PD17-05

Development and validation of a composite biomarker (luminal A, *ERBB2*, and PR) predictive of palbociclib + endocrine treatment benefit in early breast cancer: PENELOPE-B and PALLAS trials

Sibylle Loibl,[1] Carsten Denkert,[2] Yuan Liu,[3] Erik S. Knudsen,[4] Angela DeMichele,[5] Zhe Zhang,[3] Julia Teply-Szymanski,[6] Martin Filipits,[7] Peter A. Fasching,[8] Michael Gnant,[7] Shibing Deng,[3] Marija Balic,[9] Federico Rojo,[10] Mark Watson,[11] Chetan Deshpande,[3] Nicolas Turner,[12] Otto Metzger,[13] Kathy Puyana Theall,[14] Agnieszka Witkiewicz,[4] Olga Valota,[15] W. Fraser Symmans,[16] Erica L. Mayer[13]

[1]German Breast Group, Neu-Isenburg, Germany; [2]University Hospital Marburg, Marburg, Germany; [3]Pfizer Inc, San Diego, CA, USA; [4]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [5]University of Pennsylvania, Philadelphia, PA, USA; [6]Philipps University Marburg, Marburg, Germany; [7]Medical University of Vienna, Vienna, Austria; [8]University Hospital Erlangen, Erlangen, Germany; [9]Medical University of Graz, Graz, Austria; [10]IIS-Fundacion Jimenez Diaz University Hospital CIBERONC GEICAM, Madrid, Spain; [11]Washington University School of Medicine, St. Louis, MO, USA; [12]The Institute of Cancer Research, London, UK; [13]Dana-Farber Cancer Institute, Boston, MA, USA; [14]Pfizer Inc, Cambridge, MA, USA; [15]Pfizer Srl, Milan, Italy; [16]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Objective

To define and independently validate a predictive biomarker that identifies patients with EBC who could preferentially benefit from the addition of palbociclib to ET in the adjuvant setting.

Conclusions

- The composite predictive biomarker (LumA with ERBB2-high and/or LumA ER+/PR–) was defined from PENELOPE-B.
- Results from a prospectively defined retrospective analysis of a subset of intermediate/high risk patients with EBC selected from PALLAS validated the candidate predictive biomarker.
- Despite differences in the percent of patients who received prior chemotherapy in the PENELOPE-B and PALLAS HTG Sets, patients from both studies with biomarker-positive surgical resection tumor samples showed a significant improvement in iDFS with addition of palbociclib to ET.
- This predictive biomarker may be used for patient stratification and can potentially be applied to enrich future adjuvant clinical trials for the treatment of HR+/HER2– EBC.

Presenting author: Prof. Dr. Sibylle Loibl

Email for more information: Sibylle.Loibl@gbg.de

An electronic version of this poster may be obtained by scanning this Quick Response (QR) code with your smartphone app. Copies of this poster obtained through QR code are for personal use only and may not be reproduced without permission from SABCS® and the author of this poster.

References: 1. Loibl S et al. *J Clin Oncol.* 2021;39(14):1518–1530. **2.** Mayer EL et al. *Lancet Oncol.* 2021;22(2):212–222. **3.** Finn RS et al. *Clin Cancer Res.* 2020;26(1):110–121. **4.** Turner NC et al. *J Clin Oncol.* 2019;37(14):1169–1178. **5.** Zhu Z et al. *NPJ Precis Oncol.* 2022;6(1):56. **6.** Finn RS et al. *Breast Cancer Res.* 2009;11(5):R77. **7.** Denkert C et al. Presented at the San Antonio Breast Cancer Symposium® 2021. Abstract PD2-04. **8.** Denkert C et al. Presented at the American Society of Clinical Oncology Annual Meeting I 2021. Abstract 519.

Disclosures: These studies were funded by Pfizer Inc. Medical writing support was provided by Lynsey Fettig, PhD of Oxford PharmaGenesis Inc., Newtown, PA, USA, and was funded by Pfizer Inc.

Presented at the San Antonio Breast Cancer Symposium • December 6–10, 2022

Introduction

- The large prospective, randomized, phase 3 PENELOPE-B (NCT01864746)[1] and PALLAS (NCT02513394)[2] trials evaluated adjuvant palbociclib + endocrine therapy (ET) versus ET in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2–) early breast cancer (EBC); most patients in these studies were classified as high or intermediate risk.
  - However, neither trial met the primary endpoint of improving invasive disease-free survival (iDFS).[1,2]
- Based on evidence generated from biomarker analyses from PALOMA-2 and PALOMA-3, we identified 3 key elements for further investigation: 1. luminal subtypes,[3,4] 2. the *ERBB2* pathway,[3] and 3. estrogen receptor (ER)/progesterone receptor (PR) pathway activation.[5,6]
- Each of these biomarkers had prognostic value individually; we therefore hypothesized that a composite biomarker may be more precise in identifying the patients with EBC who could derive the most benefit from palbociclib treatment.

