Early Switch to Fulvestrant Plus Palbociclib Improves Outcomes in ESR1-Mutated, Estrogen Receptor-Positive Metastatic Breast Cancer

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Estrogen receptor gene (ESR1) mutations restore the ligand-independent activity of the estrogen receptor (ER) in patients with ER-positive metastatic breast cancer. Although these mutations are associated with resistance to aromatase inhibitor (AI) therapy, tumors harboring mutated ESR1 retain their sensitivity to selective estrogen receptor degraders (SERDs). Mutations in ESR1 are rare at diagnosis, occurring in <5% of patients with metastatic breast cancer. However, the prevalence of ESR1 mutations increases to 30% to 40% among patients whose disease progresses on first-line aromatase inhibitor therapy.

The presence of ESR1 mutations in the blood (bESR1), detected by cell-free circulating DNA analysis, is associated with resistance to aromatase inhibitor therapy, but not to treatment with fulvestrant or palbociclib.

The phase III PADA-1 trial was designed to evaluate the feasibility of preventing or delaying tumor progression in patients receiving first-line treatment with palbociclib plus aromatase inhibitor therapy by switching from an AI to fulvestrant as soon as a bESR1 mutation becomes detectable, while also maintaining treatment with palbociclib.

François-Clément Bidard, M.D., Ph.D., of the Institut Curie and Paris-Saclay University, presented findings from the PADA-1 trial.1

**Study Design**

The PADA-1 trial enrolled 1,017 patients with ER-positive/HER2-negative metastatic breast cancer who were undergoing first-line treatment with palbociclib plus an aromatase inhibitor. Patients provided blood samples for bESR1 mutation screening at enrollment, at month 1, and every 2 months thereafter. Blood samples were monitored for several ESR1 mutations: E380, P535, L536, Y537, and D538.

Monitoring revealed a new ESR1 mutation in 172 patients who did not experience concurrent disease progression. The median time from trial enrollment to detection of the ESR1 mutation was 14.2 months (range, 2.8 to 47.1 months). Patients with a newly detected mutation were randomly assigned to 1 of 2 treatment approaches:

- Maintain treatment with palbociclib plus an aromatase inhibitor (n = 84)
- Switch treatment to palbociclib plus fulvestrant (n = 88)

The co-primary endpoints were progression-free survival (PFS) and grade ≥3 hematologic adverse events.

Baseline characteristics were similar in both treatment groups (Table 1). The median patient age was approximately 61 years, and one-third of patients (34%-37%) had prior treatment with an aromatase inhibitor.

**Key Findings**

After a median follow-up of 26 months, the strategy of switching patients from an aromatase inhibitor to fulvestrant upon bESR1-mutation detection was associated with a 39% reduction in the risk of disease progression or death.

| Characteristics                              | Palbociclib plus aromatase inhibitor (n = 84) | Palbociclib plus fulvestrant (n = 88) |
|----------------------------------------------|---------------------------------------------|--------------------------------------|
| Median age                                   | 60 years                                    | 62 years                             |
| Prior adjuvant aromatase inhibitor therapy   |                                             |                                      |
| Yes                                          | 37%                                         | 34%                                  |
| No                                           | 63%                                         | 66%                                  |
| Metastatic sites                             |                                             |                                      |
| Bone only                                    | 23%                                         | 22%                                  |
| Visceral                                     | 49%                                         | 48%                                  |
| Non-visceral ± bone                          | 29%                                         | 31%                                  |
| ECOG performance status                      |                                             |                                      |
| 0                                            | 61%                                         | 57%                                  |
| 1-2                                          | 39%                                         | 43%                                  |

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(Table 2). The median PFS for patients who were switched to fulvestrant was 11.9 months, compared with 5.7 months for patients who remained on an aromatase inhibitor (HR, 0.61; \( p = .005 \)).

Among those who were randomized to the aromatase inhibitor arm, 69 patients progressed and were given the option to crossover to the fulvestrant arm. Of those who switched to fulvestrant (\( n = 47 \)), the second median PFS was 3.5 months. This suggests that second-line fulvestrant confers a benefit for a brief duration and underscores the importance of detecting \( ESR1 \) mutations early.

The analysis of the co-primary endpoint of grade \( \geq 3 \) hematologic adverse events found no safety signals associated with switching from an aromatase inhibitor to fulvestrant (Table 3). Dose reductions were similar in the palbociclib plus aromatase inhibitor (7.1%) and palbociclib plus fulvestrant (7.9%) groups. One patient in the fulvestrant group (1.1%) withdrew from the trial due to a treatment-related adverse event.

Findings from the PADA-1 trial support a personalized approach to treatment modification based on the early detection of \( ESR1 \) mutations in patients with ER-positive metastatic breast cancer. Results also demonstrate the utility of targeting the brief window of opportunity—after the initiation of first-line therapy but before tumor progression—to improve patient outcomes in patients who develop resistance mutations.

### Table 2. Progression-free survival in ER-positive, \( ESR1 \)-mutated metastatic breast cancer

| Endpoint   | Palbociclib plus aromatase inhibitor (\( n = 84 \)) | Palbociclib plus fulvestrant (\( n = 88 \)) | Stratified HR (95% CI) | \( p \) value |
|------------|------------------------------------------------|----------------------------------|------------------------|----------------|
| Median PFS | 5.7 months                                      | 11.9 months                      | 0.61 (0.43-0.86)       | .005          |

### Table 3. Grade 3-4 adverse events in patients with ER-positive metastatic breast cancer

| Adverse event | Palbociclib plus AI (\( n = 84 \)) | Palbociclib plus fulvestrant (\( n = 88 \)) |
|---------------|-----------------------------------|---------------------------------------------|
| Leukopenia    |                                   |                                             |
| Grade 3       | 6.0%                              | 6.8%                                        |
| Neutropenia   |                                   |                                             |
| Grade 3       | 34.5%                             | 36.4%                                       |
| Grade 4       | 2.4%                              | 0%                                          |
| Anemia        |                                   |                                             |
| Grade 3       | 2.4%                              | 0%                                          |
| Thrombocytopenia |                                 |                                             |
| Grade 3       | 1.2%                              | 2.3%                                        |
| Nausea        |                                   |                                             |
| Grade 3       | 1.2%                              | 0%                                          |
| Pneumopathy   |                                   |                                             |
| Grade 3       | 3.6%                              | 0%                                          |
| Pain          |                                   |                                             |
| Grade 3       | 1.2%                              | 4.5%                                        |
| Other         |                                   |                                             |
| Grade 3       | 6.0%                              | 0%                                          |
| Grade 4       | 0%                                | 1.1%                                        |

**Reference**

1. Bidard FC, Hardy-Bessard AC, Bachelot T, et al. Fulvestrant-palbociclib vs continuing aromatase inhibitor-palbociclib upon detection of circulating \( ESR1 \) mutation in HR+ HER2-metastatic breast cancer patients: results of PADA-1, a UCBG-GINECO randomized phase 3 trial Abstract GS3-05. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). December 7-10, 2021. Abstract GS3-05.