Check for updates

rapid communications

Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer—The Penelope-B Trial

Sibylle Loibl, MD, PhD[1,2]; Frederik Marmé, MD, PhD[3]; Miguel Martin, MD, PhD[4,5]; Michael Untch, MD, PhD[6]; Hervé Bonnefoi, MD, PhD[7]; Sung-Bae Kim, MD, PhD[8]; Harry Bear, MD, PhD[9,10]; Nicole McCarthy, MD, PhD[11]; Mireia Melé Olivé, MD[5,12]; Karen Gelmon, MD, PhD[13]; José García-Sáenz, MD[5,14]; Catherine M. Kelly, MD[15]; Toralf Reimer, MD, PhD[16]; Masakazu Toi, MD, PhD[17]; Hope S. Rugo, MD[18]; Carsten Denkert, MD, PhD[1,19]; Michael Gnant, MD, PhD[20,21]; Andreas Makris, MD[22]; Maria Koehler, MD, PhD[23]; Cynthia Huang-Bartelett, MD[23]; Maria Jose Lechuga Frean, MD[23]; Marco Colleoni, MD[24]; Gustavo Werutsky, MD[25]; Sabine Seiler, MD[1]; Nicole Burchardi, PhD[1]; Valentina Nekljudova, PhD[1]; and Gunter von Minckwitz, MD, PhD, MA (Phil), BBA[1]

abstract

PURPOSE About one third of patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative breast cancer who have residual invasive disease after neoadjuvant chemotherapy (NACT) will relapse. Thus, additional therapy is needed. Palbociclib is a cyclin-dependent kinase 4 and 6 inhibitor demonstrating efficacy in the metastatic setting.

PATIENTS AND METHODS PENELOPE-B (NCT01864746) is a double-blind, placebo-controlled, phase III study in women with hormone receptor–positive, human epidermal growth factor receptor 2–negative primary breast cancer without a pathological complete response after taxane-containing NACT and at high risk of relapse (clinical pathological staging-estrogen receptor grading score ≥ 3 or 2 and ypN+). Patients were randomly assigned (1:1) to receive 13 cycles of palbociclib 125 mg once daily or placebo on days 1-21 in a 28-day cycle in addition to endocrine therapy (ET). Primary end point is invasive disease-free survival (iDFS). Final analysis was planned after 290 iDFS events with a two-sided efficacy boundary $P < .0463$ because of two interim analyses.

RESULTS One thousand two hundred fifty patients were randomly assigned. The median age was 49.0 years (range, 19-79), and the majority were ypN+ with Ki-67 ≤ 15%; 59.4% of patients had a clinical pathological staging-estrogen receptor grading score ≥ 3. 50.1% received aromatase inhibitor, and 33% of premenopausal women received a luteinizing hormone releasing hormone analog in addition to either tamoxifen or an aromatase inhibitor. After a median follow-up of 42.8 months (92% complete), 308 events were confirmed. Palbociclib did not improve iDFS versus placebo added to ET-stratified hazard ratio, 0.93 (95% repeated CI, 0.74 to 1.17) and two-sided weighted log-rank test (Cui, Hung, and Wang) $P = .525$. There was no difference among the subgroups. Most common related serious adverse events were infections and vascular disorders in 113 (9.1%) patients with no difference between the treatment arms. Eight fatal serious adverse events (two palbociclib and six placebo) were reported.

CONCLUSION Palbociclib for 1 year in addition to ET did not improve iDFS in women with residual invasive disease after NACT.

J Clin Oncol 39:1518-1530. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Listen to the podcast by Dr Mayer at jcopodcast.libsynpro.com

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 4, 2021 and published at ascopubs.org/journal/jco on April 1, 2021: DOI https://doi.org/10.1200/JCO.20.03639

INTRODUCTION

Patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) primary breast cancer who receive chemotherapy as part of their primary treatment are at higher risk of relapse.[1] About a third of the patients with residual invasive disease after neoadjuvant chemotherapy (NACT) will relapse despite adjuvant endocrine therapy (ET).[2] The risk of relapse can be assessed more accurately using the clinical pathological staging-estrogen receptor grading (CPS-EG) scoring system.[3] This involves the tumor stage before treatment start and at surgery, the estrogen receptor (ER) status, and the pathologic grading. A higher score indicates a higher risk of relapse. Patients with a score of three and higher had a disease-free survival of 70% at 5 years despite receiving ET. When combined with the group having a CPS-EG score of two and involved lymph nodes, the disease-free survival increased to 77%. This group comprises about 25% of all patients with residual disease after NACT.[4]

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

CONTEXT

Key Objective

Patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) breast cancer and residual invasive disease after neoadjuvant chemotherapy are at high risk for relapse despite adjuvant endocrine therapy (ET). The cyclin-dependent kinase 4 and 6 inhibitor palbociclib added to ET improves progression-free survival and overall survival in HR+ and HER2− metastatic breast cancer. PENELOPE-B assesses efficacy of one year palbociclib versus placebo added to ET as (postneo)adjuvant treatment in this high-risk population.

Knowledge Generated

Palbociclib (1 year) added to ET did not improve invasive disease-free survival (iDFS) or any other efficacy end point compared with placebo (3-year iDFS, 81.2% *v* 77.7%). No new safety signals were observed.

Relevance

PENELOPE-B is the first study showing mature iDFS results on a cyclin-dependent kinase 4 and 6 inhibitor as part of (postneo)adjuvant therapy. The results do not support the addition of palbociclib to ET. Further research and pooled analyses are necessary to determine whether a high-risk HR+, HER2− population can be identified, which has a sustained long-term reduction of relapse from palbociclib.

Therapeutic inhibition of cyclin-dependent kinase 4 and 6 (CDK4/6) by palbociclib combined with ET demonstrated clinically relevant efficacy in metastatic HR+ and HER2− breast cancer irrespective of biomarker selection.[5] After the pivotal PALOMA-1 trial, which led to accelerated approval of palbociclib in February 2015, further phase III trials demonstrated that the use of CDK4/6 inhibitors in pre- and postmenopausal patients with hormone-sensitive or resistant cancers, in first-line and pretreated metastatic breast cancer, improves progression-free and overall survival (OS).[6-8]

Thus, we hypothesized that palbociclib may also be active in patients with residual disease after NACT who are at high risk of relapse. Based on the data from PALOMA-1, we designed the PENELOPE-B trial assessing the efficacy of one year palbociclib vs placebo added to any ET in HR+ and HER2− breast cancer patients with residual disease and high risk after NACT, based on the CPS-EG score.

PATIENTS AND METHODS

Patient Selection and Study Design

PENELOPE-B is a prospective, multicenter, multinational, randomized, double-blind, placebo controlled phase III study investigating the addition of palbociclib for one year to standard adjuvant ET for patients with high-risk residual disease according to the CPS-EG score after NACT for early HR+ and HER2− breast cancer.

The trial was sponsored by GBG Forschungs GmbH in collaboration with NSABP Foundation (plus I-SPY and CCTR), ABCSG, AGO-B, ANBCSG, BIG, Geicam, ICR-CTSU, JBCSG, and KCSG. Pfizer Inc funded the trial and provided drug. The trial was conducted according to ICH-GCP guidelines and the Declaration of Helsinki. The clinical trial Protocol (online only) was approved by the respective health authorities and ethics committees or institutional review boards. All patients provided written informed consent for trial participation, data transfer, and biomaterial collection. The trial was overseen by the International Steering Committee and the GBG Boards and supervised by an Independent Data Monitoring Committee (IDMC). It is registered under NCT01864746 and EudraCT 2013-001040-62.

Female patients ≥ 18 years with residual invasive disease after NACT either in the breast or the lymph nodes, ER, and/or progesterone receptor–positive and HER2− tumors based on central assessment and centrally assessed Ki-67 status (preferably on postneoadjuvant residual invasive disease of the breast, or if not possible, of residual nodal invasion or core biopsy), and a CPS-EG score of ≥ 3 or 2 with ypN+ (after amendment 3, dated February 9, 2015) were eligible. Patients must have received NACT for at least 16 weeks (including 6 weeks of a taxane) followed by definitive surgery (including resection of all clinically evident invasive disease and ipsilateral axillary lymph node dissection or sentinel node biopsy) and radiation as indicated according to local guidelines. Patients could not be included with an interval of more than 16 weeks since the date of final surgery or more than 10 weeks from completing radiotherapy. ET according to local guidelines, either with tamoxifen or an aromatase inhibitor (AI) with or without a luteinizing hormone releasing hormone analog, could have started before random assignment.

ER and progesterone receptor positivity were defined as ≥ 1% stained cells, and HER2 negativity as immunohistochemistry score 0-1 or fluorescence in-situ hybridization test ratio < 2.0. Further eligibility criteria and random assignment details are provided in Appendix 1 (online only).

Eligible patients were randomly assigned in a 1:1 manner in permuted blocks of alternating size 4/6 stratified by risk status (CPS-EG sore ≥ 3 *v* 2/ypN+), nodal involvement

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

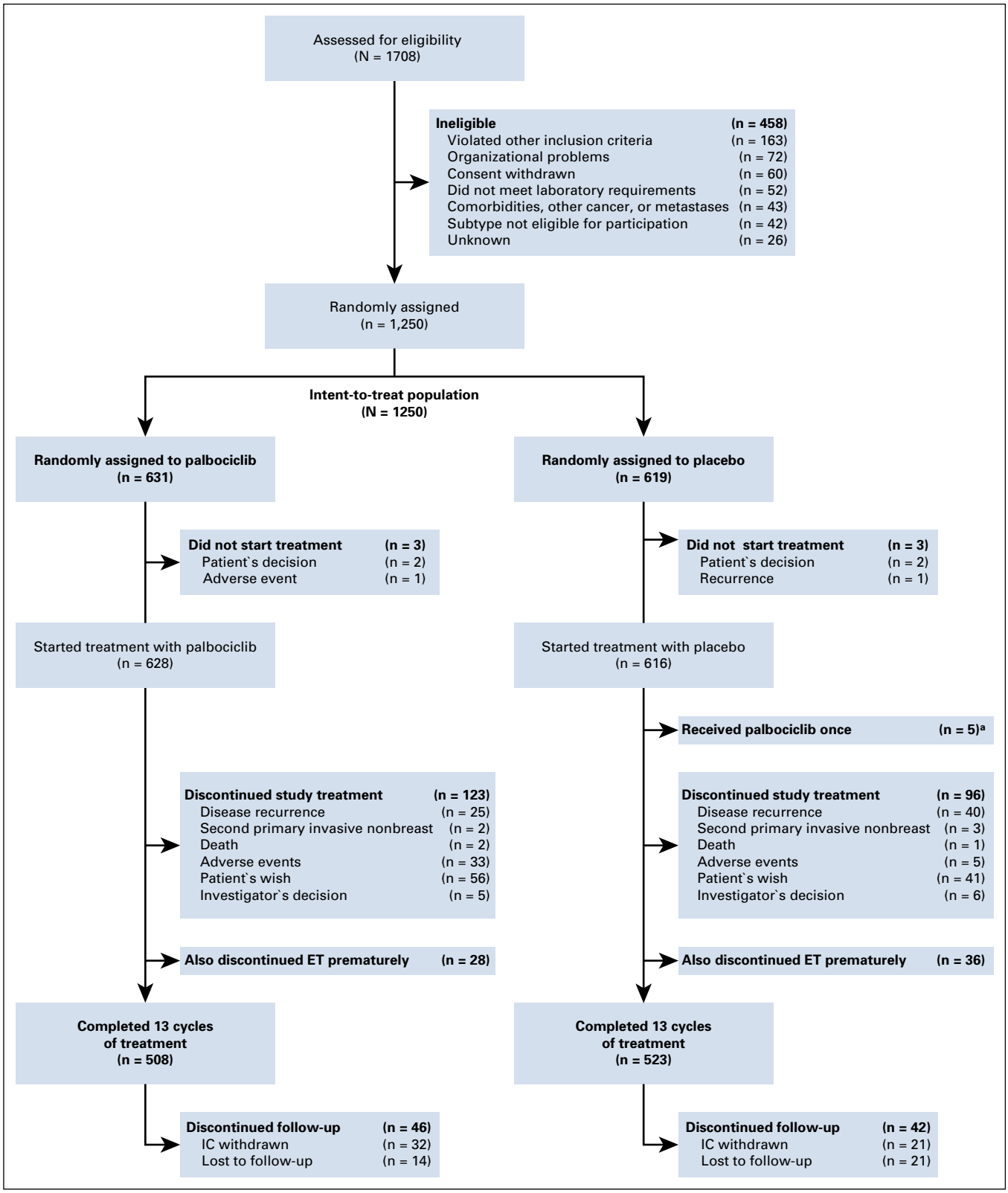

FIG 1. CONSORT diagram. [a]Analyzed for safety in the palbociclib arm. ET, endocrine therapy; IC, informed consent.

