CLINICAL STUDY REPORT

Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy

GBG-78 - BIG 1-13 - NSABP-B-54-I
EudraCT No.: 2013-001040-62
FDA IND: 123239

Investigational Product:	**Palbociclib (PD-0332991)**
Indication:	**HR-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy**
Study Protocol:	**Protocol G (Version 11, from 9-Apr-2019)**
Phase:	**III**
Report Version:	**3.0 (28-Apr-2021)**

First Patient Enrolled:	17-Feb-2014
Last Patient Completed (End of treatment):	14-Feb-2019
Data Cut-Off Date:	24-Aug-2020

Coordinating / Principal Investigator:

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Sponsor:

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Date of this report:	22-Mar-2021
First efficacy interim analysis:	21-Apr-2017
Second efficacy interim analysis:	29-Apr-2019

1. APPROVAL SIGNATURES

STUDY TITLE: Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy

STUDY NUMBER: GBG-78 - BIG 1-13 - NSABP-B-54-I (PENELOPE^B)

I, the undersigned, have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE: DATE:

..... 28.04.2021

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Chief Executive Officer
GBG Forschungs GmbH

..... 28.04.2021

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2. SYNOPSIS

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Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy

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UK

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- UPMC Cancer Center McKeesport, 1500 5th Ave, 15132 McKeesport, Adam Brufsky
- Magee Women´s Hospital of UPMC, 300 Halket St, 15213, Pittsburgh, Adam Brufsky
- UPMC Cancer Centers-Passavant (OHA), 9100 Babcock Blvd, 15237 Pittsburgh, Adam Brufsky
- Stefanie Spielman Comprehensive Cancer Center, 1145 Olentangy River Rd, 43213 Columbus, William Farrar
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- Western Pennsylvania Hospital dba West Penn Hospital, 4800 Friendship Ave, 15224 Pittsburgh, Thomas Julian
- Joe Arrington Cancer Research and Treatment Center, 4101 22nd Pl, 79410 Lubbock, Ibrahim Shalaby
- VCU Massey Cancer Ctr at Stony Point, 9000 Stony Point Pkwy, 23235 Richmond, Hetal Vachhani
- Long Beach Memorial Medical Center, 2801 Atlantic Avenue, 90806 Long Beach, Bichlien Nguyen
- Cook County Health @ John H Stroger Jr Hospital, 1950 W Polk St, 60612 Chicago, Thomas Lad

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- University Hospitals Cleveland Medical Center, 11100 Euclid Ave, 44106 Cleveland, Robert Shenk
- UHHS Westlake - Seidman Cancer Center, 960 Clague Rd, 44145 Westlake, Robert Shenk
- UHHS Chagrin Highlands - Seidman Cancer Center, 3909 Orange Pl, 44122 Orange Ville, Robert Shenk
- Houston Methodist Hospital, Cancer Ctr, 6445 Main St, 77030 Houston, Jenny Chang
- Avera Cancer Institute-Sioux Falls, 1000 E 23rd St, 57105 Sioux Falls, Amy Krie
- Western States Cancer Research, 1325 S Colorado Blvd, 80222 Denver, Keren Sturtz
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- UC San Deigo Moores Cancer Center, 3855 Health Sciences Dr, 92093 La Jolla, Anne Wallace
- University of California San Francisco, 1825 4th St, 94158 San Francisco, Hope Rugo
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- Hennepin County Medical Center, 701 Park Ave, 55415 Minneapolis, Michaela Tsai
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Publication (reference):

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https://pubmed.ncbi.nlm.nih.gov/33793299/

Studied Period (years):

Date of the first patient enrolled:	17-Feb-2014
Date of the last patient completed (End of Treatment):	14-Feb-2019
Data cut-off date:	24-Aug-2020

Phase of Development:

Phase III

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Objectives:

Primary Objectives:

Primary objective of the study was to compare invasive disease-free survival (iDFS) for palbociclib vs. placebo in patients with residual invasive breast cancer and high clinical-pathologic stage – estrogen/grade (CPS-EG) score after neoadjuvant chemotherapy receiving standard adjuvant endocrine therapy for hormone receptor (HR)-positive/ human epidermal growth factor receptor (HER2)-normal primary breast cancer.