Materials and Methods

ANALYSIS POPULATION

Figure 1. Biomarker sample analysis flow chart

AIMS, absolute intrinsic molecular subtyping; CPS-EG, clinical pathologic stage and estrogen receptor status and histologic grade; GBG, German Breast Group; OBP, oncology biomarker panel; ITT, intention-to-treat.
[a]A total of 2830 PALLAS patient samples were selected (resection samples were required; if resection sample was not available, biopsy sample was used). Sample selection composed of ~50% "PENELOPE-like" patients (ie, received prior chemotherapy and had calculated CPS-EG score ≥3 or CPS-EG score 2 and ypN+) and ~50% randomly selected patient tissue samples so that biomarker validation results could be generalized to the PALLAS population. Gene expression data for N=2604 samples (n=2085 resection samples and n=519 biopsy samples) was generated. Only surgical samples (n=2085) were used for the current analysis.

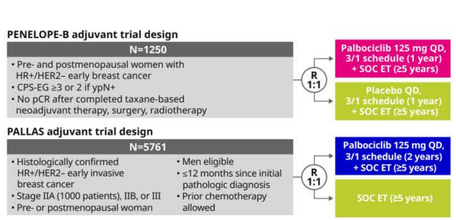
GENE EXPRESSION AND STATISTICAL ANALYSES

- Gene expression analyses were conducted on the patient tumor samples using the HTG EdgeSeq Oncology Biomarker Panel.[7]
- HTG gene expression analysis of the PENELOPE-B HTG Training Set was conducted at GBG Labs and was used to develop a composite biomarker by using a biologically driven, targeted gene interrogation.
  - HTG absolute intrinsic molecular subtyping (HTG-AIMS) classifications of LumA, LumB, HER2-enriched, basal-like, and normal-like were provided by the GBG Team for PENELOPE-B.[7]
  - A outcome-oriented approach based on iDFS utilizing a selection procedure that maximized the log-rank statistic was applied to estimate a standard Z score-based optimal cutoff for *ERBB2* gene expression.
  - These data were coupled with PR immunohistochemistry (IHC) data and analyzed to refine the composite biomarker.
  - The biomarker-positive population was defined to consist of patients with tumors that were LumA with *ERBB2*-high ("high" as defined by the Z score-based optimal cutoff) and/or LumA ER+/PR–; the biomarker-negative population was all other patients.
- iDFS rates at 3 years were estimated using the Kaplan-Meier method, and iDFS distributions between the treatment groups were compared using a log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. Interaction between treatment and composite biomarker status (positive vs negative) was assessed.
- Multivariable analyses based on the trial stratification factors were performed to adjust for potential baseline confounders.

Results

BASELINE AND CLINICAL CHARACTERISTICS

Figure 2. PENELOPE-B[1] and PALLAS[2] study designs



CPS-EG, clinical pathologic stage and estrogen receptor status and histologic grade; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; pCR, pathological complete response; R, randomized; SOC, standard of care; QD, daily.

- No differences in iDFS were observed between treatment groups in the ITT population and HTG Set for both trials.
  - PENELOPE-B
    - ITT population (N=1250), treatment effect HR: 0.92 (95% CI: 0.73–1.17), *P*=0.50
    - HTG Training Set (N=906), treatment effect HR: 0.88 (95% CI: 0.68–1.14), *P*=0.35
  - PALLAS
    - ITT population (N=5761), treatment effect HR: 0.96 (95% CI: 0.81–1.14), *P*=0.65
    - HTG Validation Set (N=2085), treatment effect HR: 1.02 (95% CI: 0.79–1.33), *P*=0.86

Table 1. Baseline characteristics in the HTG Sets were representative of the ITT populations in PENELOPE-B[1] and PALLAS[2]

Characteristics n (%)	PENELOPE-B HTG Training Set (N=906)		PALLAS HTG Validation Set (N=2085)	
	Palbociclib + ET (n=464)	Placebo + ET (n=442)	Palbociclib + ET (n=1070)	ET alone (n=1015)
Age, years				
≤50	266 (57.3)	237 (53.6)	425 (40)	418 (41)
>50	198 (42.7)	205 (46.4)	644 (60)	597 (59)
Race				
Asian	45 (9.7)	36 (8.1)	36 (3.4)	37 (3.6)
Black or African American	5 (1.1)	5 (1.1)	22 (2.1)	24 (2.4)
White	361 (77.8)	349 (79.0)	963 (90)	909 (90)
Other[a]	53 (11.4)	52 (11.8)	4 (0.4)	9 (0.9)
Unknown	–	–	45 (4.2)	36 (3.5)
Geographical region				
Asia Pacific	74 (15.9)	57 (12.9)	72 (6.7)	62 (6.1)
Europe	332 (71.6)	331 (74.9)	528 (49)	502 (49)
North America	58 (12.5)	54 (12.2)	460 (43)	442 (44)
Other	–	–	10 (0.9)	9 (0.9)
Menopausal status				
Postmenopausal	236 (50.9)	226 (51.1)	636 (59)	590 (58)
Premenopausal	228 (49.1)	216 (48.9)	427 (40)	419 (41)
Not applicable	–	–	6 (0.6)	5 (0.5)
Unknown	–	–	1 (<0.1)	1 (<0.1)