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

TABLE 1. Patient or Tumor Characteristics and First Endocrine Therapy at Baseline (ITT Analysis Set)

Parameter	Category	Palbociclib (n = 631), No. (Valid %)	Placebo (n = 619), No. (Valid %)	Overall (N = 1,250), No. (Valid %)	*P*[a]
Age, years	Median (min-max)	49.0 (22.0-76.0)	48.0 (19.0-79.0)	49.0 (19.0-79.0)	.589
	< 30	12 (1.9)	14 (2.3)	26 (2.1)	.929
	30 to < 40	87 (13.8)	82 (13.2)	169 (13.5)	
	40 to < 50	231 (36.6)	239 (38.6)	470 (37.6)	
	50 to < 60	181 (28.7)	163 (26.3)	344 (27.5)	
	60 to < 70	98 (15.5)	97 (15.7)	195 (15.6)	
	70+	22 (3.5)	24 (3.9)	46 (3.7)	
ECOG performance status	ECOG 0	537 (85.1)	527 (85.1)	1,064 (85.1)	.986
	ECOG 1	94 (14.9)	92 (14.9)	186 (14.9)	
Menopausal status	Premenopausal	300 (47.5)	316 (51.1)	616 (49.3)	.235
	Postmenopausal	331 (52.5)	303 (48.9)	634 (50.7)	
Tumor focality by sonography	Unifocal	420 (68.7)	400 (67.6)	820 (68.2)	.309
	Multifocal	132 (21.6)	119 (20.1)	251 (20.9)	
	Multicentric	59 (9.7)	73 (12.3)	132 (11.0)	
	Missing	20	27	47	
Clinical tumor stage by sonography	cT1	42 (6.7)	47 (7.6)	89 (7.1)	.688
	cT2	288 (45.8)	295 (47.8)	583 (46.8)	
	cT3	197 (31.3)	176 (28.5)	373 (29.9)	
	cT4	102 (16.2)	99 (16.0)	201 (16.1)	
	Missing	2	2	4	
Clinical nodal status by sonography	cN0	66 (10.5)	71 (11.5)	137 (11.0)	.923
	cN1	433 (68.6)	417 (67.4)	850 (68.0)	
	cN2	80 (12.7)	82 (13.2)	162 (13.0)	
	cN3	52 (8.2)	49 (7.9)	101 (8.1)	
	Missing	0	0	0	
Histological tumor stage at surgery	ypT0	24 (3.8)	11 (1.8)	35 (2.8)	.173
	ypTis	2 (0.3)	3 (0.5)	5 (0.4)	
	ypT1	212 (33.6)	194 (31.4)	406 (32.5)	
	ypT2	256 (40.6)	284 (46.0)	540 (43.2)	
	ypT3	112 (17.7)	105 (17.0)	217 (17.4)	
	ypT4	25 (4.0)	21 (3.4)	46 (3.7)	
	Missing	0	1	1	
Histological nodal status at surgery	ypN0	32 (5.1)	35 (5.7)	67 (5.4)	.955
	ypN1	277 (44.3)	274 (44.6)	551 (44.5)	
	ypN2	231 (37.0)	226 (36.8)	457 (36.9)	
	ypN3	85 (13.6)	79 (12.9)	164 (13.2)	
	Missing	6	5	11	
Overall clinical response after NACT	CR	53 (8.4)	49 (7.9)	102 (8.2)	.096
	PR	463 (73.4)	485 (78.4)	948 (75.8)	
	SD	109 (17.3)	77 (12.4)	186 (14.9)	
	PD	6 (1.0)	8 (1.3)	14 (1.1)	

(continued on following page)

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

TABLE 1. Patient or Tumor Characteristics and First Endocrine Therapy at Baseline (ITT Analysis Set) (continued)

Parameter	Category	Palbociclib (n = 631), No. (Valid %)	Placebo (n = 619), No. (Valid %)	Overall (N = 1,250), No. (Valid %)	P[a]
Hormone receptor status, central[b]	Both ER- and PgR-negative (protocol violation)	0 (0.0)	1 (0.2)	1 (0.1)	.495
	ER- and/or PgR-positive	631 (100)	618 (99.8)	1,249 (99.9)	
HER2, central[b]	Negative	631 (100)	619 (100)	1,250 (100)	NA
	Positive	0 (0.0)	0 (0.0)	0 (0.0)	
Tumor grading, local (core biopsy)	G1	31 (5.0)	36 (5.9)	67 (5.4)	.522
	G2	355 (57.0)	330 (54.0)	685 (55.5)	
	G3	237 (38.0)	245 (40.1)	482 (39.1)	
	Missing	8	8	16	
Histological tumor type	Ductal or ductal-lobular invasive	550 (87.2)	553 (89.3)	1,103 (88.2)	.153
	Lobular invasive carcinoma	58 (9.2)	52 (8.4)	110 (8.8)	
	Mucinous carcinoma	7 (1.1)	4 (0.6)	11 (0.9)	
	Invasive micropapillary carcinoma	1 (0.2)	4 (0.6)	5 (0.4)	
	Others	15 (2.4)	6 (1.0)	21 (1.7)	
CPS-EG score[c]	1 (protocol violation)	7 (1.1)	7 (1.1)	14 (1.1)	.715
	2	241 (38.2)	242 (39.1)	483 (38.6)	
	3	286 (45.3)	275 (44.4)	561 (44.9)	
	4	89 (14.1)	81 (13.1)	170 (13.6)	
	5	8 (1.3)	14 (2.3)	22 (1.8)	
Stratification factors as randomly assigned					
Histological lymph node status at surgery documented at random assignment	ypN 0-1	310 (49.1)	310 (50.1)	620 (49.6)	.777
	ypN 2-3	321 (50.9)	309 (49.9)	630 (50.4)	
Age at first diagnosis documented at random assignment	≤ 50	353 (55.9)	348 (56.2)	701 (56.1)	.955
	> 50	278 (44.1)	271 (43.8)	549 (43.9)	
Ki-67 % centrally at random assignment	≤ 15%	470 (74.5)	461 (74.5)	931 (74.5)	1.000
	> 15%	161 (25.5)	158 (25.5)	319 (25.5)	
Global region of participating site	Non-Asian	579 (91.8)	576 (93.1)	1,155 (92.4)	.396
	Asian	52 (8.2)	43 (6.9)	95 (7.6)	
Risk status	CPS-EG score 2 and ypN+	253 (40.1)	255 (41.2)	508 (40.6)	.730
	CPS-EG score ≥ 3	378 (59.9)	364 (58.8)	742 (59.4)	
Endocrine treatment					
ET	Started ET before palbociclib/placebo	562 (89.1)	555 (89.7)	1,117 (89.4)	.783
	Concomitant start of ET and palbociclib/placebo	69 (10.9)	64 (10.3)	133 (10.6)	
First ET applied	Tamoxifen with or without ovarian suppression	314 (49.8)	308 (49.8)	622 (49.8)	1.000
	AI with or without ovarian suppression	317 (50.2)	311 (50.2)	628 (50.2)	
	Additional ovarian ablation	108 (17.1)	113 (18.3)	221 (17.7)	

Abbreviations: AI, aromatase inhibitor; CPS-EG, clinical, pathological stage, estrogen receptor, grading; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ET, endocrine treatment; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITT, intent-to-treat; NA, not applicable; NACT, neoadjuvant chemotherapy; PD, progressive disease; PgR, progesterone receptor; PR, partial response; SD, stable disease.

[a]Fisher's exact test for binary, continuity-corrected chi-square test for categorical and Wilcoxon test for continuous parameters.

[b]Central pathology, preferably based on surgical tissue and if not available based on biopsy (38 patients).

[c]CPS-EG Score based on clean baseline data; missing values of parameters needed for CPS-EG score calculation and CPS-EG score of one are due to source data verification.

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

after surgery (ypN0-1 *v* ypN2-3), Ki-67 (≤ 15% *v* > 15%), age (≤ 50 *v* > 50 years), and global region of participating site (Asian *v* non-Asian).

Treatment

Patients received either palbociclib 125 mg orally once daily for 21 days followed by 1 week off treatment for a total duration of 13 4-week cycles or matching placebo in addition to standard adjuvant ET at the discretion of the investigator given for at least 5 years (Data Supplement, Supplementary Fig 1 [online only]). Dose interruptions, reductions, or delays according to predefined toxicity management were acceptable in the case of significant treatment-related toxicity (Appendix 1).

Objectives and End Points

The primary objective of the study was to compare the invasive disease-free survival (iDFS) defined as the time in months between random assignment and first event (ipsilateral invasive in-breast or locoregional recurrence, distant recurrence, invasive contralateral breast cancer, second primary invasive cancer [nonbreast], or death because of any cause) for palbociclib versus placebo.[9] Secondary end points included iDFS excluding second primary invasive nonbreast cancers, distant disease-free survival, OS, locoregional relapse-free interval (LRRFI), safety (which was reported as adverse events (AEs) irrespective of relatedness to study treatment based on National Cancer Institute Common Toxicity Criteria v4.0), and compliance. Further details on other end points are provided in the Appendix 1.

All time-to-event end points were analyzed in the intent-to-treat population comprising all randomly assigned patients. Compliance and safety were analyzed in the safety analysis set including all randomly assigned patients who took study medication at least once. For the patients randomly assigned to placebo who received palbociclib at least once during the trial, the treatment group allocation for safety and compliance analyses was the palbociclib arm.

Sample Size and Interim Analyses

In the initial sample size computation, 233 iDFS events were required to detect a hazard ratio for palbociclib/placebo of 0.67 (from 72% to 80% 3-year iDFS rate) corresponding to a clinically relevant risk reduction of 33% for invasive disease with a power of 85% using a two-sided stratified log-rank test and an overall two-sided significance level of 0.05. Eight hundred patients were planned to be enrolled. To accelerate recruitment after 68 patients had been enrolled, the population was expanded to patients with a CPS-EG score of two and ypN + who were also identified as high-risk patients but with a generally lower risk than the patients with CPS-EG three.[4] Thereafter, the target hazard ratio for palbociclib/placebo was updated to 0.685 (from 77% to 83.6% 3-year iDFS rate), and the iDFS events were increased to 255 and sample size to 1,100 patients.

The study had an adaptive design with two interim efficacy analyses to monitor futility, to test for overwhelming efficacy, and to allow for sample size re-estimation.[10] Safety was assessed at both interim analyses. O'Brien and Fleming[11] type stopping boundaries based on the Lan-DeMets spending function were used in the interim analyses. The first interim analysis in April 2017 with 67 events led to another increase of the required number of events to 290 and of the patient number to 1,250 according to the IDMC recommendation. The second interim analysis was conducted based on 200 events (194 events planned) in April 2019, neither futility nor overwhelming efficacy boundaries were crossed, and the study continued per IDMC recommendation.

Statistical Analysis

Final analysis of the primary end point iDFS was planned after 290 iDFS events with a nominal significance level of 0.0463 (two-sided). To address the concern of possible inflation of the type I error because of the sample size increase, statistical significance was determined using a weighted statistic of the stratified log-rank test (stratified by risk status, nodal involvement after surgery, Ki-67, age, but

TABLE 2. Site of First iDFS Event

First iDFS Event	Palbociclib (n = 631), No. (Valid %)	Placebo (n = 619), No. (Valid %)	Overall (N = 1,250), No. (Valid %)
Patients with event	152 (24.1)	156 (25.2)	308 (24.6)
Site of first invasive disease event[a]			
Distant recurrence	116 (76.3)	111 (71.2)	227 (73.7)
Invasive locoregional recurrence	21 (13.8)	27 (17.3)	48 (15.6)
Contralateral breast cancer	2 (1.3)	5 (3.2)	7 (2.3)
Second primary invasive nonbreast cancer	9 (5.9)	9 (5.8)	18 (5.8)
Death without previous event	4 (2.6)	4 (2.6)	8 (2.6)

Abbreviation: iDFS, invasive disease-free survival.

[a]Patients who experienced an additional invasive-disease event at the same date of their first event are reported in the category according to the following hierarchy: distant recurrence, locoregional recurrence, contralateral breast cancer, second primary invasive nonbreast cancer.