Secondary Objectives:

Secondary objectives of the study were the comparison of the two treatment arms with respect to:

- iDFS excluding second primary of non-breast cancers
- Overall survival (OS)
- Distant disease-free survival (DDFS)
- Locoregional recurrences-free (LRRFS) survival
- iDFS per treatment group in patients with luminal-B tumors (as determined by e.g. PAM50 or any other commercially available test at the time of analysis)
- Compliance and safety according to NCI-CTCAE Version 4.0
- Patients reported outcomes
- Health economic outcomes
- To explore drug-drug interaction (DDI) potential for each palbociclib – endocrine combination therapy in a subset of this patient population
- To explore correlations between exposure and efficacy and/or safety findings.

Other Objectives:

Scores and markers were analyzed for their prognostic value in this specific trial setting and their predictive information on the efficacy and/or safety of palbociclib:

- pRB immunoreactive score in residual tumor after neoadjuvant treatment
- Cyclin D immunoreactive score in residual tumor after neoadjuvant treatment
- Residual cancer burden (RCB)
- Clinical response to neoadjuvant chemotherapy
- Incidence and alterations in genes, proteins, and RNAs relevant to the cell cycle (e.g., CCND1 amplification, CDKN2A deletion), drug targets (e.g., CDK 4/6), and tumor sensitivity and/or resistance (Ki-67, pRb, tRB, cyclin E, pi3k, p16, and other markers, measured by optimal test available at the time of analysis) in tumor tissues and/or peripheral blood
- Low and high risk groups (defined by Endopredict®, ROR or other any other available test at the time of analysis)
- Low and high risk groups defined by a standardized image analysis system for Ki-67
- Circulating tumor DNA (ctDNA).

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Methodology:

PENELOPE^{B} was a prospective, international, multicenter, randomized, double blinded, placebo-controlled, parallel-group Phase III study comparing the efficacy and the safety of 13 cycles (1 year) adjuvant treatment with palbociclib versus placebo in high risk (CPS-EG score 3-6 or CPS-EG score 2 and ypN+) patients without pathological complete response after neoadjuvant chemotherapy for hormone-receptor-positive / HER2-normal primary breast cancer. Patients received standard adjuvant endocrine treatment after completion of adequate local surgical and radiotherapeutic treatment. Prior endocrine treatment as part of neoadjuvant treatment was acceptable. Adjuvant endocrine treatment could have started before randomization or could be started anytime post-surgery. Endocrine treatment consisted of either tamoxifen or an aromatase inhibitor (AI: letrozole, anastrozole, or exemestane). For premenopausal patients, concurrent LHRH agonist use was allowed.

The study had an adaptive design with two interim analyses including sample size re-estimation and non-binding stopping of the trial due to futility in the first and early stopping of the trial prematurely due to futility or overwhelming efficacy in the second efficacy interim analysis (EIA). Due to the adaptive design sample size was at least 1100 patients. The sample size could be increased to a maximum of 1250 patients depending on the result of the first EIA.

Patients were randomized in a 1:1 ratio to:

- Arm A: palbociclib at a dose of 125 mg once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for 13 cycles
- Arm B: Placebo of palbociclib once daily Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for thirteen cycles.

Randomization was stratified using block randomization by:

- Histological lymph node status at surgery (ypN 0-1 vs. ypN2-3)
- Age at first diagnosis (≤50 vs. >50 years)
- Centrally measured Ki-67 (>15% vs. ≤15%)
- Global region of participating site (Asian vs. non-Asian)
- Risk status (CPS-EG Score ≥3 vs. CPS-EG Score = 2 and ypN+).

Due to the prognostic impact of the randomization criterion risk status, randomization to the stratum CPS-EG score =2 and ypN+ was limited to 50% of the patients.

Palbociclib/placebo was given for thirteen 28-day cycles or until diagnosis of invasive local, regional or distant recurrence, diagnosis of secondary malignancy, unacceptable toxicity, or withdrawal of consent of the patient or study termination by the Sponsor, whichever occurred first.

Patients in both arms should receive standard endocrine treatment for at least 5 years.

The end of the study was defined with evaluation of the primary objective. Survival and relapse assessments will continue post study.

The International Steering Committee (ISC) and the Independent Data Monitoring Committee (IDMC) reviewed and monitored the conduct of the study.

