Comprehensive Gene Expression Biomarker Analysis of Cyclin-Dependent Kinases 4/6 and Endocrine Pathways From the PALOMA-2 Study

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BACKGROUND

- Palbociclib is an oral inhibitor of cyclin-dependent kinases (CDK) 4/6 approved for the treatment of hormone receptor–positive, human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC) in combination with
  - An aromatase inhibitor as initial endocrine-based therapy in postmenopausal women, or
  - Fulvestrant in all women with breast cancer disease progression following endocrine therapy[1,2]
- In the phase 3 PALOMA-2 study at the data cutoff of February 26, 2016, after a median of 23 months of follow-up, palbociclib in combination with letrozole demonstrated a significant improvement in progression-free survival (PFS) vs placebo plus letrozole as first-line ABC therapy (median PFS, 24.8 vs 14.5 months; hazard ratio, 0.576; *P*<0.001).[3] Patients continued on study for further follow-up, reported herein.
- Initial immunohistochemistry analyses of ER, Rb, cyclin D1, p16, and Ki-67 did not identify a subgroup of estrogen receptor-positive (ER+) patients that did not benefit from the addition of palbociclib to letrozole.[4] While the PFS of the control group (placebo plus letrozole) varied with several of these markers, palbociclib consistently improved PFS.

OBJECTIVES

- To explore predictive markers for sensitivity and resistance to CDK4/6-based therapy or endocrine therapy alone by performing a large gene expression analysis of baseline tumor tissues

METHODS

Study Design and Patients

- PALOMA-2 was a double-blind, randomized, phase 3 trial.[3]
- Postmenopausal women who had not received prior systemic therapy for ER+/HER2– ABC were randomized 2:1 to palbociclib (125 mg per day, 3/1 schedule) plus letrozole (2.5 mg per day; n=444) or placebo plus letrozole (2.5 mg per day; n=222) until disease progression, death, unacceptable toxicity, or consent withdrawal.[3]

Gene Expression Profiling

- All patients provided tumor tissues to participate in the study; 455 of 666 patients in the intent-to-treat (ITT) population had tumor tissue appropriate for gene expression evaluation (palbociclib plus letrozole: 303 [68%], placebo plus letrozole: 152 [68%]).
- The EdgeSeq Oncology Biomarker Panel (HTG Molecular Diagnostics; Tucson, AZ), assessing 2534 genes involved in a variety of cancer-related pathways, was used for mRNA profiling.

Data Analysis

- To identify predictive biomarkers, a Cox proportional hazards model of investigator-assessed PFS was used to test for interaction between treatment and continuous mRNA expression of genes and pathway signatures (data cutoff: May 31, 2017).
- The results were visualized using Kaplan-Meier plots by median or quartile dichotomization.
- A log-rank test was used to compare PFS differences within each treatment arm, with multiple testing corrections made via false discovery rates (FDR) based on the Benjamini-Hochberg procedure.
- Cox models and survival curves were also adjusted for baseline demographic covariates as potential confounding factors through multivariate regression and a corrected group prognosis method, respectively.
- Molecular subtypes of breast tumors were determined using the Absolute Intrinsic Molecular Subtyping (AIMS) algorithm.[5]
- Biomarker analyses were performed using both hypothesis-driven (supervised) and data-driven (unsupervised) approaches.

