A Phase II Proof-of-Concept Study of Palbociclib Rechallenge in Patients with HR+/HER2- Metastatic Breast Cancer and Clinical Benefit to Prior Palbociclib-Based Treatment: BIOPER

SAN ANTONIO BREAST CANCER SYMPOSIUM®

MEDSIR MEDICA SCIENTIA INNOVATION RESEARCH

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INTRODUCTION

- The addition of a cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor to letrozole or fulvestrant significantly improves progression-free survival (PFS)[1-6] and overall survival (OS)[7-9] in hormone receptor-positive (HR+)/Human Epidermal Growth Factor Receptor 2-negative (HER2-) metastatic breast cancer (MBC) patients (pts).
- At present, the optimal endocrine therapy (ET) after progression on a CDK4/6 inhibitor remains unknown. However, preliminary findings revealed drivers of adaptive resistance more frequently related to ET than to CDK4/6 inhibitors.[10]
- BIOPER explored the preliminary efficacy and safety of continuing the same CDK4/6 inhibitor in combination with a different ET agent beyond progression on prior palbociclib (P)-based regimen in HR+/HER2- MBC and assessed predictive biomarkers to identify those pts who are more likely to benefit from this strategy.

METHODS

Study Design

Key eligibility criteria:

1. Premenopausal* or postmenopausal women aged ≥18 years
2. HR+/HER2- MBC
3. Confirmed PD after having achieved CB on immediately prior P+ET-based regimen
4. ≤2 prior ET lines for MBC
5. Not more than one line of prior CT for MBC
6. Measurable and biopsable MBC

N = 33# → **Palbociclib** 75/100/125mg PO, once daily, 3 weeks on, 1 week off + **ET of Physician's choice**† → **Treatment until PD per investigator or intolerable toxicity**

Baseline: Blood + Tissue; 2 weeks: Blood; 12 weeks: Blood; EoT/PD: Blood + Tissue (if feasible)

* If premenopausal, an ovarian suppression method was required.
# The target sample size was =33 pts, based on binomial exact test (H0: ≤5%). The analyses were designed to attain an 80% power (HA: ≥20%) at α=2.5% one-sided level.
† Based on prior administered agent and included tamoxifen, exemestane, fulvestrant, anastrozole, or letrozole.
CB: Clinical benefit; CT: Chemotherapy; EoT: End of treatment; ET: Endocrine therapy; HER2: Human Epidermal Growth Factor Receptor 2; HR: Hormonal receptor; MBC: Metastatic breast cancer; PD: Progressive disease; PO: Oral administration.

Co-Primary Endpoints

- Clinical: The percentage of pts who achieve clinical benefit (complete response [CR], partial response [PR], or stable disease [SD] ≥ 24 weeks) per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1.
- Biological: The percentage of pts who showed loss of retinoblastoma (Rb) protein expression at baseline.

Secondary endpoints:

- Overall response rate (ORR), duration of response (DoR), PFS per RECIST v1.1, and OS.
- Safety and tolerability as per Common Terminology Criteria for Adverse Events v. 4.03.
- Protein expression of markers involved in the cyclin D1-CDK4/6-Rb axis: cyclins D1 and E1, CDK4, CDK6, phosphorylated Rb (pRB), and pRB/Rb ratio.

Immunohistochemical Analysis

- Formalin-fixed and paraffin-embedded (FFPE) biopsies were obtained at baseline from metastatic lesions since the last progression with P-containing regimen.
- Protein status was evaluated on 3 µm–thick tissue slides by immunohistochemistry (IHC).
- The loss of Rb protein expression was defined as <1% nuclear staining. For the remaining markers, the median value was used as cut-off point.

RESULTS

Baseline Characteristics

Between June 2017 and April 2019, a total of 33 pts from 21 centers in 2 countries were enrolled (Italy and Spain). One patient who did not achieve clinical benefit on prior P-based regimen was excluded from the efficacy analysis (Table 1).

Table 1. Summary of patients' demographics at baseline.