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The original study protocol was amended several times. Substantial changes were as follows:

- Protocol B (Version 7, 12-Jun-2014): Editorial Amendment to update the protocol version B, with the administrative letters 1-4 (DIL) into the protocol, update of Appendix 10 (Declaration of Helsinki)
- Protocol C (Version 8, 06-Aug-2014): Prognostic Marker Inclusion Criterion #12 with score CPS-EG, allowed now the use of surgical biopsy: … using local estrogen receptor status and grade assessed on core biopsies taken before start of neoadjuvant treatment either / or surgical biopsy. Predictive Marker Inclusion Criterion #5, had to be PR positive in residual tissue or with the core biopsy: … (≥1% ER and/or PR positive stained cells). Retreatment and dose reduction section: Increased clarifications to guidance was provided based on gained experience in the palbociclib program. Exclusion criterion #14 now allowed prior neoadjuvant treatment to allow the entry of patients from ADAPT and similar trials: Prior neoadjuvant treatment was acceptable. Section 6.3.3 “Human Pharmacokinetik Data”, Section 6.3.4 “QTc Evaluation Data, Chapter 6.3.7 “Combination with other endocrine agents”, and Section 6.3.8 “Long Term Toxicity Data” were updated with the most recent nonclinical and clinical information. The blood sample for ctDNA was increased from 10 ml to 20 ml. Editorial amendment to update protocol version C with administrative letter 5 (DIL), FDA-IND number amended.
- Protocol D (Version 9, 09-Feb-2015): Inclusion criterion #5: Clarification for testing in case of bilateral breast cancer; inclusion criterion #6: Centrally testing possibility was extended to core biopsy; inclusion criterion #12: Now allowed patients with a CPS-EG Score of 2, if ypN+, to participate; exclusion criterion #15: Proton Pump Inhibitors were no longer unallowed. Addition of additional stratification criteria: CPS EG score 3 vs. 2 and ypN+. Update of Section 6.3.3 “Human Pharmacokinetic (PK) Data; update of Section 12.5.1 “Prohibited Medication”, proton pump inhibitors removed; update of section 15.5 ff: Statistical Analysis due to change of inclusion criterion.
- Protocol E (Version 10, 12-Apr-2016): Inclusion criterion #2: Specification for bilaterial breast cancer was added; inclusion criterion #5: Specification which tissue could be used for central testing was added; inclusion criterion #6: Specification for bilaterial breast cancer was added; inclusion criterion #10: Radiotherapy requirements were adjusted to standard guidelines; exclusion criterion #5: Specified to electrolyte disorders in general, exclusion criterion #13: Removal of endocrine treatment timing which was a description but not an exclusion criterion (was replaced with definition of radiotherapy window); exclusion criterion #16: Study entry time was specified as date of randomization. Endocrine treatment options were updated. Patients could now receive either tamoxifen or AI (letrozole, anastrozole, or exemestane). For premenopausal patients, concurrent LHRH agonist use was allowed. Patients could now concurrently receive bisphosphonates or rank ligand inhibitors, if necessary, for treatment or prevention of osteopenia or osteoporosis. Safety monitoring frequency was adjusted to IDMC recommendation. Ophthamologic assessment was removed due to new information in palbociclib IB versions. Optional samples for circulating tumor cells (CTC), RNAlater and fresh frozen tissue was removed. An optional ctDNA sample collection time-point at detection of progressive disease was added. Specification of relevant overdose definition and removal of notification requirement for non-relevant overdose.
- Protocol G (Version 11, 04-May-2017) Specification of potential outcomes of the EIA (futility,

