# Palbociclib, pembrolizumab, and endocrine therapy (ET) in HR+/HER2- metastatic breast cancer (MBC): Updated results from a phase I/II trial

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## Introduction

- Preclinical studies demonstrate that CDK4/6 inhibitors (CDK4/6i) may have a synergistic effect when combined with immune checkpoint inhibitors (ICI).[1,2]
- CDK4/6i promote anti-tumor immunity through increased antigen presentation, suppression of regulatory T cells, and stimulation of cytotoxic T cells.
- We previously reported that adding pembrolizumab to palbociclib and ET was safe and showed promising clinical activity when pembrolizumab was initiated in pts with HR+/HER2- MBC and stable disease for at least 6 months (Arm 1) or in the first-line (1L) setting (Arm 2).[3]
- To investigate the immune-stimulatory effect of CDK4/6i prior to the initiation of pembrolizumab, we enrolled pts into Arm 3, which consisted of a palbociclib + ET lead-in on Day-28, followed by pembrolizumab on C1D1.
- Here, we present updated trial results of Arm 2 and new data from Arm 3 evaluating a 28-day lead-in of palbociclib + ET followed by pembrolizumab.

## Methods and Materials

- In this single-center, open-label, phase I/II study, pts with HR+/HER2- MBC were treated with palbociclib, pembrolizumab, and ET.
- Arm 1 enrolled pts with stable disease on palbociclib + ET for at least 6 months (Arm 1 closed early due to limited accrual, data previously reported[3]).
- Arms 2 and 3 enrolled pts in the first-line (1L) setting to palbociclib + ET with concurrent ICI (Cohort 2, data previously reported[3]) or sequential ICI following a 28-day lead-in.
- The primary endpoint was overall response rate (ORR). Secondary endpoints included progression free survival (PFS), overall survival (OS), and treatment-related adverse events (TRAEs).

## Results

**Table 1.** Patient and clinical characteristics across treatment arms.

| Baseline Characteristics | Arm 2 (n=19) | Arm 3 (n=24) | Combined Arm 2 + 3 (1L) (n=43) |
|---|---|---|---|
| **Age (y), median (IQR)** | 51.0 (45.8 - 65.3) | 55.5 (44.1 - 63.0) | 55.0 (44.7 – 63.8) |
| **Female gender** | 19 (100.0%) | 23 (95.8%) | 42 (97.7%) |
| **Race** | | | |
| White | 13 (68.4%) | 13 (54.2%) | 26 (60.5%) |
| Asian | 5 (26.3%) | 6 (25.0%) | 11 (25.6%) |
| Black | 0 (0.0%) | 3 (12.5%) | 3 (7.0%) |
| Unknown | 1 (5.3%) | 2 (8.3%) | 3 (7.0%) |
| **Ethnicity** | | | |
| Non-Hispanic | 11 (57.9%) | 19 (79.2%) | 30 (69.8%) |
| Hispanic/Latino | 7 (36.8%) | 5 (20.8%) | 12 (27.9%) |
| Unknown | 1 (5.3%) | 0 (0.0%) | 1 (2.3%) |
| **Tumor stage at diagnosis** | | | |
| Stage I | 2 (10.5%) | 5 (20.8%) | 7 (16.3%) |
| Stage II | 6 (31.6%) | 5 (20.8%) | 11 (25.6%) |
| Stage III | 4 (21.1%) | 1 (4.2%) | 5 (11.6%) |
| Stage IV | 7 (36.8%) | 13 (54.2%) | 20 (46.5%) |

**Table 2.** Treatment response across treatment arms.

| Treatment and Response6 | Arm 2 (n=19) | Arm 3 (n=24) | Combined Arm 2 + 3 (1L) (n=43) |
|---|---|---|---|
| **Best response per RECIST** | | | |
| CR | 2 (10.5%) | 1 (4.2%) | 3 (7.0%) |
| PR/UPR* | 9 (47.4%) | 15 (62.5%) | 24 (55.8%) |
| SD | 3 (15.8%) | 6 (25.0%) | 9 (20.9%) |
| PD | 3 (15.8%) | 2 (8.3%) | 5 (11.6%) |
| NE | 2 (10.5%) | 0 (0.0%) | 2 (4.6%) |
| **ORR, (95% CI)** | 57.9% (33.4, 82.3) | 66.7% (46.3, 87.0) | 62.8% (47.7, 77.8) |
| **Clinical benefit rate (95% CI)** | 73.7% (51.9, 95.5) | 95.8% (87.2, 100) | 86.0% (75.3, 96.8) |
| **Off treatment reason** | | | |
| Patient withdrawal | 4 (21.1%) | 5 (20.8%) | 9 (20.9%) |
| Progression | 12 (63.2%) | 11 (45.8%) | 23 (53.5%) |
| Toxicity | 2 (10.5%) | 1 (4.2%) | 3 (7.0%) |
| Still on | 1 (5.3%) | 7 (29.2%) | 8 (18.6%) |
| **Follow-up (months), median (95% CI)** | 84.9 (53.6, NR) | 32.6 (14.5, 42.6) | 43.0 (31.7, 54.3) |
| **PFS (months), median (95% CI)** | 25.2 (5.3, 59.5) | 29.1 (11.2, NR) | 27.1 (13.9, 42.5) |
| **OS (months), median (95% CI)** | 50.9 (31.2, 80.6) | NR (37.6, NR) | 56.8 (37.6, NR) |

*3 patients achieved CR of target lesions with bone metastases as the only non-target lesion with non-CR/non-PD.
Abbreviations: CR, complete response; PR, partial response; UPR, unconfirmed partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; NR, not reached.