RESULTS

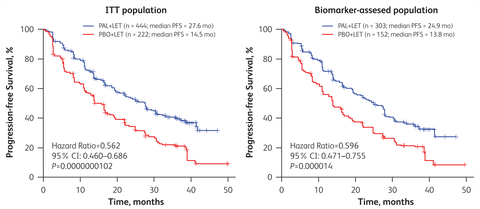
- Baseline demographics for patients with biomarker-assessed data generally were similar between the treatment arms and to the overall ITT population **(Table 1)**.
- As of May 31, 2017, in the overall ITT population with a median follow-up of 38 months, median PFS was 27.6 months with palbociclib plus letrozole vs 14.5 months with placebo plus letrozole (hazard ratio, 0.56; *P*<0.000001; **Figure 1**).
- In the biomarker-assessed population, PFS was similar to that seen in the overall ITT population **(Figure 1)**.
- Irrespective of the level (high or low) of gene expression of cyclin *(CCN) D1, CCNE1/2, CDK2/4/6*, retinoblastoma-1 *(RB1)*, and *CDKN2A*, palbociclib plus letrozole demonstrated a consistent benefit over placebo plus letrozole, similar to that seen in the overall ITT population **(Figure 2)**.
- Higher CDK4 expression was identified as a resistance marker for the placebo plus letrozole arm (FDR=0.095; interaction *P*=0.016; **Figure 3**).
- Based on unsupervised analysis, tumors with higher levels of growth factor receptors (fibroblast growth factor receptor 2 [FGFR2] FDR=0.032, interaction *P*=0.056; Erb-B2 receptor tyrosine kinase 3 [ERBB3] FDR=0.221, interaction *P*=0.043) were associated with greater sensitivity to palbociclib plus letrozole vs placebo plus letrozole **(Figure 4)**.
- Patients with lower *RB1* expression also benefited from palbociclib plus letrozole over placebo plus letrozole **(Figure 5)**.
- Patients of luminal A or luminal B subtypes as defined by gene expression subtype classification both benefited from palbociclib plus letrozole compared with placebo plus letrozole **(Figure 6)**.
- Patients with lower levels of tumor programmed cell death protein 1 (PD-1) expression showed more benefit from palbociclib plus letrozole than patients with higher levels of PD-1 expression (FDR=0.099, interaction *P*=0.021; **Figure 7**).

Table 1. Baseline Demographics for Biomarker-Assessed Population

Characteristic	Palbociclib + Letrozole (n=303)	Placebo + Letrozole (n=152)
Age, median (range), y	61 (30–89)	61 (28–88)
Race, n (%)		
White	243 (80.2)	116 (76.3)
Black	5 (1.7)	1 (2.0)
Asian	36 (11.9)	22 (14.5)
Other*	19 (6.3)	11 (7.2)
Disease site, n (%)		
Visceral	148 (49)	78 (51)
Nonvisceral	155 (51)	74 (49)
Disease-free interval, n (%)		
>12 months	111 (37)	65 (43)
≤12 months	74 (24)	38 (25)
De novo metastatic	118 (39)	49 (32)
Prior (neo)adjuvant hormonal therapy, n (%)		
Prior hormonal therapy	171 (56)	91 (60)
No prior hormonal therapy	132 (44)	61 (40)

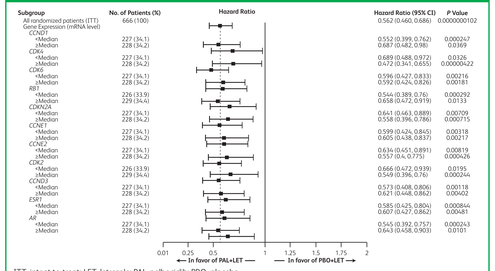
*Other included not reported/missing patients.

Figure 1. PFS in Overall ITT Population (N=666) and Biomarker-Assessed Population (N=455)



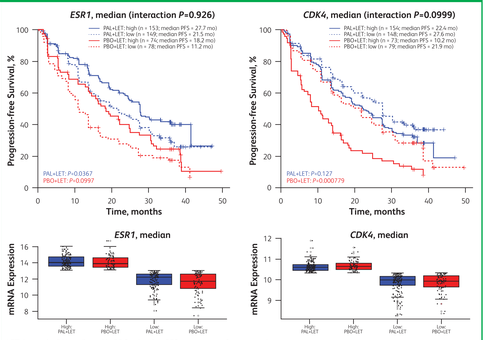
ITT=intent-to-treat; LET=letrozole; PAL=palbociclib; PBO=placebo; PFS=progression-free survival.

Figure 2. Subgroup Analysis Based on Target Gene Expression in the Cyclin D–CDK4/6–RB Pathway



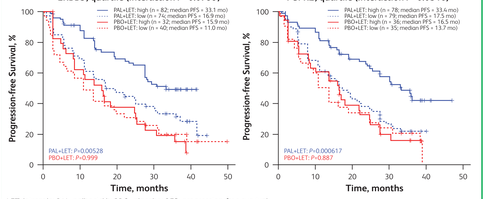
ITT=intent-to-treat; LET=letrozole; PAL=palbociclib; PBO=placebo.