sample size re-estimation up to a new total number of 1250 patients, efficacy) were added to the statistical sections. Rationale: The adaptive design of the study allowed adjustment of the patient number based on outcome of the 1st EIA. New information on human PK data based on the IB (2017) was added.
Number of patients (planned and analyzed): Planned: N=1250 (according to the results of the first EIA, in April 2017, screened: N=1708, randomized: N=1250, analyzed (safety analysis set): N=1244, analyzed (ITT set): N=1250.
Diagnosis and Main Criteria for Inclusion: The study included patients at least 18 years of age with histologically confirmed unilateral or bilateral primary invasive, HR-positive, HER-normal breast cancer. Residual invasive disease post-neoadjuvant was identified either in the breast or as residual nodal invasion. CPS-EG score was to be ≥3, or score 2, if nodal status at surgery was ypN+, calculated using local ER and grade assessed on either core biopsies taken before start of neoadjuvant treatment or surgical specimen. Patients had to have received neoadjuvant chemotherapy of at least 16 weeks. This period had to include 6 weeks of a taxane-containing neoadjuvant therapy (exception: in patients with progressive disease that occurred after at least 6 weeks of taxane-containing neoadjuvant treatment, a total treatment period of less than 16 weeks was also eligible). Patients had to have adequate surgical treatment including resection of all clinically evident disease and ipsilateral axillary lymph node dissection, and had to have completed adjuvant radiotherapy according to standard guidelines.
Test Products, Dose and Mode of Administration, Batch Number: Investigational product in this study was palbociclib. Palbociclib/placebo (randomized in a 1:1 ratio) was orally administered at a dose of 125 mg once a day at the same day time for 21 days followed by 7 days off treatment of every 28-day cycle. A delay of up to 3 days due to administrative reason was acceptable. A total of thirteen 28-day cycles should be administered. Patients were instructed to swallow palbociclib/placebo capsules whole and not to chew them prior to swallowing. Palbociclib/placebo capsules were administered together with endocrine treatment. The following batch numbers for the study medication (palbociclib and placebo) were used in this study: 13-110015, 14 001183, 15-000797, 15-005237, 16-001582, 13-110014, 15-000796, 15-005234, 16 001579, 17-001586, 16-001578, 17-001604, 15-000795, 15-005225, 17-001235, 13 109625, 13-109624, 13-109622, 13-110013, 14-001181, 14-001182.
Duration of Treatment: Patients were treated by a total of thirteen 28-day cycles with palbociclib/placebo.
Reference Therapy, Dose and Mode of Administration: Reference therapy was the placebo of palbociclib. See above for details on therapy and dose.
Criteria for Evaluation: **Efficacy:** **Primary efficacy objective/endpoint:**

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The primary objective of the study was to compare iDFS for palbociclib vs. placebo in patients with residual invasive breast cancer and high CPS-EG score - after neoadjuvant chemotherapy receiving standard adjuvant endocrine therapy for HR-positive/HER2-normal primary breast cancer.

The primary endpoint iDFS was defined as the time in months between randomization and first event. The following events were considered as first events: ipsi- or contralateral invasive in-breast or loco- regional recurrence, distant recurrence, death from breast cancer, death from non-breast cancer cause, death from unknown cause, invasive contralateral breast cancer, second primary invasive cancer (non-breast).

Key secondary efficacy objective/endpoint:

The key secondary objective was to compare iDFS excluding second primary invasive non- breast cancer for palbociclib vs. placebo.

The respective endpoint was defined as the time in months between randomization and first event. iDFS excluding second primary invasive non-breast cancer was analyzed at the time of the second interim iDFS analysis and at the final iDFS analysis.

Further secondary efficacy objectives/endpoints:

Overall survival, locoregional recurrences-free interval (LRRFI), distant disease-free survival, iDFS in patients with luminal-B tumors.

Safety:

Safety objective of the study was to assess the overall toxicity of the study treatment.

The corresponding endpoints were:

- Toxicity (adverse events, including predefined adverse events of special interest) were assessed according to the NCI-CTCAE version 4.0; laboratory parameters)
- Treatment compliance [dose reductions, treatment delays, treatment interruptions, premature treatment discontinuations, relative total dose (RTD) and relative total dose intensity (RTDI)].

Other assessments:

Patients reported outcomes: Quality of Life (QoL) was evaluated by General QoL questionnaire (EORTC QLQ-C30), breast cancer questionnaire (QLQ-BR23) module, fatigue questionnaire (EORTC QLQ FA13 Fatigue), mood questionnaire (GAD7), EQ-5D instrument.

Various specific scores and markers were analyzed for their prognostic value in this study and their predictive information on the efficacy and/or safety of palbociclib.

Statistical Methods:

Primary Efficacy Analyses:

The study had an adaptive design with two efficacy interim analyses (EIAs). The objectives of the first EIA were sample size re-estimation and the opportunity for early stopping of the study due to futility. Sample size re-estimation was planned to be performed only in one of the two interim analyses. Therefore, this objective was dropped in the second interim analysis and the remaining objectives were the opportunity for early stopping of the study due to futility or overwhelming efficacy, respectively. The decision about early stopping of the study due to futility or overwhelming efficacy was made on the basis of the primary efficacy parameter, iDFS.