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

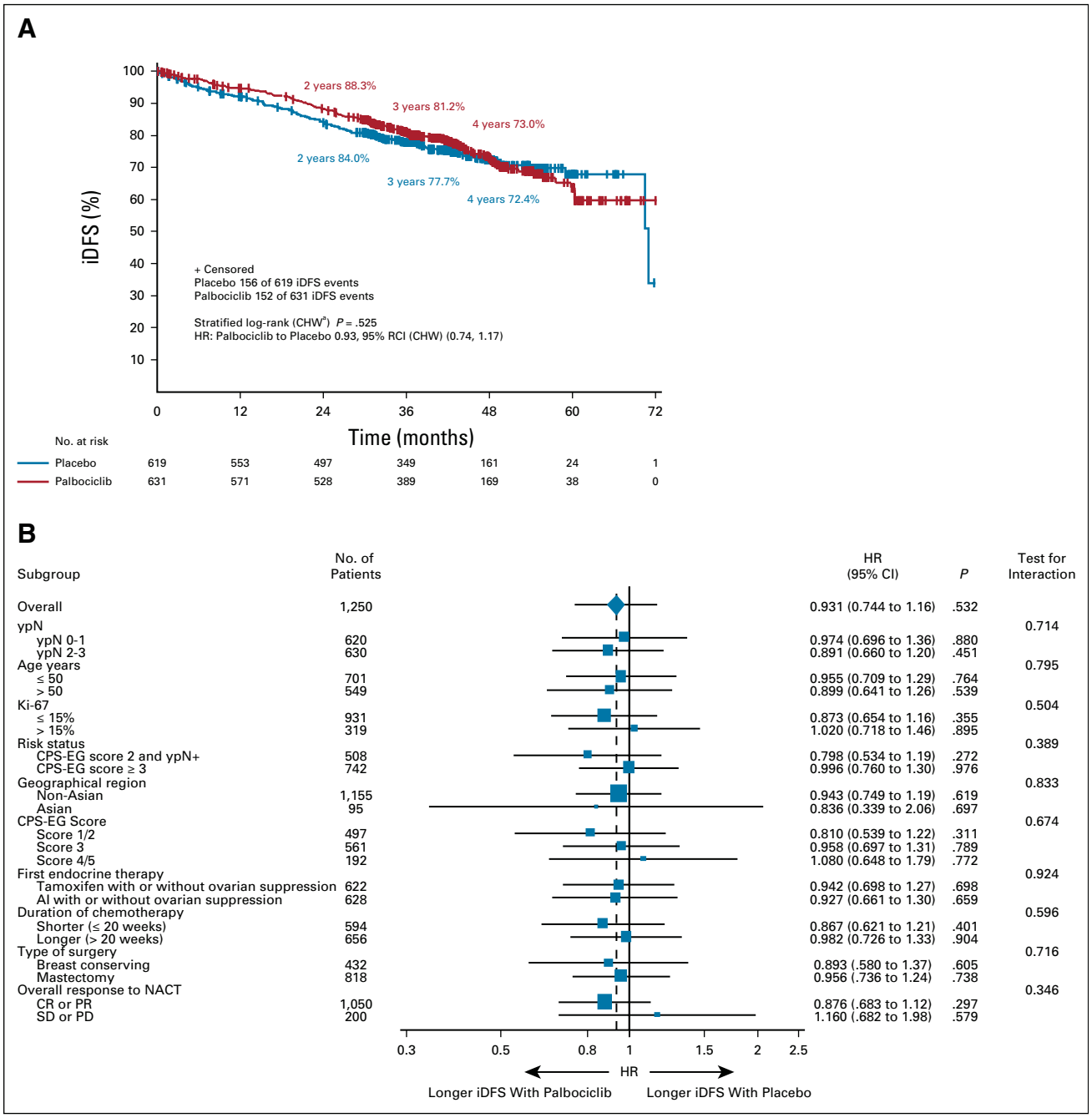

FIG 2. (A) Kaplan-Meier estimates for iDFS. The 95% CI for 2-year iDFS rates: palbociclib, 85.5% to 90.6% and placebo, 80.9% to 86.7%; for 3-year iDFS rates: palbociclib, 77.8% to 84.1% and placebo, 74.1% to 80.9%; and for 4-year iDFS rates: palbociclib, 68.6% to 76.9% and placebo, 68.1% to 76.1%. [a]Weighted log-rank test based on the CHW method, taking into account the adaptive sample size re-estimation and group sequential nature of the design. (B) Forest Plot of univariable Cox Regression for iDFS in subgroups. AI, aromatase inhibitor; CHW, Cui-Hung-Wang method; CPS-EG, clinical, pathological stage, estrogen receptor, grading; CR, complete response; HR, hazard ratio; iDFS, invasive disease-free survival; NACT, neoadjuvant chemotherapy; PD, progressive disease; PR, partial response; SD, stable disease.

not global region of participating site, as prespecified in the Protocol) based on the method of Cui, Hung, and Wang[12] (CHW) with CHW interim monitoring implemented in EAST version 6.5 (Cytel Inc). The 95% repeated CI was reported taking into account the adaptive sample size re-estimation and group sequential nature of the design.

For all other tests, the alpha was set to 0.05 (two-sided). Adjustment for multiple testing in the other tests was not planned. The Kaplan-Meier method was used to estimate the survival probability at specific time points together with a two-sided 95% CI. Univariable Cox-proportional hazards models stratified by the same factors as in the primary

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

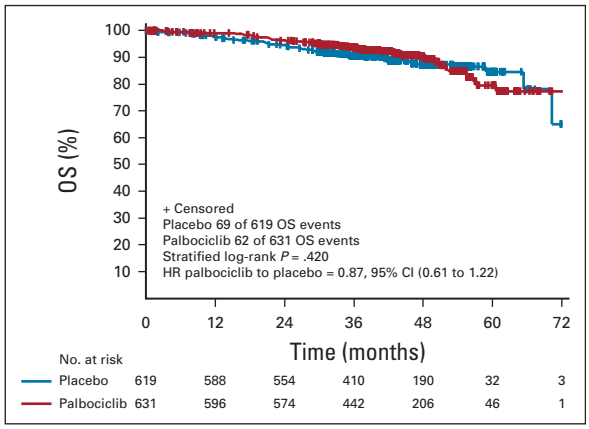

FIG 3. Kaplan-Meier estimates for OS. The 95% CI for 2-year OS rates: palbociclib, 94.5% to 97.6% and placebo, 92.3% to 96.1%; for 3-year invasive disease-free survival rates: palbociclib, 91.3% to 95.3% and placebo, 87.8% to 92.6%; and for 4-year invasive disease-free survival rates: palbociclib, 87.3% to 92.8% and placebo, 83.9% to 90.1%. OS, overall survival.

analysis were used for time-to-event end points (except LRRFI) to report hazard ratios with 95% CI. LRRFI was analyzed using the cumulative incidence function for rates at specific time points with stratified Gray's test for comparison and stratified univariate Fine-Gray model to report hazard ratio for treatment. Fisher's exact test was used to compare frequencies of AEs between arms.

All statistical analyses were performed using SAS Version 9.4 with SAS Enterprise Guide Version 7.1 on Microsoft Windows 10 Enterprise. Data cutoff date was August 24, 2020.

RESULTS

Patients and Treatment

Between February 2014 and December 2017, 1,708 patients were screened and 1,250 patients were randomly assigned in 221 sites and 11 countries to receive either palbociclib or placebo plus ET. One thousand two hundred forty-four patients started therapy, 628 in the palbociclib arm and 616 in the placebo arm (Fig 1). The baseline characteristics were well-balanced between the treatment arms (Table 1). The median age was 49 (range, 19-79) years. One hundred ninety-five of 1,250 (15.6%) were younger than 40 years. The majority were enrolled with a CPS-EG score of three and higher (59.4%) and had a Ki-67 ≤ 15% (74.5%). Almost all patients had received an anthracycline-taxane–based chemotherapy (98.6%) and adjuvant radiotherapy (98.8%) and had already started ET before enrollment (89.4%). Tamoxifen (49.8%) or AI (50.2%) with or without a luteinizing hormone releasing hormone agonist was equally used as first type of ET and was comparable between treatment arms (Table 1), but differed by menopausal status (Appendix Table A1, online only). Tamoxifen was the preferred first ET in premenopausal women (85.4%) and AI in postmenopausal women (84.9%). 203 patients (33.0%) of the premenopausal women received ovarian ablation in addition.

Efficacy

After a median follow-up of 42.8 months (92% complete),[13] 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 [73.7%]), and locoregional events were reported in 48 patients (15.6%) (Table 2). There was no difference between the two treatment arms (stratified hazard ratio 0.93 [95% repeated CI, 0.74 to 1.17], P [CHW] = .525). The estimated 3-year iDFS was 81.2% (77.8%-84.1%) with palbociclib and 77.7% (74.1%-80.9%) with placebo (Fig 2A). No subgroup could be identified, which benefitted from the addition of palbociclib to ET after NACT (Fig 2B).

The analysis of iDFS excluding second primary invasive nonbreast cancers showed a similar result (hazard ratio, 0.93 [95% CI, 0.74 to 1.16]; P = .501). LRRFI was not significantly different between the two arms. The locoregional recurrence cumulative incidence rate at 3 years was 3.7% (95% CI, 2.4% to 5.4%) with palbociclib and 4.6% (95% CI, 3.1% to 6.5%) with placebo (hazard ratio, 0.83 [95% CI, 0.49 to 1.39]; P = .514). The only subgroup that seems to 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 to 0.95]; P = .043 [Data Supplement, Supplementary Fig 2]).

At the time of final iDFS analysis, an interim analysis for OS was performed with 131 deaths reported. OS was not significantly different between the two arms (hazard ratio, 0.87 [95% CI, 0.61 to 1.23]; P = .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 (Fig 3).

Safety and Compliance

One thousand two hundred forty-four patients who started therapy, 633 with palbociclib and 611 with placebo, comprised the safety set. All patients except one in each treatment arm reported at least one AE. At least one grade 3-4 AE was significantly more often reported in the palbociclib group compared with the placebo group (79.6% *v* 20.1%). There was no difference between nonhematologic grade 3-4 AEs between the treatment groups (19.9% *v* 19.0%), but there were significantly more hematologic grade 3-4 AEs with palbociclib compared with placebo (73.1% *v* 1.3%). The most frequent AEs with a significantly higher incidence in the palbociclib arm were neutropenia of any grade (95.7% *v* 23.4%) and grade 3-4 (70.0% *v* 1.0%), leukopenia any grade (99.2% *v* 69.9%) and grade 3-4 (56.1% *v* 0.7%), thrombocytopenia any grade (56.6% *v* 16.2%), anemia any grade (73.9% *v* 30.3%), hypocalcaemia any grade (35.2% *v* 24.4%), fatigue any grade (66.4% *v* 51.1%), stomatitis any grade

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

TABLE 3. Adverse Events > 10% in Either Treatment Arm

Adverse Event	Grade	Palbociclib (n = 631), No. (Valid %)	Placebo (n = 619), No. (Valid %)	Overall (N = 1,250), No. (Valid %)	*P*
Anemia	Any	468 (73.9)	185 (30.3)	653 (52.5)	< .001
	3-4	2 (0.3)	1 (0.2)	3 (0.2)	1.000
Leukopenia	Any	628 (99.2)	427 (69.9)	1,055 (84.8)	< .001
	3-4	355 (56.1)	4 (0.7)	359 (28.9)	< .001
Neutropenia	Any	606 (95.7)	143 (23.4)	749 (60.2)	< .001
	3-4	443 (70.0)	6 (1.0)	449 (36.1)	< .001
Thrombocytopenia	Any	358 (56.6)	99 (16.2)	457 (36.7)	< .001
	3-4	5 (0.8)	2 (0.3)	7 (0.6)	.452
ALAT increased	Any	138 (21.8)	141 (23.1)	279 (22.4)	.634
	3-4	3 (0.5)	4 (0.7)	7 (0.6)	.721
Blood AP increased	Any	106 (16.7)	120 (19.6)	226 (18.2)	.187
	3-4	1 (0.2)	1 (0.2)	2 (0.2)	1.000
ASAT increased	Any	131 (20.7)	102 (16.7)	233 (18.7)	.081
	3-4	3 (0.5)	1 (0.2)	4 (0.3)	.625
Hyperkalemia	Any	67 (10.6)	80 (13.1)	147 (11.8)	.188
	3-4	3 (0.5)	3 (0.5)	6 (0.5)	1.000
Hypocalcaemia	Any	223 (35.2)	149 (24.4)	372 (29.9)	< .001
	3-4	3 (0.5)	0 (0.0)	3 (0.2)	.250
Hypomagnesemia	Any	186 (29.4)	173 (28.3)	359 (28.9)	.707
	3-4	2 (0.3)	0 (0.0)	2 (0.2)	.500
Alopecia	Any	93 (14.7)	52 (8.5)	145 (11.7)	< .001
Arthralgia	Any	261 (41.2)	286 (46.8)	547 (44.0)	.052
	3-4	5 (0.8)	9 (1.5)	14 (1.1)	.291
Back pain	Any	71 (11.2)	81 (13.3)	152 (12.2)	.299
	3-4	4 (0.6)	1 (0.2)	5(0.4)	.374
Bone pain	Any	109 (17.2)	117 (19.1)	226 (18.2)	.379
	3-4	2 (0.3)	4 (0.7)	6 (0.5)	.444
Blood creatinine increased	Any	78 (12.3)	67 (11.0)	145 (11.7)	.480
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Constipation	Any	140 (22.1)	84 (13.7)	224 (18.0)	< .001
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Cough	Any	132 (20.9)	99 (16.2)	231 (18.6)	.041
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Diarrhea	Any	116 (18.3)	96 (15.7)	212 (17.0)	.228
	3-4	1 (0.2)	3 (0.5)	4 (0.3)	.366
Fatigue	Any	420 (66.4)	312 (51.1)	732 (58.8)	< .001
	3-4	17 (2.7)	9 (1.5)	26 (2.1)	.166
Headache	Any	147 (23.2)	141 (23.1)	288 (23.2)	1.000
	3-4	3 (0.5)	3 (0.5)	6 (0.5)	1.000
Hot flushes	Any	277 (43.8)	311 (50.9)	588 (47.3)	.012
	3-4	5 (0.8)	6 (1.0)	11 (0.9)	.770

(continued on following page)

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

TABLE 3. Adverse Events > 10% in Either Treatment Arm (continued)

Adverse Event	Grade	Palbociclib (n = 631), No. (Valid %)	Placebo (n = 619), No. (Valid %)	Overall (N = 1,250), No. (Valid %)	*P*
Infection	Any	379 (59.9)	312 (51.1)	691 (55.5)	.002
	3-4	20 (3.2)	24 (3.9)	44 (3.5)	.540
Insomnia	Any	102 (16.1)	101 (16.5)	203 (16.3)	.878
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Myalgia	Any	128 (20.2)	113 (18.5)	241 (19.4)	.473
	3-4	3 (0.5)	5 (0.8)	8 (0.6)	.499
Nausea	Any	150 (23.7)	126 (20.6)	276 (22.2)	.195
	3-4	2 (0.3)	2 (0.3)	4 (0.3)	1.000
Edema peripheral	Any	126 (19.9)	99 (16.2)	225 (18.1)	.091
	3-4	0 (0.0)	1 (0.2)	1 (0.1)	.491
Pain in extremity	Any	81 (12.8)	61 (10.0)	142 (11.4)	.130
	3-4	3 (0.5)	2 (0.3)	5 (0.4)	1.000
Stomatitis	Any	174 (27.5)	53 (8.7)	227 (18.2)	< .001
	3-4	3 (0.5)	1 (0.2)	4 (0.3)	.625

Abbreviations: ALAT, alanine aminotransferase; AP, alkaline phosphatase; ASAT, aspartate aminotransferase; NA, not applicable.