Figure 3. PFS by *ESR1* and *CDK4* Expression Level



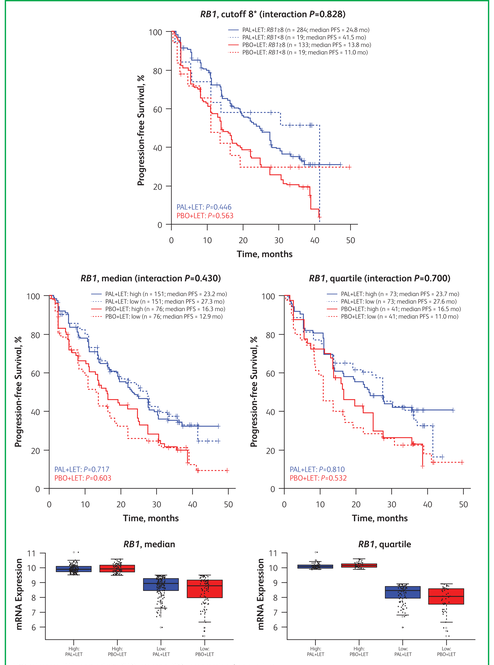
LET=letrozole; PAL=palbociclib; PBO=placebo; PFS=progression-free survival.

Figure 4. PFS by *ERBB3* and *FGFR2* Expression Level



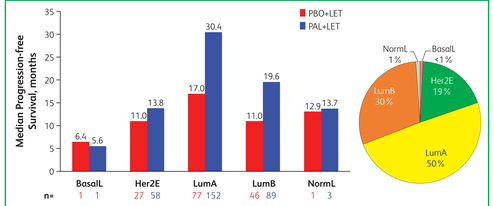
LET=letrozole; PAL=palbociclib; PBO=placebo; PFS=progression-free survival.

Figure 5. PFS by *RB1* Expression Level



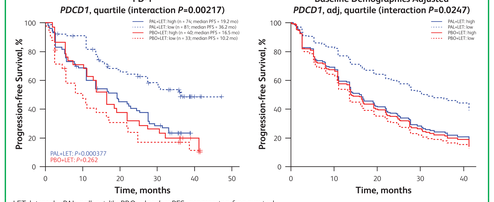
LET=letrozole; PAL=palbociclib; PBO=placebo; PFS=progression-free survival.
*Cutoff of 8 is based on the expression pattern of negative control probes on the EdgeSeq Oncology Biomarker Panel.

Figure 6. Median PFS in Patients With Various Intrinsic Molecular Subtypes



Basal=basal-like; Her2E=human epidermal growth factor receptor 2–enriched; LET=letrozole; LumA=luminal A; LumB=luminal B; NormL=normal-like; PAL=palbociclib; PBO=placebo.

Figure 7. PFS by PD-1 Expression Level



LET=letrozole; PAL=palbociclib; PBO=placebo; PFS=progression-free survival.

CONCLUSIONS

- This is the first comprehensive examination of a CDK4/6 inhibitor plus endocrine therapy using a large gene expression panel. These findings confirm that the treatment effects of palbociclib in combination with endocrine therapy were consistent across all the analyzed biomarker subgroups. These results support the use of ER+ as the only biomarker for sensitivity to CDK4/6 inhibition.
- Expression levels (whether higher or lower) of target genes in the cyclin D-CDK4/6-RB pathway did not predict sensitivity or resistance to palbociclib plus letrozole vs placebo plus letrozole.
- Patients with luminal A or luminal B subtypes both benefited from palbociclib plus letrozole, supporting the investigation of palbociclib in early stage ER+ breast cancer, regardless of luminal A or B status.
- These data provide evidence that the interplay between steroid hormone and peptide growth factor signaling in ER+ breast cancer drives dependence on CDK4/6 and benefit shown from CDK4/6 inhibition with palbociclib.
- These data can be used to guide additional therapeutic opportunities in patients with ER+/HER2– ABC.

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