Final analysis of the primary endpoint was to be conducted when 290 events in iDFS had been observed and

documented in the database. The primary analysis was the comparison of survivor functions between treatment arms in the primary efficacy endpoint iDFS in the ITT population. The Kaplan-Meier curves of iDFS, Kaplan-Meier estimates of 3-, and 5-year probability of iDFS and the corresponding 95% CI were provided. Frequency (number and percentage) of patients with each type of iDFS event and censoring reasons were presented by treatment arm. Duration of follow-up in the treatment arms was summarized using the inverse Kaplan- Meier method, reversing the OS censoring and event indicators. Null hypothesis was: Survivor functions of the two treatment arms are equal; Alternative hypothesis was: Survivor functions of the two treatment arms are not equal. A two-sided stratified log-rank test at the overall significance level of 0.05 was performed. The stratification factors were: histological lymph node status at surgery (ypN 0-1 vs. ypN2-3), age at first diagnosis (<=50 vs. >50 yrs.), Ki-67 (>15% vs. <=15%) and risk status (CPS-EG score ≥3 vs. CPS-EG score = 2 and ypN+). In the primary analysis the stratification factors were used as randomized, i.e. with the values collected at the time of randomization. Based on the estimated treatment effect and its standard error from the stratified Cox proportional hazards model the weighted statistic (CHW) and the repeated 95% CI of the HR were derived from the CHW Interim Monitoring dashboard in EAST taking into account the adaptive sample size re-estimation and group-sequential nature of the design. This study was considered a positive study if the two-sided p-value from the weighted log-rank test based on the CHW method was significant at the significance level of 0.0463 at the time of the final analysis. In addition, the unweighted stratified log-rank test was presented to support the main analysis of the primary endpoint. The primary endpoint was also analyzed in the pre-specified subgroups. Time-to-event data (iDFS, iDFS excluding second non-breast cancers, OS, LRRFI and DDFS) were analyzed using univariate Cox-proportional hazards models to calculate hazard ratios for subgroups based on stratification factors.

There was no adjustment for multiple comparisons in the analyses in subgroups. Univariate and multivariate Cox-proportional hazards model were used for iDFS to report hazard ratios with 95% CI and to adjust for covariates. Sensitivity analyses were performed to explore the robustness of the primary analysis results. These analyses are regarded as purely exploratory.

Secondary Efficacy Analyses:

Final analysis on the secondary efficacy endpoints (except for OS) were to be conducted when 290 events in iDFS had been observed and documented in the database. The analysis of the key secondary endpoint was performed to test the null hypothesis that the survivor functions of iDFS excluding second primary invasive non-breast cancers are the same for the two treatment arms vs. the alternative hypothesis that the survivor functions are different for the two treatment arms. At the time of the final iDFS analysis an interim OS analysis was to be conducted. At the time of interim iDFS analyses, iDFS excluding second primary invasive non-breast cancers was to be hierarchically tested for significance, provided the primary endpoint, iDFS was statistically significant. As iDFS was not significant, iDFS excluding second primary invasive non-breast cancers was not statistically evaluated. At the time of final iDFS analyses, the hierarchical testing was to be performed in the following sequence: iDFS, iDFS excluding second primary invasive non-breast cancers and OS. The next level of testing was only to be provided if the prior level was significant. If a test was not significant, the next test was not statistically evaluated. The Kaplan-Meier curves of the time-to-event data, Kaplan-Meier estimates of 3-, and 5- year probability of the time-to-event data and the corresponding 95% CI were provided. The time-to-event data were: iDFS excluding second non-breast cancers, OS, DDFS, iDFS per treatment group in patients with luminal-B tumors. LRRFI including competing risks was analyzed using the Fine-Gray model, both univariately (the cumulative incidence function was presented graphically per treatment arm with stratified Gray's test for comparison) and multivariately to report HR for treatment and

to adjust for the stratification factors. Null hypothesis was: Survivor functions of the two treatment arms are equal; Alternative hypothesis was: Survivor functions of the two treatment arms are not equal. A two-sided stratified log-rank test at the overall significance level 0.05 was performed to compare time-to-event efficacy outcomes between treatment arms, the same stratification factors were used as for the primary endpoint. The secondary time-to event endpoints were analyzed in the stratified subgroups. There was no adjustment for multiple comparisons in the analyses in subgroups. Univariate and multivariate Cox proportional hazards model were used for time-to-event data to report hazard ratios with 95% CI and to adjust for the covariates.