(27.5% *v* 8.7%), constipation any grade (22.1% *v* 13.7%), cough any grade (20.9% *v* 16.2%), and infection (59.9% *v* 51.1%). Arthralgia (41.2% *v* 46.8%) and hot flushes (43.8% *v* 50.9%) were less frequent with palbociclib than placebo (Table 3). Serious adverse events were reported in 113 (9.1%) patients, with no difference between treatment arms; eight were fatal, two in the palbociclib arm (cardiogenic shock and influenza, both not related to study drug) and six in the placebo arm (leukemia, myeloid leukemia, hepatorenal failure, lung embolism, and two cases of sudden death because of unknown reasons).

Overall, 219 (17.5%) patients discontinued study treatment (n = 38, 3.0% because of toxicity) and 64 (5.1%) discontinued ET prematurely. 301 patients (47.6%) in the palbociclib arm compared with 11 patients (1.8%) in the placebo arm had at least one dose reduction ($P < .001$). In the last cycle, 256 patients (49.7%) still received 125 mg palbociclib, but 512 (98.5%) received full dose in the placebo arm (Data Supplement, Supplementary Fig 3). Thirteen cycles were completed by 80.5% versus 84.5% with palbociclib and placebo, respectively (Fig 1). The median duration of therapy was 52.9 weeks with palbociclib and 52.0 weeks with placebo ($P < .001$). The relative total dose intensity was significantly lower with palbociclib (82.1% *v* 98.9%, $P < .001$).

DISCUSSION

The PENELOPE-B trial failed to demonstrate that the addition of 1 year palbociclib to standard ET improved iDFS compared with placebo in a specific high-risk HR+/HER2− primary breast cancer population. All patients were considered to be at high risk to receive NACT. Almost all patients received adjuvant radiotherapy, underlining the high-risk nature of this population. The 3-year iDFS was 81.2% with palbociclib and 77.7% with placebo, with an absolute difference of 3.5%. At 2 years, the absolute difference was 4.3%. Although there is no statistical evidence for a difference in the two arms, further analyses should elucidate potential early effects of the therapy. Long-term follow-up of the other CDK4/6 inhibitor trials will show whether there is evidence for time-dependent efficacy as hypothesized in the PENELOPE-B trial, enrolling high-risk postneoadjuvant patients. It can be argued that palbociclib might delay relapses rather than sustaining a long-term effect, so 1 year of therapy may be too short and in retrospect two or more years of CDK4/6 inhibitor therapy may be needed.

About 20% of the patients in the PENELOPE-B trial, the only double-blind, placebo controlled phase III trial, did not complete 13 cycles and stopped treatment prematurely, whereas in a feasibility study, 37%[14] and in PALLAS, 42% of patients did not complete 2 years of adjuvant palbociclib.[15] In monarchE, 16% stopped abemaciclib because of AEs, and this rate was lower in PENELOPE-B.[16] In the KATHERINE trial for HER2-positive breast cancer, 31% of the patients did not complete 14 cycles of therapy.[17] This is a heavily pretreated population, and despite the high-risk status of the patients and the proven efficacy in the metastatic setting, the persistence with therapy in the adjuvant setting is lower than that in metastatic breast cancer.[18] The initially more conservative AE management was adapted to try to maintain a higher relative total dose intensity, and with more than 80%, this is acceptable.[19] The safety results in

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

the study were as expected. Interestingly, the rate of menopausal symptoms was lower with palbociclib, namely, hot flushes and arthralgia. This had also been reported in other CDK4/6 inhibitor trials and seems to be a real positive side effect of CDK4/6 inhibitors.[14,20]

Another explanation for the results could be that most patients had a low Ki-67 at surgery: Ki-67 above 15% was present in 25.5% and above 25% in only 14% of the patients. At first diagnosis (core biopsy), Ki-67 was high in three quarters of patients, showing that the low postoperative Ki-67 is a selection bias as the high-proliferating cells respond to chemotherapy. In the group with the higher Ki-67, 47% of the patients had a relapse versus only 21% in the group with a low Ki-67. However, the subgroup analysis does not suggest a differential effect for patients with high Ki-67 tumors. In fact, patients with luminal A tumors, with low Ki-67, show the same benefit when CDK4/6 inhibitors were used as neoadjuvant therapy.[21] When the PENELOPE-B trial was designed, we discussed selecting a population with high Ki-67 based on previous data.[22] In the PENELOPE-B trial, Ki-67 was the strongest prognostic factor in multivariable analysis (data not shown), emphasizing the importance of the marker. The CPS-EG score, however, was demonstrated to be a stronger independent prognostic factor and a better discriminator between low-risk and high-risk patients with residual disease and was therefore chosen as the primary inclusion criterion.[4] Biomarker analysis, that is, defined by gene expression analysis, is ongoing and might help to identify a subgroup benefiting from the addition of palbociclib to ET.[23]

None of the prespecified subgroup analysis reveals a group clearly benefitting from palbociclib. The subgroup results for locoregional relapse seem to be counterintuitive, but the interaction test is clearly negative and the results should not be overinterpreted.

At the time of the trial conception, only premature data from PALOMA-1 were available. The study was opened in December 2013 and started recruitment in February 2014, before registration of the drug. On this basis with limited safety data, the high-risk population and 1 year of therapy were chosen to justify the potential added toxicity, which in retrospect might have been too short.

Other postneoadjuvant trials in HR+ and HER2− patients also failed to improve outcome. Capecitabine in CREATE-X seemed to be beneficial in triple-negative breast cancer only.[24] The NATAN trial with zoledronic acid given for 5 years in addition to ET in patients with residual disease after NACT did not improve outcome.[25] Postneoadjuvant patients were also enrolled in the two large adjuvant studies, 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 ET 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 NACT.[13,14]

Strengths of this study are the placebo-controlled design, the clear hypothesis, which was generated based on the GBG database, and the selection of patients based on these data. HER2, hormone receptor status, and Ki-67 were centrally assessed. With a 43-month follow-up, this is the most mature early breast cancer CDK4/6 inhibitor study. The completeness of follow-up is 92%, demonstrating the high quality and robustness of the data. The control arm often improves over time and invalidates the initial study hypothesis; however, in PENELOPE-B, the control arm performed close to that estimated with an iDFS at 3 years of 77%.

In conclusion, the PENELOPE-B trial did not demonstrate that the addition of one year palbociclib to standard adjuvant ET improves iDFS in patients at high risk of relapse after NACT defined by the CPS-EG score. 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.

AFFILIATIONS

[1]German Breast Group, Neu-Isenburg, Germany
[2]Center for Hematology and Oncology Bethanien, Frankfurt, Germany
[3]Department of Gynaecology and Obstetrics, University Hospital Mannheim, Mannheim, Germany
[4]Instituto de Investigacion Sanitaria Gregorio Marañon, CIBERONC, Universidad Complutense, Madrid, Spain
[5]GEICAM, Madrid, Spain
[6]Department of Gynaecology and Obstetrics, Breast Cancer Center, HELIOS Klinikum Berlin Buch, Berlin, Germany
[7]UCBG (Unicancer Breast Cancer Group) and Institut Bergonié, Université de Bordeaux, Bordeaux, France
[8]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, and KCSG (Korean Cancer Study Group), Korea
[9]Division of Surgical Oncology, Massey Cancer Center, Virginia Commonwealth University, VCU Health, Richmond, VA
[10]NSABP Foundation, Pittsburgh, PA
[11]Breast Cancer Trials Australia and New Zealand, Newcastle, Australia
[12]Oncology Research Group, Hospital Universitario Sant Joan de Reus, Reus, Spain
[13]BC Cancer Agency, Vancouver, British Columbia, Canada
[14]Instituto de Investigación Sanitaria Hospital Clinico San Carlos (IdISSC), Madrid, Spain
[15]Mater Misericordiae University Hospital and Breast Group, Cancer Trials, Dublin, Ireland
[16]Department of Obstetrics and Gynecology, University of Rostock, Rostock, Germany
[17]Breast Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[18]Breast Department, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

[19]Institute of Pathology, University Hospital Marburg and Philipps-Universität Marburg, Germany
[20]Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria
[21]ABCSG, Vienna, Austria
[22]Mount Vernon Cancer Centre, Northwood, United Kingdom
[23]Pfizer Inc, New York, NY
[24]IEO, European Institute of Oncology, IRCCS, Milan, Italy
[25]Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil

CORRESPONDING AUTHOR

Sibylle Loibl, MD, PhD, German Breast Group, c/o GBG Forschungs GmbH, Martin-Behaim-Straße 12, 63263 Neu-Isenburg, Germany; e-mail: sibylle.loibl@gbg.de.

PRIOR PRESENTATION

Presented in part at the 2020 San Antonio Breast Cancer Symposium, Virtual Symposium, December 8-11, 2020.

SUPPORT

Supported by Pfizer in conducting the trial and drug support.

CLINICAL TRIAL INFORMATION

NCT01864746

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.03639.

DATA SHARING STATEMENT

All relevant data are within this paper and its supporting information files. The data underlying the results presented in the study are available from German Breast Group. Some restrictions apply because of confidentiality of patient data. Since these data are derived from a prospective clinical trial with ongoing follow-up collection, there are legal and ethical restrictions to share sensitive patient-related data publicly. Interested groups may use the Cooperation Proposal Form on https://www.gbg.de/en/research/trafo.php Data can be requested in context of a translational research project by sending the form to trafo@gbg.de. Translational research proposals are approved by the GBG scientific boards.

AUTHOR CONTRIBUTIONS

Conception and design: Sibylle Loibl, Hervé Bonnefoi, Harry Bear, Karen Gelmon, Masakazu Toi, Hope S. Rugo, Carsten Denkert, Michael Gnant, Andreas Makris, Maria Koehler, Cynthia Huang-Bartelett, Gustavo Werutsky, Nicole Burchardi, Valentina Nekljudova, Gunter von Minckwitz
Administrative support: Maria Koehler
Provision of study materials or patients: Frederik Marmé, Miguel Martin, Harry Bear, Mireia Melé Olivé, Karen Gelmon, Catherine M. Kelly, Hope S. Rugo, Michael Gnant, Cynthia Huang-Bartelett, Gustavo Werutsky
Collection and assembly of data: Sibylle Loibl, Frederik Marmé, Miguel Martin, Michael Untch, Sung-Bae Kim, Harry Bear, Nicole McCarthy, Mireia Melé Olivé, Karen Gelmon, José García-Sáenz, Catherine M. Kelly, Toralf Reimer, Carsten Denkert, Michael Gnant, Andreas Makris, Cynthia Huang-Bartelett, Maria Jose Lechuga Frean, Gustavo Werutsky, Sabine Seiler, Gunter von Minckwitz
Data analysis and interpretation: Sibylle Loibl, Michael Untch, Sung-Bae Kim, Harry Bear, Nicole McCarthy, Karen Gelmon, José García-Sáenz, Catherine M. Kelly, Masakazu Toi, Carsten Denkert, Andreas Makris, Cynthia Huang-Bartelett, Maria Jose Lechuga Frean, Marco Colleoni, Gustavo Werutsky, Sabine Seiler, Nicole Burchardi, Valentina Nekljudova, Gunter von Minckwitz
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank all patients and their families, the network of investigators (available in Appendix Table A2 [online only]), the international SC and the neoadjuvant Subboard of GBG and AGO-B and the IDMC, Pfizer for drug and financial support, and the team at the GBG Headquarters including data managers, monitoring, statistics, project management, and medical writing.

