treatment with palbociclib plus standard ET prolongs invasive disease free survival (iDFS) compared to standard ET-alone. In the ET-alone control group, the 3-year iDFS is assumed to be 76% on the basis of CALOR patients who had ER+ ILRRs. The yearly hazards of iDFS events are assumed 0.158, 0.036, 0.077 during years 1, 2, 3 and 0.051 thereafter. After observation of 66 iDFS events, there is 80% power to detect a 50% reduction in hazard (HR=0.50) for palbociclib plus ET versus ET-alone, using a log-rank test with two-sided α=0.05 test. Under the alternative hypothesis, the observation of 66 iDFS events is expected approximately 5 years since the inclusion of the first patient (1.5 years since inclusion of the last patient), assuming 5% drop-out by 1 year and 10% by 6 years. The primary analysis will occur after the observation of 66 iDFS events or maximum of 3 years since inclusion of the last patient. One interim analysis for efficacy is anticipated at 50% information (expected approximately 3 years since the inclusion of the first patient).