Safety analyses

All safety analyses were performed using the evaluable subset for safety. Analyses of AEs were performed using any AE that occurred after first dose of study medication ignoring baseline events. The extent of study treatment exposure and compliance was assessed and summarized by the actual treatment received within the "All randomized and treated patients population".

SUMMARY

Efficacy Results:

After a median follow-up of 42.8 months, 308 confirmed iDFS events (24.6%) were documented, 152 (24.1%) in the palbociclib arm and 156 (25.2%) in the placebo arm. Most iDFS events were distant recurrences (227 patients, 73.7%), invasive locoregional events were reported in 48 patients (15.6%). There was no significant difference between the two treatment arms [stratified hazard ratio 0.93 (95% RCI 0.74-1.17), p-value (CHW) 0.525]. The estimated 3-year iDFS was 81.2% (77.8%-84.1%) with palbociclib and 77.7% (74.1%-80.9%) with placebo. No subgroup could be identified which benefitted from the addition of palbociclib to endocrine treatment after NACT.

The analysis of iDFS excluding second primary invasive non-breast cancers showed a similar result [hazard ratio 0.93 (95% CI 0.74-1.16), p-value 0.501]. As within the hierarchical testing procedure the first p-value was not significant, the p-values for iDFS excluding second primary invasive non-breast cancers and for OS are to be considered descriptive in nature. LRRFI was not significantly different between the two arms. The loco-regional recurrence cumulative incidence rate at 3 years was 3.7% (2.4%-5.4%) with palbociclib and 4.6% (3.1%-6.5%) with placebo (hazard ratio 0.83 (95% CI 0.49-1.39), p-value 0.514). The only subgroup that might have a benefit from palbociclib in terms of LRRFI was the group without response to NACT (stable or progressive disease, N=200, hazard ratio 0.20 (95%CI 0.04-0.95), p-value 0.043). DDFS was also not significantly different between the two arms. The estimated 3-year DDFS was 82.4% (79.1%, 85.3%) with palbociclib and 80.0% (76.6%, 83.1%) with placebo (hazard ratio 0.94 (95% CI 0.74-1.18), p-value 0.579). No subgroup could be identified which benefitted from the addition of palbociclib to endocrine treatment after NACT.

At the time of final iDFS analysis, an interim analysis for OS was performed. OS was not significantly different between the two arms [hazard ratio 0.87 (95%CI 0.61-1.23) p-value 0.420] with no differences according to subgroups. The 3-year OS was 93.6% (91.3%-95.3%) with palbociclib and 90.5% (87.8%-92.6%) with placebo.

Safety Results:

All patients except one in each treatment arm reported at least one AE. At least one AE grade 3-4 was significantly more often reported in the palbociclib group compared to the placebo group (79.6% vs. 20.1%).

There was no difference between non-hematologic AEs grade 3-4 between the treatment groups (19.9% vs. 19.0%), but there were significantly more hematologic AEs with palbociclib compared to placebo (73.1% vs. 1.3%). The most frequent AEs with a significantly higher incidence in the palbociclib arm were neutropenia of any grade (95.7% vs. 23.4%) and grade 3-4 (70.0% vs. 1.0%), leukopenia of any grade (99.2% vs. 69.9%) and grade 3-4 (56.1% vs. 0.7%), thrombocytopenia any grade (56.6% vs. 16.2%), anemia any grade (73.9% vs. 30.3%), hypocalcaemia any grade (35.2% vs. 24.4%), fatigue any grade (66.4% vs. 51.1%), stomatitis any grade (27.5% vs. 8.7%), constipation any grade (22.1% vs. 13.7%), cough any grade (20.9% vs. 16.2%), and infection (59.9% vs. 51.1%). Arthralgia (41.2% vs. 46.8%) and hot flushes (43.8% vs. 50.9%) were less frequent with palbociclib than placebo.