REFERENCES

1. von Minckwitz G, Untch M, Blohmer JU, et al: Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 30:1796-1804, 2012
2. Cortazar P, Zhang L, Untch M, et al: Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet 384: 164-172, 2014
3. Mittendorf EA, Jeruss JS, Tucker SL, et al: Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol 29:1956-1962, 2011
4. Marmé F, Lederer B, Blohmer JU, et al: Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 53:65-74, 2016
5. Finn RS, Crown JP, Ettl J, et al: Efficacy and safety of palbociclib in combination with letrozole as first-line treatment of ER-positive, HER2-negative, advanced breast cancer: Expanded analyses of subgroups from the randomized pivotal trial PALOMA-1/TRIO-18. Breast Cancer Res 18:67, 2016
6. Cristofanilli M, Turner NC, Bondarenko I, et al: Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): Final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 17:425-439, 2016
7. Turner NC, Slamon DJ, Ro J, et al: Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med 379:1926-1936, 2018
8. Loibl S, Turner NC, Ro J, et al: Palbociclib combined with fulvestrant in premenopausal women with advanced breast cancer and prior progression on endocrine therapy: PALOMA-3 results. Oncologist 22:1028-1038, 2017
9. Hudis CA, Barlow WE, Costantino JP, et al: Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: The STEEP system. J Clin Oncol 25:2127-2132, 2007
10. Mehta CR, Pocock SJ: Adaptive increase in sample size when interim results are promising: A practical Guide with examples. Stat Med 30:3267-3284, 2011
11. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. Biometrics 35:549-556, 1979
12. Cui L, Hung HM, Wang SJ: Modification of sample size in group sequential clinical trials. Biometrics 55:853-857, 1999
13. Clark TG, Altman DG, De Stavola BL: Quantification of the completeness of follow-up. Lancet 359:1309-1310, 2002

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

14. Mayer EL, DeMichele A, Rugo HS, et al: A phase II feasibility study of palbociclib in combination with adjuvant endocrine therapy for hormone receptor-positive invasive breast carcinoma. Ann Oncol 30:1514-1520, 2019
15. Mayer EL, Dueck AC, Martin M, et al: PALLAS: Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): Interim analysis of a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 22:212-222, 2021
16. Johnston SRD, Harbeck N, Hegg R, et al: Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol 38:3987-3998, 2020
17. von Minckwitz G, Huang CS, Mano MS, et al: Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 380:617-628, 2019
18. Hershman DL, Kushi LH, Shao T, et al: Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 28:4120-4128, 2010
19. Loibl S, Skacel T, Nekljudova V, et al: Evaluating the impact of Relative Total Dose Intensity (RTDI) on patients' short and long-term outcome in taxane- and anthracycline-based chemotherapy of metastatic breast cancer- a pooled analysis. BMC Cancer 11:131, 2011
20. Johnston S, Puhalla S, Wheatley D, et al: Randomized phase II study evaluating palbociclib in addition to letrozole as neoadjuvant therapy in estrogen receptor-positive early breast cancer: PALLET trial. J Clin Oncol 37:178-189, 2019
21. Ma CX, Gao F, Luo J, et al: NeoPalAna: Neoadjuvant palbociclib, a cyclin-dependent kinase 4/6 inhibitor, and anastrozole for clinical stage 2 or 3 estrogen receptor-positive breast cancer. Clin Cancer Res 23:4055-4065, 2017
22. von Minckwitz G, Schmitt WD, Loibl S, et al: Ki67 measured after neoadjuvant chemotherapy for primary breast cancer. Clin Cancer Res 19:4521-4531, 2013
23. Loibl S, Weber K, Huober J, et al. Risk assessment after neoadjuvant chemotherapy in luminal breast cancer using a clinicomolecular predictor. Clin Cancer Res 24:3358-3365, 2018
24. Masuda N, Lee SJ, Ohtani S, et al: Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 376:2147-2159, 2017
25. von Minckwitz G, Rezai M, Tesch H, et al: Zoledronate for patients with invasive residual disease after anthracyclines-taxane-based chemotherapy for early breast cancer—the phase III NeoAdjuvant Trial Add-oN (NaTaN) study (GBG 36/ABCSG 29). Eur J Cancer 64:12-21, 2016

ASCO Journals

Gain Recognition as an ASCO Journal Reviewer

Participate as a journal reviewer and play an integral role in maintaining the quality and integrity of ASCO journals. Benefits and recognition for reviewing ASCO journals content include:

- Staying up to date on the latest oncology research
- Increased exposure to key leaders in oncology
- Career advancement opportunities
- ASCO members who become reviewers can earn FASCO points

Get started today at **ascopubs.org/reviewers**

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer—The Penelope-B Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Sibylle Loibl
Honoraria: Chugai Pharma
Consulting or Advisory Role: Pfizer, Roche, Novartis, Seattle Genetics, Celgene, Lilly, AstraZeneca/MedImmune, Bristol-Myers Squibb, Merck KGaA, Abbvie, Amgen, Prime/Medscape, Daiichi Sankyo, Samsung, Puma Biotechnology, Pierre Fabre, Immunomedics, GlaxoSmithKline, EirGenix, Bayer
Research Funding: Abbvie, AstraZeneca, Vifor Pharma, Amgen, Celgene, Novartis, Pfizer, Roche, Myriad Genetics, Immunomedics, Seattle Genetics, Daiichi Sankyo, Pierre Fabre
Patents, Royalties, Other Intellectual Property: Patent Pending EP14153692.0

Frederik Marmé
Honoraria: Roche/Genentech, Novartis, Pfizer, AstraZeneca, Tesaro, Clovis Oncology, Clovis Oncology, Eisai, Celgene, Genomic Health, PharmaMar, Amgen, CureVac, MSD Oncology, Janssen-Cilag, Immunomedics, Seagen, Myriad Genetics
Consulting or Advisory Role: AstraZeneca, Tesaro, Pfizer, Roche, Novartis, Genomic Health, CureVac, Amgen, Vaccibody, Immunomedics, Celgene, Eisai, Janssen-Cilag, Immunomedics, Immunomedics
Research Funding: Roche/Genentech, Novartis, AstraZeneca, Eisai, Tesaro, Tesaro, Tesaro, Clovis Oncology, MSD Oncology, Vaccibody
Travel, Accommodations, Expenses: Roche, Roche, Pfizer, Novartis, PharmaMar, AstraZeneca

Miguel Martin
Honoraria: Roche/Genentech, Lilly, Pfizer, Novartis, Pierre Fabre
Consulting or Advisory Role: Roche/Genentech, Novartis, Pfizer, Lilly, AstraZeneca, Taiho Pharmaceutical, PharmaMar
Speakers' Bureau: Lilly/ImClone, Lilly/ImClone, Roche/Genentech, Pierre Fabre
Research Funding: Novartis, Roche, Puma Biotechnology

Michael Untch
Honoraria: AstraZeneca, Art tempi, Bristol-Myers Squibb, Celgene, Daiji Sankyo, Roche Pharma AG, Pfizer, Mundipharma, MSD Oncology, Pierre Fabre, Sanofi, Seattle Genetics, Agendia
Consulting or Advisory Role: Amgen, Abbvie, Celgene, Lilly, Mundipharma, Novartis, MSD Oncology, Pfizer, Roche Pharma AG, Agendia, Pierre Fabre, Seattle Genetics

Hervé Bonnefoi
Honoraria: Roche
Research Funding: Bayer
Travel, Accommodations, Expenses: Roche, Pfizer

Sung-Bae Kim
Honoraria: DAEHWA Pharmaceutical, ISU ABXIS
Consulting or Advisory Role: Lilly, AstraZeneca, DAEHWA Pharmaceutical, ISU Abxis
Research Funding: Novartis, Dongkook Pharma, Genzyme

Harry Bear
Stock and Other Ownership Interests: Abbvie, Pfizer, Viatris
Honoraria: Genomic Health, Merck
Consulting or Advisory Role: Merck, RNADx
Speakers' Bureau: Genomic Health
Research Funding: Merck
Travel, Accommodations, Expenses: Merck
Open Payments Link: https://openpaymentsdata.cms.gov/physician/691364

Nicole McCarthy
Consulting or Advisory Role: Roche, Pfizer, Novartis, Lilly
Travel, Accommodations, Expenses: Novartis

Karen Gelmon
Honoraria: AstraZeneca, Merck Sharp & Dohme
Consulting or Advisory Role: Pfizer, Novartis, Astrazeneca, Merck, Lilly, Bristol-Myers Squibb, NanoString Technologies, Genomic Health, Janssen Oncology, Roche, Mylan
Research Funding: Pfizer, Bristol-Myers Squibb, AstraZeneca, Roche
Expert Testimony: Genentech

José Angel García-Sáenz
Consulting or Advisory Role: Novartis, AstraZeneca, Lilly, Seagen, Daiichi Sankyo, Eisai, MSD
Research Funding: AstraZeneca
Travel, Accommodations, Expenses: Roche, Novartis

Catherine M. Kelly
Honoraria: Roche, Pfizer, Novartis, MSD Oncology, Exact Sciences, Daiichi Sankyo Europe GmbH
Travel, Accommodations, Expenses: Roche, pfizer

Toralf Reimer
Consulting or Advisory Role: Pfizer
Research Funding: Else KrÃ¶ner-Fresenius-Stiftung, German Cancer Aid
Other Relationship: Pfizer

Masakazu Toi
Honoraria: Novartis, TAKEDA, AstraZeneca, Eisai, Chugai Pharma, Taiho Pharmaceutical, Daiichi Sankyo, Yakult Pharmaceutical, Shimadzu, Pfizer, Konica Minolta, Lilly, Kyowa Kirin, Devicore medical Japan, Exact Sciences, Nippon Kayaku
Consulting or Advisory Role: Daiichi Sankyo, Kyowa Kirin, Bertis, Athenex, Bristol-Myers Squibb, Kansai Medical Net, Terumo, Luxonus, Luxonus, AstraZeneca, Lilly
Speakers' Bureau: Pfizer, AstraZeneca, Lilly, Daiichi Sankyo
Research Funding: Taiho Pharmaceutical, Chugai Pharma, Shimadzu, Astellas Pharma, AFI technology, Japan Breast Cancer Research Group, Pfizer, Eisai, Daiichi Sankyo, AstraZeneca, Ono Pharmaceutical, Nippon Kayaku, Kyoto Breast cancer Research Network
Patents, Royalties, Other Intellectual Property: JP 2017-143763 WO2017/131162A1, PCT/JP2016/004374
Travel, Accommodations, Expenses: Eisai, Takeda
Other Relationship: Japan Breast Cancer Research Group, Kyoto Breast Cancer Research Network, Organization for Oncology and Translational Research

Hope S. Rugo
Consulting or Advisory Role: Samsung, Celltrion, Puma Biotechnology
Research Funding: Macrogenics, OBI Pharma, Eisai, Pfizer, Novartis, Lilly, Genentech, Merck, Immunomedics, Odonate Therapeutics, Daiichi Sankyo, Seattle Genetics
Travel, Accommodations, Expenses: Pfizer, Novartis, Macrogenics, Mylan, Daiichi Sankyo, AstraZeneca Spain
Open Payments Link: https://openpaymentsdata.cms.gov/summary

Carsten Denkert
Stock and Other Ownership Interests: Sividon Diagnostics (now Myriad)
Honoraria: Novartis, Roche
Consulting or Advisory Role: MSD Oncology, Daiichi Sankyo, Molecular Health
Research Funding: Myriad Genetics
Patents, Royalties, Other Intellectual Property: VMScope digital pathology software, Patent application: EP18209672—cancer immunotherapy, Patent application EP20150702464—therapy response, Patent application EP20150702464—therapy response
Travel, Accommodations, Expenses: Roche

Michael Gnant
Employment: Sandoz
Honoraria: Celgene, Roche, Novartis, AstraZeneca, Amgen, NanoString Technologies, Lilly, Medison, Pfizer
Consulting or Advisory Role: AstraZeneca, Lilly
Travel, Accommodations, Expenses: AstraZeneca, Pfizer, Amgen, Ipsen, Lilly, Medtronic, Roche/Genentech

Andreas Makris
Honoraria: NanoString Technologies, Lilly, Roche, Pfizer
Consulting or Advisory Role: Roche, Lilly, Pfizer
Speakers' Bureau: NanoString Technologies, Pfizer, Lilly, Roche
Travel, Accommodations, Expenses: Roche

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

Maria Koehler
Employment: Bicycle Therapeutics, Repare Therapeutics
Stock and Other Ownership Interests: Pfizer, Agios, Amgen, Merck, Gilead Sciences
Honoraria: GLG, Atheneum
Consulting or Advisory Role: ERVAXX, Lilly Asia Ventures

Cynthia Huang-Bartelett
Employment: Pfizer, Merck, AstraZeneca
Stock and Other Ownership Interests: Pfizer, AstraZeneca

Maria Jose Lechuga Frean
Employment: Pfizer
Stock and Other Ownership Interests: Pfizer

Sabine Seiler
Stock and Other Ownership Interests: Roche
Consulting or Advisory Role: Mundipharma, Amgen
Travel, Accommodations, Expenses: Novartis

Gunter von Minckwitz
Stock and Other Ownership Interests: CARA GmbH

No other potential conflicts of interest were reported.