Table 1. Baseline characteristics in the HTG Sets were representative of the ITT populations in PENELOPE-B[1] and PALLAS[2] (continued)

Characteristics n (%)	PENELOPE-B HTG Training Set (N=906)		PALLAS HTG Validation Set (N=2085)	
	Palbociclib + ET (n=464)	Placebo + ET (n=442)	Palbociclib + ET (n=1070)	ET alone (n=1015)
Hormone receptor status				
ER+/PR–	96 (20.7)	102 (23.1)	273 (26)	225 (22)
ER+/PR+	368 (79.3)	337 (76.2)	796 (74)	788 (78)
ER–/PR+	0 (0)	2 (0.5)	0 (0)	2 (0.2)
ER–/PR–	0 (0)	1 (0.2)	1 (<0.1)	0 (0)
Nodal status at surgery				
ypN 0–1	212 (45.7)	224 (50.7)	–	–
ypN 2–3	252 (54.3)	218 (49.3)	–	–
N0/N0(i+)/N1/NX	–	–	722 (67)	701 (69)
N2	–	–	224 (21)	198 (20)
N3	–	–	123 (11)	116 (11)
Unknown	–	–	1 (<0.1)	0 (0)
Stage[b]				
I	1 (0.2)	1 (0.2)	4 (0.4)	3 (0.3)
IIA	29 (6.3)	35 (7.9)	239 (22)	246 (24)
IIB	185 (39.9)	195 (44.1)	352 (33)	342 (34)
III	249 (53.7)	211 (47.7)	474 (44)	424 (42)
Unknown	–	–	1 (<0.1)	0 (0)
Tumor grading at surgery				
G1	9 (1.9)	15 (3.4)	140 (13)	135 (13)
G2	233 (50.2)	207 (46.8)	646 (60)	626 (62)
G3	221 (47.6)	219 (50.0)	233 (22)	206 (20)
Gx	–	–	48 (4.5)	48 (4.7)
Unknown	1 (0.2)	1 (0.2)	3 (0.3)	0 (0)
Central Ki-67 at surgery				
≤15%	332 (71.6)	305 (69.0)	–	–
>15%	132 (28.5)	133 (30.1)	–	–
Unknown	0 (0)	(0.9)	–	–
Risk status				
CPS-EG score ≥3	282 (60.8)	263 (59.5)	–	–
CPS-EG score 2 and ypN+	182 (39.2)	179 (40.5)	–	–
Prior neoadjuvant or adjuvant chemotherapy				
No	0 (0)	0 (0)	438 (41)	435 (43)
Yes	464 (100)	442 (100)	632 (59)	580 (57)
Neoadjuvant	464 (100)	442 (100)	474 (44)	444 (44)
Adjuvant	–	–	148 (14)	116 (11)
Neoadjuvant/adjuvant	–	–	10 (1)	20 (2)

[a]Other included Native Hawaiian or other Pacific Islander and American Indian or Alaska Native. [b]Clinical stage in PENELOPE-B, anatomic stage in PALLAS.
CPS-EG, clinical pathologic stage and estrogen receptor status and histologic grade; ER, estrogen receptor; ET, endocrine therapy; ITT, intention-to-treat; PR, progesterone receptor.

Table 2. HTG-AIMS intrinsic molecular subtype distributions were similar between PENELOPE-B and PALLAS HTG Sets, as were the subtype prognostic profiles[a] (data not shown)

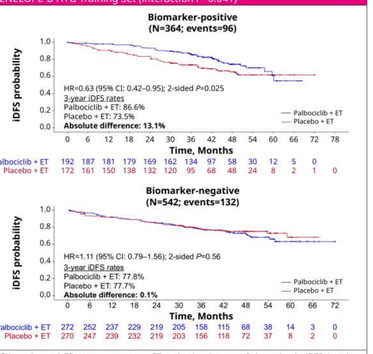
Molecular Subtype (HTG-AIMS), n (%)	PENELOPE-B HTG Training Set Total (N=906)	PALLAS HTG Validation Set Total (N=2085)
Basal-like	16 (1.8)	37 (1.8)
HER2-enriched	28 (3.1)	49 (2.5)
Luminal A	**663 (73.2)**	**1516 (72.7)**
Luminal B	64 (7.1)	172 (8.2)
Normal-like	135 (14.9)	311 (13.6)

AIMS, absolute intrinsic molecular subtyping; HER2, human epidermal growth factor receptor 2.