In total, 129 serious adverse events (SAEs) were reported (palbociclib: 64 SAEs, placebo: 65 SAEs). Most frequently affected system organ classes (SOCs) were infections and infestations (44 SAEs), injury, poisoning and procedural complications (21 SAEs), and vascular disorders (10 SAEs). SAEs were reported in 113 (9.1%) patients, with no difference between the palbociclib arm (9.3%) and the placebo arm (8.8%); 8 SAEs were fatal, 2 in the palbociclib arm and 6 in the placebo arm, 2 (leukemia and hepatorenal failure) in the placebo arm were considered related to study drug, 1 (lung embolism) in the palbociclib arm considered related to endocrine treatment.

Table 36: Serious adverse events by system organ class and preferred term (preferred terms are listed if they occurred more than once) (safety population)

System organ class Preferred term	Palbociclib N=633 No. of SAEs	Placebo N=611 No. of SAEs	Overall N=1244 No. of SAEs
Total number of SAEs	**64**	**65**	**129**
Infections and infestations	**19**	**25**	**44**
Cellulitis	4	5	9
Erysipelas	3	1	4
Influenza	3	1	4
Postoperative wound infection	0	3	3
Wound infection	1	2	3
Infection	1	1	2
Neutropenic sepsis	2	0	2
Pharyngitis	2	0	2
Injury, poisoning and procedural complications	**11**	**10**	**21**
Overdose	7	3	10
Fracture	2	2	4
Seroma	2	0	2

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Vascular disorders	**6**	**4**	**10**
Pulmonary embolism	2	1	3
Thrombosis	0	2	2
General disorders and administration site conditions	**3**	**4**	**7**
Impaired healing	1	1	2
Nervous system disorders	**1**	**5**	**6**
Headache	1	1	2
Blood and the lymphatic system disorders	**5**	**0**	**5**
Febrile neutropenia	2	0	2
Neutropenia	2	0	2
Musculoskeletal, connective tissue and bone disorders	**3**	**2**	**5**
Neoplasms benign and malignant (including cysts and polyps)	**1**	**4**	**5**
Gastrointestinal disorders	**3**	**1**	**4**
Reproductive system and breast disorders	**2**	**2**	**4**
Respiratory, thoracic and mediastinal disorders	**2**	**2**	**4**
Hepato-biliary disorders	**0**	**3**	**3**
Psychiatric disorders	**1**	**2**	**3**
Renal and urinary disorders	**3**	**0**	**3**
Cardiac disorders	**2**	**0**	**2**
Eye disorders	**1**	**0**	**1**
Ear and labyrinth disorders	**1**	**0**	**1**
Surgical and medical procedures	**0**	**1**	**1**

Source: PT-Table 14-66

Overall, 219 (17.5%) patients discontinued study treatment and 64 (5.1%) discontinued endocrine treatment prematurely. 301 patients (47.6%) in the palbociclib arm compared to 11 patients (1.8%) in the placebo arm had at least one dose-reduction ($p<0.001$). In the last cycle, 256 patients (49.7%) still received 125mg palbociclib, but 512 (98.5%) received full dose in the placebo arm. 13 cycles were completed by 80.5% vs. 84.5% with palbociclib and placebo, respectively. The median duration of therapy was 52.9 weeks with palbociclib and 52.0 weeks with placebo ($p<0.001$). The relative total dose intensity (RTDI) was significantly lower with palbociclib (82.1% vs. 98.9%, $p<0.001$).

CONCLUSIONS:

In conclusion, the PENELOPEB trial did not demonstrate that the addition of one year palbociclib to standard adjuvant endocrine treatment improves iDFS in patients at high risk of relapse after neoadjuvant chemotherapy defined by the CPS-EG score. Postneoadjuvant patients were also enrolled in two large adjuvant studies (PALLAS and monarchE trials), but without further defining the risk status. In contrast to the PALLAS trial, the monarchE study showed an improvement in iDFS by adding abemaciclib to endocrine treatment after a median follow-up of 14 months.

The subgroup analysis also revealed a clear benefit at this early time point for the patients who received neoadjuvant chemotherapy.

Further research is warranted by pooling the data from this specific population enrolled in PENELOPE^{B} with other trials to determine whether this group has a sustained long-term reduction of relapse from a CDK4/6 inhibitor and to characterize this population by molecular markers. This will take some time, as the follow-up from these trials is either too short or recruitment is still ongoing.

Date of the Report:

28-Apr-2021