© 2021 by American Society of Clinical Oncology

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

APPENDIX 1

Patient Selection and Study Design

Further main eligibility criteria were Eastern Cooperative Oncology Group performance status 0 or 1; the resolution of all acute toxic effects of previous anticancer therapy or surgical procedures to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion); an estimated life expectancy of ≥ 5 years irrespective of the diagnosis of breast cancer; no known severe hypersensitivity reactions to compounds similar to palbociclib or palbociclib/placebo excipients or endocrine treatments; no inadequate organ function immediate before random assignment, including hemoglobin < 10 g/dL (100 g/L); absolute neutrophil count (ANC) < 2,000/mm³ (<2.0 × 10^9/L); platelets < 100,000/mm³ (<100 × 10^9/L); AST or ALT > 1.5 × upper limit of normal (ULN); alkaline phosphatase > 2.5 × ULN; total serum bilirubin > 1.25 × ULN; serum creatinine > 1.25 × ULN; or estimated creatinine clearance < 60 mL/min as calculated using the method standard for the institution; severe and relevant co-morbidity that would interact with the participation in the study; no evidence for infection including wound infections, HIV, or any type of Hepatitis; QTc ≤ 480 msec; no uncontrolled electrolyte disorders (eg, hypocalcemia, hypokalemia, and hypomagnesemia); no myocardial infarction, severe or unstable angina, ongoing cardiac dysrhythmias of National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 grade ≥ 2, atrial fibrillation of any grade, coronary or peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism within 6 months of random assignment; no active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper GI surgery including gastric resection; no previous malignancy (including invasive or ductal in situ breast cancer) within 5 years before random assignment, except curatively treated basal cell carcinoma of the skin and carcinoma in situ of the cervix; no current severe acute or uncontrolled chronic systemic disease (eg, diabetes mellitus) or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study; no recent (within the past year) or active suicidal behavior; no pregnancy or lactation period (women of childbearing potential had to implement adequate nonhormonal contraceptive measures during study treatment and for 90 days after discontinuation, negative serum pregnancy test in premenopausal women or women with amenorrhea of < 12 months); no major surgery within 2 weeks before random assignment; no previous treatment with any cyclin-dependent kinase 4 and 6 inhibitor; no treatment within the last 7 days before random assignment with and/or concurrent use of drugs known to be strong CYP3A4 inhibitors or inducers; no concurrent treatment with other experimental drugs; and no participation in another clinical trial with any investigational not marketed drug within 30 days before random assignment.

CPS-EG score for the inclusion was calculated according to the following table:

Clinical stage		Points
I	T1N0; T0N1mi; T1N1mi	0
IIA	T0N1; T1N1; T2N0	0
IIB	T2N1; T3N0	1
IIIA	T0-2N2	1
IIIB	T4N0-2	2
IIIC	Any T N3	2
Pathologic stage after neoadjuvant chemotherapy		
0	T0/isN0	0
I	T1N0; T0N1mi; T1N1mi	0
IIA	T0N1; T1N1; T2N0	1
IIB	T2N1; T3N0	1
IIIA	T0-2 N2; T3N1-2	1
IIIB	T4 N0-2	1
IIIC	Any T N3	2
Tumor biologic factors		
ER-negative		1
Nuclear grade 3		1

According to Mittendorf et al.[3]

Objectives and end points. Among other end points, distant disease-free survival was defined as the time period between random assignment and diagnosis of any distant recurrence of disease, any second primary invasive cancer (nonbreast), or death because of any cause, whichever occurs first; overall survival was defined as the time period in months between random assignment and death because of any cause; locoregional relapse-free interval was defined as the time period in months between random assignment and diagnosis of any stand-alone locoregional (ipsilateral breast (invasive or ductal carcinoma in situ) and local or regional lymph nodes) recurrence of disease or any stand-alone invasive contralateral breast cancer, whichever occurs first; distant recurrence, second primary invasive nonbreast cancers, and death were considered competing events.

Relative total dose intensity (RTDI) is the total dose intensity within the entire treatment achieved by a patient relative to intended dose intensity based on the planned schedule of the treatment. RTDI was calculated according to the following step-by-step algorithm:

Planned dose is the amount of a drug planned to be given in a cycle.

Planned total dose is the planned cumulative dose over the entire treatment duration, ie, if a patient was planned to receive n cycles of drug, then sum the total amount of drug planned during those n cycles,

$$\text{ie,}\quad PTD(\text{mg}) = \sum_{i=1}^{n} PD_i.$$

Planned total dose intensity (PTDI) is the planned average dose intensity over the entire treatment duration,

$$\text{ie,}\quad PTDI\ (\text{mg/wk}) = \frac{PTD}{planned\ duration\ of\ therapy\ (wk)}.$$

Actual dose is the total amount of drug that the patient has received over one cycle.

Actual total dose (ATD) is the cumulative dose of the drug that has been given over the treatment duration of n cycles,

$$\text{ie,}\quad ATD\ (\text{mg}) = \sum_{i=1}^{n} \text{actual dose}_i.$$

ATD is similar to the cumulative dose.

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

Actual total dose intensity (ATDI) is defined as the dose intensity of what has actually been administered over the n cycles,

$$\text{ie,} \quad ATDI\ (\text{mg/wk}) = \frac{ATD}{duration\ of\ therapy\ (wk)}.$$

If a patient has not received the drug at all, ATDI is considered to be 0.

RTDI is the ratio of ATDI and PTDI, expressed as a percentage (described as RDI in the study Protocol),

$$\text{ie,} \quad RTDI\ (\%) = \frac{ATDI}{PTDI} \times 100.$$

Note that RTDI expresses the effect of reductions, interruptions, and delays and premature discontinuation of a treatment.

For patients who die during study treatment or who discontinue study treatment because of disease relapse or second primary invasive nonbreast cancers, in the calculation of the planned total dose and the planned total dose intensity, the planned number of weeks of the last cycle and remaining cycles was equal to the number of weeks actually completed and the remaining cycles were not counted. For all other patients who discontinued treatment prematurely, the actual dose of the remaining weeks was considered zero doses without delay.

Available dose levels are as follows:

Dose Level	Palbociclib/Placebo for 3 of 4 Weeks (3/1 Schedule)
Starting dose	125 mg/d
−1	100 mg/d
−2	75 mg/d[a]

Discontinue study treatment or consider 75 mg/d 2/2 schedule

Toxicity management is given as follows:

Protocol A:

Toxicity	Restart Palbociclib/Placebo Treatment at
Any grade 2 toxicities for more than 3 weeks	↓ 1 Dose Level
Uncomplicated grade 3 neutropenia (ANC 500 to < 1,000/mm^3)	Same dose level ↓ 1 Dose level if neutrophil recovery delayed
Grade 3 neutropenia (ANC < 1,000/mm3) associated with a documented infection or fever ≥ 38.5°C	↓ 1 Dose level; ↓ 2 Dose levels if neutrophil recovery delayed[a]
Grade 4 neutropenia (ANC < 500/mm^3)	↓ 1 Dose level ↓ 2 Dose levels if neutrophil recovery delayed,[a] consider in addition, introduction of 3 days of treatment break in the middle of the next cycle.
Grade 3 or grade 4 thrombocytopenia (platelet count < 50,000/mm^3)	↓ 1 Dose level[b]

(continued in next column)

(continued)

Toxicity	Restart Palbociclib/Placebo Treatment at
Grade ≥ 3 nonhematologic toxicity (including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)	↓ 1 Dose level and ↓ additional Dose level if repeated toxicity in next cycle. Consider ↓ 2 Dose level if recovery from grade 3 delayed.[a] Consider introduction of 3 days of treatment break in the middle of the next cycle.

Protocol G11:

Toxicity	First Episode	Second Episode	Subsequent Episodes
Uncomplicated grade 3 neutropenia (ANC 500 to < 1,000/mm^3) with recovery to ≤ grade 2 until planned D1 of next cycle	Same dose level (DL)	Same DL	Same DL
Uncomplicated grade 3 or 4 neutropenia without recovery to ≤ grade 2 at planned D1 of next cycle Uncomplicated grade 4 neutropenia (ANC < 500/mm^3) with recovery to ≤ grade 2 until planned D1 of next cycle	Reduce to dose level-1 (DL-1)	DL-1 and break from day 10-12	DL-2 and break from day 10 to 12. Next episode is stopped or continued with 2 weeks treatment and 2 weeks holiday
Neutropenia grade 3 or 4 associated with a documented infection; Febrile neutropenia Thrombocytopenia grade 3 or 4	DL-1 and either break from day 10-12 or 2 week drug holiday	DL-2 and either break from day 10-12 or 2 week drug holiday	Stop
Any grade 2 toxicities for more than 3 weeks (except for neutropenia or alopecia)	DL-1	DL-2	Stop
Nonhematologic toxicity grade 3 or 4 (including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment; nonincluding alopecia)	DL-1 Consider break from day 10-12 Consider DL-2 for 2 weeks ***or*** 2 weeks holiday if recovery is delayed	DL-2 Consider break from day 10-12 Consider DL-2 for 2 weeks ***or*** 2 weeks holiday if recovery is delayed	Stop

© 2021 by American Society of Clinical Oncology

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

Method for sample size re-estimation. The study design in the PENELOPE[B] trial included the possibility of a sample size re-estimation (SSR) to increase the number of events based on the result of the first interim analysis. For the decision about the SSR, the promising zone[10] for the possible outcomes of the interim analysis was defined based on conditional power (the probability of achieving statistical significance at the end of the trial, given the interim analysis' result) to be ranging from 30% conditional power (lower limit) to 85% conditional power (upper limit). In case the results of the first interim analysis fall in the promising zone, it was planned to perform a fixed sample size increase to a predefined maximum number of events, to prevent reverse engineering, the possibility to back calculate the interim analysis treatment effect on the basis of the increase of events. An upper limit of approximately 14% increase from the planned number of 255 events to a maximum number of 290 events was defined, corresponding to a maximum sample size of 1,250 patients. The first interim analysis was performed by an unblinded statistician providing the results to the Independent Data Monitoring Committee where the decision about the SSR was made based on predefined rules determined in the Independent Data Monitoring Committee charter. The study team remained blinded to the interim result.

TABLE A1. Overview of First Endocrine Therapy by Menopausal Status, ITT Analysis Set

First Endocrine Therapy	Premenopausal (n = 616), No. (Valid %)	Postmenopausal (n = 634), No. (Valid %)	Overall (N = 1,250), No. (Valid %)	*P*
Started ET before palbociclib/placebo	558 (90.6)	559 (88.2)	1,117 (89.4)	.170
Concomitant start of ET and palbociclib/placebo	58 (9.4)	75 (11.8)	133 (10.6)	
First ET applied				
Tamoxifen ± ovarian suppression	526 (85.4)	96 (15.1)	622 (49.8)	< .001
AI ± ovarian suppression	90 (14.6)	538 (84.9)	628 (50.2)	
Additional ovarian ablation	203 (33.0)	18 (2.8)	221 (17.7)	

Abbreviations: AI, aromatase inhibitor; ET, endocrine treatment; ITT, intent-to-treat.