COMPOSITE BIOMARKER IDENTIFICATION AND VALIDATION

PENELOPE-B HTG TRAINING SET (N=906)

Figure 3. The biomarker-positive subgroup (composite of LumA with *ERBB2*-high and/or LumA ER+/PR–) demonstrated a preferential benefit from palbociclib + ET, which was not seen in the biomarker-negative subgroup (all other samples) of the PENELOPE-B HTG Training Set (interaction *P*=0.041)



CI, confidence interval; ER, estrogen receptor; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival; LumA, luminal A; PR, progesterone receptor.

- The number of patients from the PENELOPE-B HTG Training Set with different components of the biomarker was n=298 LumA with *ERBB2*-high (32.9%), n=122 LumA with ER+/PR– (13.5%), n=485 *ERBB2*-high and/or ER+/PR– (53.5%) and n=364 LumA with *ERBB2*-high and/or LumA ER+/PR– (40.2%).

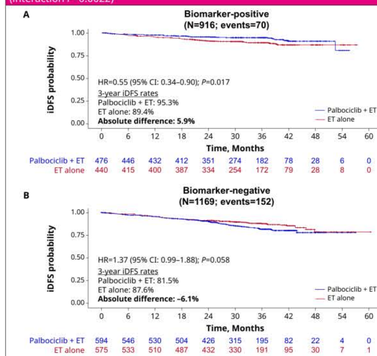
Table 3. Significant treatment effect remained in the PENELOPE-B biomarker-positive subgroup (n=364) after adjusting for potential confounding from the stratification factors used at randomization (multivariate Cox regression analysis)

Variable	PENELOPE-B Biomarker-positive subgroup HR (95% CI)	*P*-value
Treatment		
Palbociclib + ET vs placebo + ET	0.63 (0.42–0.95)	0.03
Age at first diagnosis (years)		
≤50 vs >50	0.99 (0.65–1.50)	0.96
Central Ki67		
≤15% vs >15%	0.67 (0.43–1.03)	0.07
Global region		
Asian vs non-Asian	0.68 (0.27–1.70)	0.41
Histological lymph node status at surgery		
ypN 0–1 vs ypN 2–3	0.95 (0.63–1.44)	0.81
Risk status		
CPS-EG 2 and ypN+ vs CPS-EG ≥3	0.75 (0.49–1.15)	0.19

CI, confidence interval; CPS-EG, clinical pathologic stage and estrogen receptor status and histologic grade; ET, endocrine therapy; HR, hazard ratio.

PALLAS HTG VALIDATION SET (N=2085)

Figure 4. Independent validation of the biomarker with tumor samples from the PALLAS HTG Validation Set confirmed significant benefit from palbociclib + ET in the biomarker-positive subgroup, but not in the biomarker-negative subgroup (interaction *P*=0.0022)



CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival.

- The number of patients from the PALLAS HTG Validation Set with different components of the biomarker was n=763 LumA with *ERBB2*-high (36.6%), n=294 LumA with ER+/PR– (14.1%), n=1206 *ERBB2*-high and/or ER+/PR– (57.8%) and n=916 LumA with *ERBB2*-high and/or LumA ER+/PR– (43.9%).

Table 4. Significant treatment effect remained in the PALLAS biomarker-positive subgroup (n=916) after adjusting for potential confounding from the stratification factors used at randomization (multivariate Cox regression analysis)

Variable	PALLAS Biomarker-positive subgroup HR (95% CI)	*P*-value
Treatment		
Palbociclib + ET vs ET alone	0.55 (0.34–0.89)	0.02
Age at randomization (years)		
≤50 vs >50	0.97 (0.60–1.58)	0.91
Anatomic stage		
IIA vs IIB/III	0.67 (0.35–1.30)	0.24
Neo/adjuvant chemotherapy		
No vs yes	0.48 (0.27–0.82)	0.01
Geographic region		
Europe vs North America	0.60 (0.36–0.98)	0.04
Other vs North America	0.85 (0.36–2.04)	0.72
Europe vs other	0.70 (0.29–1.69)	0.42

CI, confidence interval; ET, endocrine therapy; HR, hazard ratio.

This presentation is the intellectual property of the author/presenter. Contact them at Sibylle.Loibl@gbg.de for permission to reprint and/or distribution. Copyright ©2022. All rights reserved.