Characteristics	All subjects (N=32)
Median age (years, range)	59.5 (42.0–80.0)
ECOG performance status	
0	16 (50.0%)
1	16 (50.0%)
Visceral involvement	
Yes	25 (78.1%)
No	7 (21.9%)
Number of disease sites	
<3	13 (40.6%)
≥3	19 (59.4%)
Previous regimens	
(Neo)Adjuvant ET (n, % yes)	15 (46.9%)
(Neo)Adjuvant CT (n, % yes)	15 (46.9%)
CT for MBC (n, % yes)	4 (12.5%)
Lines of prior ET for MBC (excluding the prior P-based regimen)	
0	26 (81.2%)
1	6 (18.8%)
ET agent used in prior P-based regimen	
Letrozole	15 (46.9%)
Fulvestrant	14 (43.8%)
Exemestane	3 (9.4%)
Median PFS for the prior P-based regimen, months (95% CI)	13.8 (5.6–47.1)
Lines of previous systemic therapy for MBC (including the prior P-based regimen), median (range)	1 (1–3)
1	24 (75.0%)
2	7 (21.9%)
3	1 (3.1%)
ET agent used in 2nd P-based regimen	
Fulvestrant	19 (59.4%)
Letrozole	8 (25.0%)
Others	5 (15.6%)
P starting dose in 2nd P-based regimen	
125 mg	23 (71.9%)
100 mg	6 (18.8%)
75 mg	3 (9.4%)

Data are n (%), unless otherwise specified. CI: Confidence interval; CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; ET: Endocrine therapy; MBC: Metastatic breast cancer; P: Palbociclib; PFS: Progression-free survival.

Clinical Primary Objective

The study met its primary clinical objective because CBR was 34.4% (95% confidence interval [CI] 18.6–53.2%) (one-sided P <0.001). Of 32 pts, 2 had PR and 9 had SD lasting at least 24 weeks (Table 2).

Biological Primary Objective

The study met its primary biological objective in biomarker evaluable set (N=21). Pts with loss of Rb protein expression were 19% (95% CI 5.4–41.9%) (one-sided P <0.02).

Clinical Secondary Objectives

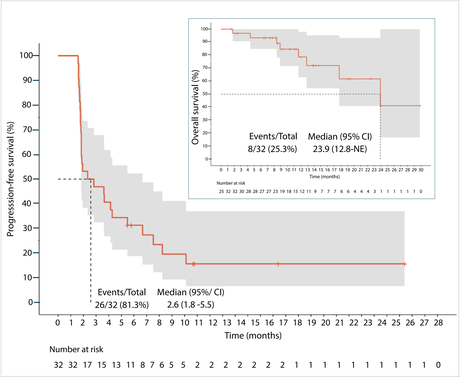
ORR was 6.3% (95% CI 0.1–20.8%). Among responders, mean DoR was 17 (8.3–25.7) months (Table 2). Median PFS was 2.6 (95%CI: 1.8–5.5) months and median OS was 23.9 (95% CI 12.8–Not estimated) (Figure 1).

Table 2. Clinical response according to local assessment *

Best response	All subjects (N=32)	95% CI
CBR, n (%) #	11 (34.4)	18.6–53.2
CR	0	-
PR	2 (6.3)	0.1–20.8
SD ≥24 weeks	9 (28.1)	13.7–46.7
PD, n (%)	20 (62.5)	43.7–78.9
NE †	1 (3.1%)	0.01–16.2
DoR, mean (months, range)	17 (8.3–25.7)	-

95% CI: 95% confidence interval; CR: Complete response; CBR: Clinical benefit rate; DoR: Duration of response; N: Number of pts; NE: Not evaluated; PR: Partial response; PD: Progressive disease; SD: Stable disease.
* Including pts with measurable disease at baseline "as per" RECIST v.1.1 who received ≥1 cycle of study treatment.
# CR + PR + SD ≥24 weeks in all pts. PR were confirmed at the subsequent tumor assessment as per RECIST v.1.1.
† One patient was excluded from the efficacy analysis because of lack of clinical benefit on prior P-based regimen.

Figure 1. PFS and OS rates in the intention to treat population

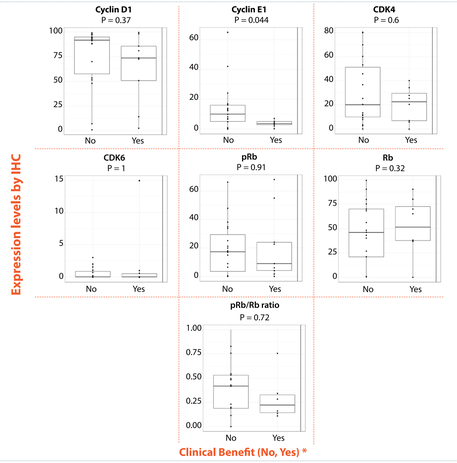


95% CI: 95% confidence interval ; NE: Not estimated.