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

TABLE A2. Participating Investigators (the following investigators have contributed patients to the Penelope-B study)

Organization	Department	City	Country	First Name	Last Name	No. of Patients
Universitätsklinikum Hamburg-Eppendorf	Klinik und Poliklinik für Gynäkologie	Hamburg	Germany	Isabell	Witzel	9
Universitätsklinikum Heidelberg	NCT, Gynäkologische Onkologie	Heidelberg	Germany	Andreas	Schneeweiss	34
Universitätsklinikum Mannheim GmbH	Frauenklinik	Mannheim	Germany	Frederik	Marmé	1
Universitätsmedizin Mainz, Klinik für Gynäkologie und Frauenheilkunde	Gebäude 102, Raum 502 (EG)	Mainz am Rhein	Germany	Marcus	Schmidt	3
Rotkreuzklinikum München	Frauenklinik	München	Germany	Claus	Hanusch	16
Klinikum rechts der Isar der Techn. Univ. München	Frauenklinik, Studienzentrale (Zi 1.31)	München	Germany	Stefan	Paepke	4
Klinikum am Steinenberg	Frauenklinik	Reutlingen	Germany	Martina	Negwer	2
Agaplesion Ev. Klinikum Schaumburg	Frauenklinik	Obernkirchen	Germany	Sabine	Lemster	1
Universitätsklinikum Münster	Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe	Münster	Germany	Joke	Tio	6
Klinikum Südstadt	Universitätsfrauenklinik	Rostock	Germany	Toralf	Reimer	4
Klinikum Kassel GmbH	Frauenklinik	Kassel	Germany	Gabriele	Feisel-Schwickardi	4
ViDia Christliche Kliniken/St Vincentius-Kliniken	Klinik für Gynäkologie und Geburtshilfe	Karlsruhe	Germany	Oliver	Tomé	5
Universitätsklinikum Ulm	Frauenklinik	Ulm	Germany	Jens	Huober	12
Praxis für Frauenheilkunde und Geburtshilfe	Facharzt für Frauenheilkunde und Geburtshilfe	Wunstorf	Germany	Guido	Süttmann	1
DIAKOVERE Henriettenstift Gynäkologie	Frauenklinik	Hannover	Germany	Kristina Maria	Lübbe	11
Universitätsklinikum Schleswig-Holstein	Klinik für Gynäkologie und Geburtshilfe SGO Kiel	Kiel	Germany	Marion Tina	van Mackelenbergh	12
Sana Klinikum Offenbach GmbH	Frauenklinik, Studienambulanz AOZ	Offenbach am Main	Germany	Christian	Jackisch	8
Brustzentrum Mittelthüringen	Onkologische Praxis	Mühlhausen	Germany	Steffi	Busch	1
Gemeinschaftspraxis für Hämatologie und Onkologie		Langen	Germany	Roswitha	Fuchs	2
Klinikum Bremen Mitte	Klinik für Gynäkologie und Geburtshilfe	Bremen	Germany	Mustafa	Aydogdu	2
Kliniken Essen-Mitte Evang. Huyssens-Stiftung/ Knappschaft GmbH	Klinik für Senologie/Brustzentrum	Essen	Germany	Sherko	Kümmel	16
Klinikum Hanau GmbH	Frauenklinik	Hanau	Germany	Thomas	Müller	4
Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden	Frauenklinik	Dresden	Germany	Theresa	Link	16
Klinikum Rosenheim	Abt. Gynäkologie u. Geburtshilfe	Rosenheim	Germany	Andreas	Schnelzer	1
Charité Universitätsmedizin Campus Charité Mitte	Klinik für Gynäkologie & Brustzentrum	Berlin	Germany	Jens-Uwe	Blohmer	2
Evangelisches Krankenhaus	Klinik für Senologie	Gelsenkirchen	Germany	Hans Holger	Fischer	6
Universitätsklinikum Tübingen	Frauenklinik	Tübingen	Germany	Eva-Maria	Grischke	6
g.SUND Gynäkologie Kompetenzzentrum Stralsund	Studiensekretariat	Stralsund	Germany	Carsten	Hielscher	1
Kreiskrankenhaus Torgau	Gynäkologie	Torgau	Germany	Eike	Simon	4
SRH Wald-Klinikum Gera GmbH	Zentrum für klinische Studien; Standort 1/Hauptgebäude/Ebene 1	Gera	Germany	Dirk-Michael	Zahm	9
DONAUISAR Klinikum Deggendorf	Abt. f. Senologie, Mammazentrum	Deggendorf	Germany	Sara	Tato-Varela	4
HELIOS Dr Horst Schmidt Kliniken Wiesbaden	Klinik für Gynäkologie und gynäkologischen Onkologie Zentrallager, Weiterleitung an Studiensekr., Fr. Sabine Schoen, Station A63 Raum 06 A3 05 oder 06 A3 06	Wiesbaden	Germany	Tatjana	Cordes	4
Schwerpunktpraxis	der Gynäkologie und Onkologie	Fürstenwalde	Germany	Georg	Heinrich	7
Vinzenz-von-Paul-Kliniken, Marienhospital	Frauenklinik	Stuttgart	Germany	Manfred	Hofmann	9

(continued on following page)

© 2021 by American Society of Clinical Oncology

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

TABLE A2. Participating Investigators (the following investigators have contributed patients to the Penelope-B study) (continued)

Organization	Department	City	Country	First Name	Last Name	No. of Patients
Klinikum Frankfurt Höchst GmbH	Klinik für Gynäkologie und Geburtshilfe	Frankfurt am Main	Germany	Joachim	Rom	4
MediOnko-Institut GbR	Praxisklinik Krebsheilkunde	Berlin	Germany	Peter	Klare	9
Johanniter-Krankenhaus Genthin-Stendal	Klinik für Frauenheilkunde und Geburtshilfe	Stendal	Germany	Andrea	Stefek	1
Heinrich-Heine-Universität Düsseldorf	Frauenklinik	Düsseldorf	Germany	Eugen	Ruckhäberle	2
Ruppiner Kliniken	Frauenklinik	Neuruppin	Germany	Bernd	Christensen	2
HELIOS Klinikum Berlin Buch	Frauenklinik, Studiensekretariat, Brustzentrum, B2, Raum B2U-012	Berlin	Germany	Michael	Untch	9
Kreiskliniken Böblingen gGmbH	Frauenklinik	Böblingen	Germany	Grischa	Wachsmann	6
MVZ in der Klinik Dr Hancken	Onkologie/Hämatologie	Stade	Germany	Johannes	Meiler	3
Centrum für Hämatologie und Onkologie am Bethanien-Krankenhaus	Onkologie/Tagesklinik	Frankfurt am Main	Germany	Hans	Tesch	17
Universitätsklinikum Erlangen	Frauenklinik mit Poliklinik	Erlangen	Germany	Peter	Fasching	7
Universitätsklinikum Essen	Klinik für Frauenheilkunde und Geburtshilfe; Brustzentrum, Studiensekretariat Raum 0.26	Essen	Germany	Oliver	Hoffmann	4
MVZ Nordhausen gGmbH im Südharz Krankenhaus	Frauenklinik	Nordhausen	Germany	Andrea	Grafe	3
Caritasklinik St Theresia	Frauenklinik	Saarbrücken	Germany	Mustafa	Deryal	7
Schwarzwald-Baar-Klinikum	Klinik für Frauenheilkunde und Geburtshilfe	Villingen-Schwenningen	Germany	Judith	Maier Burgoa	2
Onkologische Schwerpunktpraxis	Studiengesellschaft Onkologie Bielefeld GbR	Bielefeld	Germany	Marianne	Just	10
Klinikum der Otto-v.-Guericke-Universität	Frauenklinik	Magdeburg	Germany	Franziska	Thele	2
Klinikum Wels-Grieskirchen GmbH	Abt. f. Innere Medizin IV	Wels-Grieskirchen	Österreich	Renate	Pusch	2
Brustzentrum Kärnten am Krankenhaus der Barmherzigen Brüder	Interne Abteilung	St Veit a. d. Glan	Österreich	Harald	Weiss	1
Christliches Klinikum Unna Mitte	Geburtshilflich-Gynäkologische Abteilung	Unna	Germany	Van Anh	Tran Nguyen	1
Ortenau Klinikum Offenburg-Kehl	Frauenklinik mit Brustzentrum	Offenburg	Germany	Matthias	Frank	7
Brustzentrum im Hanuschkrankenhaus	III. Med. Abteilung	Wien	Germany	Ursula	Selim	1
Gemeinschaftspraxis	Dres. Heinrich/Bangerter	Augsburg	Germany	Bernhard	Heinrich	8
Krankenhaus St Elisabeth und St Barbara Halle	Klinik für Gynäkologie und Geburtshilfe	Halle	Germany	Tilmann	Lantzsch	1
St Elisabeth-Krankenhaus	Brustzentrum Köln-Hohenlind	Köln	Germany	Gertrud	Helling-Giese	2
Klinikum Chemnitz	Frauenklinik	Chemnitz	Germany	Petra	Krabisch	3
Caritas-Krankenhaus St Josef	Klinik für Frauenheilkunde und Geburtshilfe	Regensburg	Germany	Stephan	Seitz	1
Klinikum Esslingen GmbH	Klinik für Frauenheilkunde, Brustzentrum	Esslingen am Neckar	Germany	Thorsten	Kühn	14
GOSPL - Gesellschaft für onkologische Studien	Hämatologie und Onkologie	Troisdorf	Germany	Helmut	Forstbauer	1
Cardiac Research/Onco Research/St Johannes Hospital	Klinische Forschung	Dortmund	Germany	Georg	Kunz	4
Luisenkrankenhaus GmbH & Co KG		Düsseldorf	Germany	Maren	Darsow	7
Johannes Wesling Klinikum Minden	Zentrum für Innere Medizin, Klinik für Hämatologie/Onkologie	Minden	Germany	Martin	Grießhammer	1
Hochwaldkrankenhaus, Gesundheitszentrum Wetterau gGmbH	Frauenklinik, Gynäkologie—Senologie	Bad Nauheim	Germany	Ulrich	Groh	4
Sana Klinikum Hameln-Pyrmont	Frauenklinik/Brustzentrum	Hameln	Germany	Thomas	Noesselt	3
Helios Klinikum Gifhorn	Interdisziplinäres Brustzentrum	Gifhorn	Germany	Thomas H.	Dewitz	2
Kliniken der Stadt Köln GmbH	Brustzentrum Köln-Holweide	Köln	Germany	Mathias	Warm	4
Gemeinschaftspraxis Dr Illmer, Dr Wolf, Dr Jacobasch, Dr Freiberg-Richter	Innere Medizin/Hämatologie	Dresden	Germany	Thomas	Illmer	1

(continued on following page)

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

TABLE A2. Participating Investigators (the following investigators have contributed patients to the Penelope-B study) (continued)

Organization	Department	City	Country	First Name	Last Name	No. of Patients
Klinikum Oldenburg AöR	Universitätsklinik für Innere Medizin - Onkologie und Hämatologie	Oldenburg	Germany	Claus-Henning	Köhne	3
Hämato-Onkologie im Medicum		Bremen	Germany	Ralf	Meyer	6
Robert-Bosch-Krankenhaus		Stuttgart	Germany	Andreas	Gerteis	4
Gemeinschaftspraxis für Gynäkologie und Geburtshilfe		Salzgitter	Germany	Wolfgang	Dietz	2
Diakonissen-Stiftungs-Krankenhaus Speyer	Klinik für Gynäkologie und Geburtshilfe/ Studienmanagement	Speyer	Germany	Anette	Ligl-Löhner	1
Leopoldina-Krankenhaus der Stadt Schweinfurt	Frauenklinik	Schweinfurt	Germany	Michael	Weigel	3
Gynäkologisches Zentrum Schwerpunkt Gyn. Onkologie	Gynäkol. Onkologie	Bonn	Germany	Christian	Kurbacher	1
Gemeinschaftspraxis Saarbrücken	Drs. Hauptmann, Wagner, Brandner	Saarbrücken	Germany	Steffen	Wagner	5
Klinikum Darmstadt	Frauenklinik	Darmstadt	Germany	Sven	Ackermann	3
Marienhospital Bottrop gGmbH	Klinik f. Gynäkologie u. Geburtshilfe	Bottrop	Germany	Hans-Christian	Kolberg	2
Studienzentrum Onkologie Ravensburg	Fachärzte für Innere Medizin, Hämatologie und Onkologie	Ravensburg	Germany	Thomas	Decker	6
Klinikum Ludwigsburg	Frauenklinik	Ludwigsburg	Germany	Claudia	Hänle	2
Praxis Dr B. Adhami	Facharzt für Frauenheilkunde und Geburtshilfe	Erkelenz	Germany	Barmak	Adhami	2
Institut für Versorgungsforschung in der Onkologie	Praxisklinik für Hämatologie und Onkologie	Koblenz am Rhein	Germany	Jörg	Thomalla	5
Universitäts Klinikum Innsbruck	Klinische Abteilung für Gynäkologie und Geburtshilfe	Innsbruck	Österreich	Daniel	Egle	1
Oncologianova GmbH	Onkologie	Recklinghausen	Deutschland	Till-Oliver	Emde	9
Gynäkologische Schwerpunktpraxis		Wolfenbüttel	Germany	Walter	Dallacker	1
St Josef KH	Brustgesundheitszentrum—Vinzenzgruppe Wien	Wien	Österreich	Leopold	Öhler	4
KH Hietzing Wien	Gyn. Abt.; Karl Landsteiner Institut f. gyn. Onkologie	Wien	Österreich	Paul	Sevelda	3
MedUni Graz—Univ-. Klinik f. Frauenheilkunde u. Geb.hilfe	Klin. Abt. f. Gynäkologie	Graz	Österreich	Vesna	Bjelic-Radisic	2
MedUni Graz—Med. Univ.-Klinik	Klin. Abt. f. Onkologie	Graz	Österreich	Herbert	Stöger	2
LKH Rottenmann	Chir. Abteilung	Rottenmann	Österreich	Dieter	Gunegger	1
Ballarat Oncology and Haematology Services		Wendouree	Australia	George	Kannourakis	1
Cabrini Hospital		Brighten	Australia	Yoland	Antill	15
Icon Cancer Care Wesley	Wesley Medical Center	Auchenflower	Australia	Nicole	McCarthy	1
Macarthur Cancer Therapy Center		Campbelltown	Australia	Belinda	Kiely	7
Maroondah Hospital	Maroondah Breast Clinic	Ringwood East	Australia	Jacqueline	Chirgwin	7
Mater Adult Hospital, Brisbane	Division of Cancer Services	South Brisbane	Australia	Natasha	Woodward	10
Mater Hospital, Sydney		North sydney	Australia	Frances	Boyle	14
Monash Health	Clinical Trial Center, Level 7	Clayton	Australia	Michelle	White	12
Royal Adelaide Hospital	Medical Oncology	Adelaide	Australia	Nick	Murray	1
Royal Brisbane and Women's Hospital	Cancer Care Services	Herston, Brisbane	Australia	Po-ling	Inglis	1
Fiona Stanley Hospital	Dept. Oncology	Murdoch	Australia	Andrew	Redfern	6
Royal Prince Alfred Hospital/Chris O'Brien Lifehouse		Camperdown	Australia	Jane	Beith	4
Victorian Breast & Oncology Care	Victorian Breast & Oncology Care	East Melbourne	Australia	Mitchell	Chipman	8
Sunshine Hospital	Department of Cancer	St Albans	Australia	Catherine	Oakman	2
Hospital Teresa Herrera, Complejo Hospitalario A Coruña	Servicio de Oncología	A Coruña	Spain	Lourdes	Calvo Martínez	8
Complejo Hospitalario de Jaen		Jaen	Spain	Maria	Lomas Garrido	2