**Figure 1.** PFS across the 3 arms.

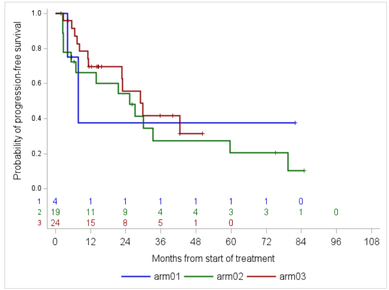



**Figure 2.** OS across the 3 arms.

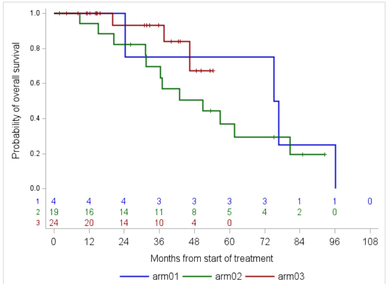



**Figure 3.** PFS and OS of combined Arms 2 and 3.

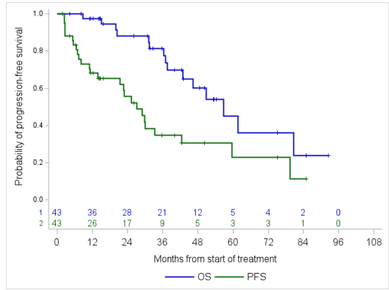
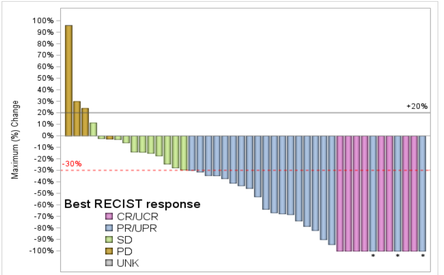



**Figure 4.** Waterfall plot of percent change of tumor size of the whole cohort.




*Achieved CR of target lesions with bone metastases as the only non-target lesion with non-CR/non-PD

**Table 3.** Grade 2 or higher TRAE occurring in at least 10% of pts in combined Arms 2 and 3.

| | Total AE | Grade 3 | Grade 4 |
|---|---|---|---|
| **Hematologic adverse events** | | | |
| White blood cell decreased | 41 (95.3%) | 23 (53.5%) | 2 (4.7%) |
| Neutrophil count decreased (ANC) | 40 (93.0%) | 34 (79.1%) | 4 (9.3%) |
| Lymphocyte count decreased | 27 (62.8%) | 5 (11.6%) | 2 (4.7%) |
| Anemia | 11 (25.6%) | 2 (4.7%) | 0 (0.0%) |
| Platelet count decreased | 7 (16.3%) | 4 (9.3%) | 0 (0.0%) |
| **Non-hematologic adverse events** | | | |
| Fatigue | 12 (27.9%) | 0 (0.0%) | 0 (0.0%) |
| Upper respiratory infection | 12 (27.9%) | 0 (0.0%) | 0 (0.0%) |
| Alanine aminotransferase (ALT) increased | 11 (25.6%) | 6 (14.0%) | 1 (2.3%) |
| Aspartate aminotransferase (AST) increase | 10 (23.5%) | 6 (14.0%) | 0 (0.0%) |
| Diarrhea | 6 (14.0%) | 2 (4.7%) | 0 (0.0%) |
| Nausea | 6 (14.0%) | 2 (4.7%) | 0 (0.0%) |
| Arthralgia | 6 (14.0%) | 0 (0.0%) | 0 (0.0%) |
| Hypoalbuminemia | 5 (11.6%) | 0 (0.0%) | 0 (0.0%) |
| **Immune-related adverse events** | | | |
| Hepatitis | 12 (27.9%) | 12 (27.9%) | 0 (0.0%) |
| Rash | 5 (11.6%) | 0 (0.0%) | 0 (0.0%) |
| Thyroiditis | 4 (9.3%) | 0 (0.0%) | 0 (0.0%) |
| Pneumonitis | 3 (7.0%) | 1 (2.3%) | 1 (2.3%) |
| Arthritis | 2 (4.7%) | 1 (2.3%) | 0 (0.0%) |

## Discussion

- With a median follow-up of 42.6 months for patients treated with palbociclib, pembrolizumab, and ET in the 1L setting, ORR was 62.8%, median PFS was 27.1 months, and median OS was 56.8 months.
- Arm 3 showed numerically higher ORR (66.7% vs 57.9%) and longer PFS (29.1 mo vs. 25.2 mo) compared to Arm 2.
- Compared to the PALOMA-2 trial which investigated palbociclib + ET in 1L HR+/HER2- MBC, the addition of pembrolizumab led to improved ORR (62.8 % vs. 55.3%) and comparable PFS (27.1 months vs. 24.8 months).[4]
- The combination was generally well-tolerated, with no unexpected TRAEs.
- Compared to the phase Ib study of abemaciclib, pembrolizumab, and ET in 1L HR+/HER2- MBC, palbociclib led to higher rates of grade 3-4 neutropenia (88.4% vs. 30.8%) and lower rates of grade 3-4 elevated LFTs (ALT/AST increase: 16%/14% vs. 42.3%/34.6%).[5]

## Conclusions

- The combination of palbociclib, pembrolizumab, and ET in the 1L setting was tolerable in pts with HR+/HER2- MBC with no unexpected TRAEs.
- We report an improved ORR compared to PALOMA-2 of 62.8% vs. 55.3%, respectively; with a comparable median PFS of 27.1 months vs. 24.8 months, respectively.
- Correlative studies are currently underway to explore immune biomarkers including tumor-infiltrating lymphocytes scoring and tumor immune microenvironment composition to identify pts who may have an improved response to this combination treatment which led to improved PFS and OS in some pts.

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