Molecular Assessments

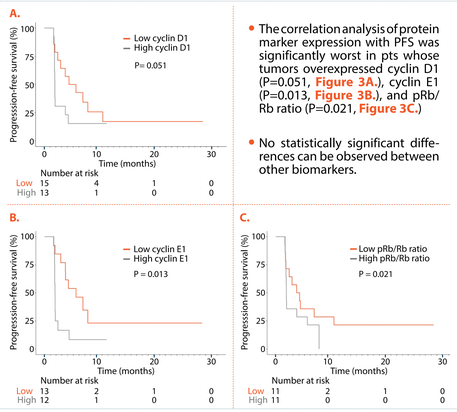
- Immunohistochemical analysis was performed on 30 available FFPE biopsies. Of them, 21 samples (67.7%) had a result for all the 6 markers analyzed. Among the remaining 9 samples (23.3%), not all the biomarkers could be evaluated due to insufficient tissue material or absence of tumoral component.
- Expression of cyclin E1 was significantly greater in pts with progressive disease compared with that of pts who obtained clinical benefit (P=0.044) (Figure 2).

Figure 2. Correlation between clinical benefit and protein expression of markers involved in the cyclin D1-CDK4/6-Rb axis.



* No refers to pts with progressive disease; Yes refers to pts with PR or SD ≥24 weeks.
Correlation analyses were perfomed using the Wilcoxon signed rank test.

Figure 3. Kaplan-Meier survival curves according to the expression of markers involved in the cyclin D1-CDK4/6-Rb axis.



- The correlation analysis of protein marker expression with PFS was significantly worst in pts whose tumors overexpressed cyclin D1 (P=0.051, Figure 3A.), cyclin E1 (P=0.013, Figure 3B.), and pRb/Rb ratio (P=0.021, Figure 3C.)
- No statistically significant differences can be observed between other biomarkers.

Low identifies tumors whose staining status was less than or equal to the median value. High identifies tumors whose staining status was greater than the median value.

Safety

- All-cause adverse events (AEs) occurred in 90.9% of pts (Grade 3-4, 48.5%). The most common Grade 3-4 AEs were neutropenia (42.4%) and leukopenia (6.1%).
- The combination of P + ET was administered for a median of 3 cycles.
- The average dose intensity and relative dose intensity for P were 636.4 mg/week and 99.7%, respectively. For ET the relative dose intensity was 98.2%.
- Dose interruptions and delays were required in 10 (30.2%) and 8 (24.2%) pts, respectively. One (3.0%) patient had a dose reduction of P.
- No discontinuations due to AEs and treatment-related deaths occurred. The treatment is ongoing in 3 pts.
- The most frequent AEs are summarized in Table 3.

Table 3. Most frequent AEs from any cause that occurred in at least 10% of the pts (N=33).

Adverse Events	Any grade	Grade 3	Grade 4
Any	30 (90.9%)	15 (45.5%)	1 (3.0%)
Hematologic	19 (57.6%)	13 (39.4%)	1 (3.0%)
Neutropenia	19 (57.6%)	13 (39.4%)	1 (3.0%)
Leukopenia	6 (18.2%)	2 (6.1%)	0 (0.0%)
Anemia	5 (15.2%)	0 (0.0%)	0 (0.0%)
Non-hematologic	23 (69.7%)	4 (12.1%)	0 (0.0%)
Fatigue	10 (30.3%)	0 (0.0%)	0 (0.0%)
Asthenia	5 (15.2%)	0 (0.0%)	0 (0.0%)
Diarrhea	4 (12.1%)	0 (0.0%)	0 (0.0%)

CONCLUSIONS

- The BIOPER study achieved the prespecified clinical and biological endpoints among pts with HR+/HER2- MBC and the safety profile was in line with that reported in previous studies. This strategy is currently being evaluated in the international, randomized phase II PALMIRA trial (NCT03809988).
- The preliminary molecular analyses are consistent with cyclin E1 overexpression rendering the tumor resistant and preventing benefit from P treatment rechallenge beyond progression.
- Further research is ongoing to characterize the evolution of genetic mechanisms of resistance to P + ET.

REFERENCES

1. Finn RS, *et al.* N Engl J Med 2016; 375: 1925–36.
2. Hortobagyi GN, *et al.* N Engl J Med 2016; 375: 1738–48.
3. Goetz MP, *et al.* J Clin Oncol 2017; 35: 3638–46.
4. Turner NC, *et al.* N Engl J Med 2015; 373: 209–19.
5. Sledge GW Jr, *et al.* J Clin Oncol 2017; 35: 2875–84.
6. Slamon DJ, J Clin Oncol 2018; 36: 2465–72.
7. Turner NC, *et al.* N Engl J Med 2018; 379: 1926–36.
8. Sledge GW, *et al.* JAMA Oncol 2019; 6: 116–24.
9. Slamon DJ, *et al.* N Engl J Med 2020; 382:514-524.
10. Ben O'Leary, *et al.* Cancer Discov. 2018; 8: 1390–1403.

Conflicts of interest: https://medsir.org/bioper

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