(continued on following page)

© 2021 by American Society of Clinical Oncology

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

TABLE A2. Participating Investigators (the following investigators have contributed patients to the Penelope-B study) (continued)

Organization	Department	City	Country	First Name	Last Name	No. of Patients
Hospital Gregorio Marañon	Servicio de Oncologìa Médica	Madrid	Spain	Miguel	Martin	11
Hospital Clinic i Provincial		Barcelona	Spain	Montserrat	Muñoz Mateu	4
Hospital Universitario de Canarias		Tenerife	Spain	Josefina	Cruz Jurado	17
HU ARNAU DE VILANOVA		Lleida	Spain	Serafin	Morales	1
Hospital Reina Sofia	Servicio Oncología Planta sotano	Cordoba	Spain	Juan	de la Haba Rodriguez	12
Hospital Clinico Univ Virgen de la Arrixaca		Murcia	Spain	Jose Luis	Alonso Romero	8
Hospital Universitario Infanta Cristina	Centro de Investigacíon Clinica e Área de Salud de Badajoz - Planta Semisótano	Badajoz	Spain	Juan Ignacio	Delgado Mingorance	5
Hospital San Pedro de Alcantara		Caceres	Spain	Santiago	González Santiago	6
Instituto Valenciano Oncologia	Clinica del Servicio de Oncologia Medica	Valencia	Spain	Amparo	Ruiz Simon	12
Hospital Parc Tauli		Sabadell	Spain	Elsa	Dalmau Portulas	9
Hospital Clinico Universitario Virgen De La Victoria		Malaga	Spain	Emilio	Alba Conejo	14
Seoul National University Hospital		Seoul	Korea, Republik (Südkorea)	Seock-Ah	Im	22
Asan Medical Center		Seoul	Korea, Republik (Südkorea)	Sung-Bae	Kim	28
Kyoto University Hospital		Kyoto	Japan	Masahiro	Takada	3
Tsukuba University Hospital		Nagoya	Japan	Hiroko	Bando	7
Chiba Cancer Center		Chiba	Japan	Naohito	Yamamoto	12
Tokyo Metropolitan Komagome Hospital		Tokyo	Japan	Tomoyuki	Aruga	7
National Hospital Organization Osaka National Hospital		Osaka	Japan	Masuda	Norikazu	6
National Kyushu Cancer Center		Fukuoka	Japan	Eriko	Tokunaga	10
Institut Bergonié	Oncologie Médicale	Bordeaux	Frankreich/France	Hervè, Renè, Claude	Bonnefoi	19
CHD Vendee - Service Onco-hematologie		La Roche-sur-Yon	Frankreich/France	Tifenn	I\\'Haridon	1
Center Georges François Leclerc		Dijon	Frankreich/France	Bruno	Coudert	8
Center Paul Strauss	Oncologie Médicale	Strasbourg	Frankreich/France	Thierry	Petit	1
Institut Sainte Catherine		Avignon	Frankreich/France	Julien	Grenier	1
Center Alexis Vautrin, Institut cancérologie de Lorraine		Vandœuvre-lès-Nancy	Frankreich/France	Elisabeth	Luporsi	1
CHU Limoges		Limoges	Frankreich/France	Laurence	Venat-Bouvet	6
Hôpital René Huguenin/Institut Curie		Saint-Cloud	Frankreich/France	Etienne	Brain	10
Clinique Mutualiste de I\\'Estuaire		Saint-Nazaire	Frankreich/France	Valérie	Delecroix	1
Center François Baclesse		Caen	Frankreich/France	Christelle	Levy	5
Center Eugène Marquis		Rennes	Frankreich/France	Thibault	De la Motte Rouge	9
Center Henri Becquerel		Rouen	Frankreich/France	Cristian	Moldovan	6
CHU Brest Morvan, ICH, Bat 3		Brest	Frankreich/France	Hélène	Simon	5
Hopitaux Universitaires de Strasbourg		Strasbourg	Frankreich/France	Jean-Emmanuel	Kurtz	7
Hospital Universitario Ramón y Cajal		Madrid	Spain	Noelia	Martinez Janez	22
Hospital Germans Trias i Pujol		Badalona	Spain	Mireia	Margeli Vila	9
H. Santa Creu I Sant Pau		Barcelona	Spain	Agusti	Barnadas Molins	5
Hospital Universitario Basurto	Servicio de Oncología médica	Bilbao	Spain	Purificación	Martínez Del Prado	6
Hospital Universitario La Fe		Valencia	Spain	Ana	Santaballa Bertrán	4
Hospital Universitario Miguel Servet		Zaragoza	Spain	Antonío	Antón Torres	18
Center Catherine de Sienne		Nantes	Frankreich/France	Alain	Lortholary	6

(continued on following page)

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

TABLE A2. Participating Investigators (the following investigators have contributed patients to the Penelope-B study) (continued)

Organization	Department	City	Country	First Name	Last Name	No. of Patients
Institut Claudius Regaud		Toulouse	Frankreich/France	Florence	Dalenc	11
Medical University of Vienna	Brustambulanz AKH Wien	Wien	Österreich	Günther	Steger	3
Ordensklinikum Linz	Internal Medicine I: Medical Oncology and Hematology	Linz	Österreich	Andreas	Petzer	3
Univ. Klinik für Innere Medizin III		Salzburg	Österreich	Richard	Greil	2
University of Iowa Hospitals and Clinics	Department of Medical Oncology C 32 GH	Iowa City	United States	Mark	Karwal	2
Hillman Cancer Center		Pittsburgh	United States	Adam	Brufsky	2
UPMC Cancer Center McKeesport		McKeesport	United States	Adam	Brufsky	2
Magee Women's Hospital of UPMC		Pittsburgh	United States	Adam	Brufsky	3
UPMC Cancer Center Passavant (OHA)		Pittsburgh	United States	Adam	Brufsky	1
SMBD Jewish General Hosptial		Montreal	Canada	Jean-Francois	Boileau	3
Stefanie Spielman Comprehensive Breast Center		Columbus	United States	William B.	Farrar	6
Rush University Medical Center		Chicago	United States	Melody	Cobleigh	1
McGill University Health Centre-Montreal General Hospital		Montreal	Canada	Michael	Thirlwell	4
Cross Cancer Institute		Edmonton	Canada	Karen	King	8
Rex Cancer Center		Raleigh	United States	Susan	Moore	2
Rex Cancer Center		Raleigh	United States	Susan	Moore	1
CHU de Québec - Hopital du Saint-SacrementCentre des Maladies du Sein Deschênes-Fabia		Quebec City	Canada	Louise	Provencher	19
Breast Cancer Care Consultants		Vancouver	Canada	Karen	Gelmon	18
Columbia University		New York	United States	Melissa	Accordino	9
Cleveland Clinic Foundation		Cleveland	United States	Jame	Abraham	2
Stanford University		Stanford	United States	Irene	Wapnir	6
UF Cancer Center at Orlando Health		Orlando	United States	Reagan	Rostorfer	7
Penn State Hershey Cancer Inst		Hershey	United States	Cristina	Truica	3
West Penn Hosptial		Pittsburgh	United States	Thomas	Julian	1
Covenant Health System dba Joe Arrington Cancer Research and Treatment Center		Lubbock	United States	Ibrahim	Shalaby	1
Virginia Commonwealth University Health System, Massey Cancer Center		Richmond	United States	Hetal	Vachhani	2
Center Hospitalier de l'Université de Montréal (CHUM)-Hôtel Dieu		Montreal	Canada	Andre	Robidoux	4
Long Beach Memorial		Long Beach	United States	Bichlien	Nguyen	2
Stroger Hospital		Chicago	United States	Thomas	Lad	3
University Hospitals Case Medical Center - Seidman Cancer Center		Cleveland	United States	Robert	Shenk	1
UHHS Westlake-Seidman Cancer Center		Westlake	United States	Robert	Shenk	1
UHHS Chagrin Highlands-Seidman Cancer Center		Orange Village	United States	Robert	Shenk	1
The Methodist Hospital		Houston	United States	Jenny	Chang	4
Avera Cancer Institute		Sioux Falls	United States	Amy	Krie	5
Colorado Cancer Research Program		Denver	United States	Keren	Sturtz	2
Providence Portland Medical Center		Portland	United States	Alison	Conlin	2
Kaiser Permanente		San Diego	United States	Jonathan	Polikoff	2
Kaiser Permanente		Riverside	United States	Jonathan	Polikoff	1
UC San Deigo Moores Cancer Center		La Jolla	United States	Anne	Wallace	1
UCSF		San Francisco	United States	Hope	Rugo	7
Swedish Cancer Institute		Seattle	United States	Henry	Kaplan	3
Loyola University Medical Center		Maywood	United States	Kathy	Albain	1

(continued on following page)

© 2021 by American Society of Clinical Oncology

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.

TABLE A2. Participating Investigators (the following investigators have contributed patients to the Penelope-B study) (continued)

Organization	Department	City	Country	First Name	Last Name	No. of Patients
University of Minnesota		Minneapolis	United States	Heather	Beckwith	3
Women and Infants Hospital-Breast Health Center		Providence	United States	William	Sikov	6
Blood and Cancer Ca		Laguna Hills	United States	Bichlien	Nguyen	1
Bon Secours Hospital		Cork	Ireland	Conleth	Murphy	4
St James's Hospital		Dublin	Ireland	John	Kennedy	8
University Hospital Waterford		Waterford	Ireland	Miriam	O'Connor	2
Park Nicollet Frauenshuh Cancer Center		Saint Louis Park	United States	Michaela	Tsai	4
Minnesota Oncology Minneapolis		Minneapolis	United States	Michaela	Tsai	2
Hennepin County Medical Center		Minneapolis	United States	Michaela	Tsai	1
Cleveland Clinic Florida		Weston	United States	Jame	Abraham	3
Cancer Care Specialist of Central Illinois		Decatur	United States	James	Wade	1
West Virginia University		Morgantown	United States	Mohamad Adham	Salkeni	2
Royal Bournemouth Hospital		Bournemouth	Großbritannien/United Kingdom	Tamas	Hickish	2
Western General Hospital		Edinburgh	Großbritannien/United Kingdom	Olga	Oikonomidou	2
Tom Baker Cancer Center	Department of Medicine	Calgary	Canada	Alexander	Paterson	4
St Vincent's Uni Hospital	Medical Oncology	Dublin	Ireland	Giuseppe	Gullo	9
Cork Uni Hospital	Oncology Dept	Cork	Ireland	Seamus	O'Reilly	5
Beaumont Hospital	Cancer Clinical Trials Unit	Dublin	Ireland	Patrick	Morris	2
Mater Misericordiae Uni Hospital	Oncology	Dublin	Ireland	Catherine	Kelly	8
Galway Uni Hospital	Oncology Dept	Galway	Ireland	Maccon	Keane	9
Norton Healthcare Inc		Louisville	United States	John	Hamm	1
Barwon Health	Andrew Love Cancer Center	Geelong	Australia	Karen Louise	White	1
Hospital Universitario Clínico San Carlos	Servicio Oncología	Madrid	Spain	José Ángel	García Sáenz	28
Hosp San Joan de Reus		Reus	Spain	Kepa	Amillano Parraga	28
Hospital Universitario Virgen del Rocio		Sevilla	Spain	Manuel	Ruiz Borrego	10
Hospital Clínico Universitario de Valencia	Servicio de Oncologia Médica	Valencia	Spain	Begoña	Bermejo de las Heras	15
Hospital Vall d'Hebron	Servicio de Oncologia Medica	Barcelona	Spain	Meritxell	Bellet Ezquerra	9
Institut Curie		Paris	Frankreich/France	Paul	Cottu	12
Center Oscar Lambret		Lille	Frankreich/France	Audrey	Mailliez	6
Center Antoine Lacassagne		Nice	Frankreich/France	Jean Marc	Ferrero	2
Institut Jean Godinot		Reims	Frankreich/France	Christelle	Jouannaud	4

Downloaded from ascopubs.org by 139.226.100.36 on October 10, 2022 from 139.226.100.036
Copyright © 2022 American Society of Clinical Oncology. All rights reserved.