

# Breast Cancer: ASCO20 Virtual Scientific Program Highlights for the Advanced Practitioner



**Paula Anastasia, RN, MN, AOCN®**, of UCLA Health Medical Center, and **Wendy H. Vogel, MSN, FNP, AOCNP®**, of Harborside,

discuss results from studies evaluating therapies in women with de novo metastatic breast cancer and HER2-positive breast cancer, along with targeted therapies for *PIK3CA* and *ESR1* mutations. Reporting provided by *The ASCO Post*.

## Abstract LBA2

### No Survival Benefit from Local Therapy in de Novo Metastatic Breast Cancer Study

By *The ASCO Post Staff*

Visit <https://meetinglibrary.asco.org/record/186884/abstract> to read the full abstract and view author disclosures.

**R**esults of the phase III E2108 study indicate that surgery and radiotherapy given after systemic treatment afforded no additional survival benefit among women with newly diagnosed metastatic breast cancer. The practice may, however, reduce locoregional progression of disease, according to a report presented in the Plenary Session of the ASCO20 Virtual Scientific Program.<sup>1</sup>

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“Based on the results of our study, women who present with a new diagnosis of breast cancer already in stage IV should not be offered surgery and radiation for the primary breast tumor with the expectation of a survival benefit,” said lead investigator Seema A. Khan, MD, Professor of Surgery and the Bluhm Family Professor of Cancer Research at Northwestern University, Chicago. “When making these decisions, it is important to focus energy and resources on proven therapies that can prolong life.”

### Study Addressed Conflicting Data

“About 6% of patients with newly diagnosed breast cancer present with stage IV disease and an intact primary tumor. Locoregional treatment for this primary was hypothesized to improve survival, based on retrospective analyses,” Dr. Khan said.

In a combined analysis of more than 15 trials, a reduction in risk of about 30% had been estimated for the addition of surgery and radiotherapy, she noted. “However, these studies were biased in that women receiving surgery were younger and had smaller tumors, more estrogen receptor-positive disease, and a lower metastatic burden,” pointed out Dr. Khan.

Further complicating matters, two randomized clinical trials published in the past 5 years had conflicting results. A study from Tata Memorial Hospital in Mumbai, India, found no survival advantage with early locoregional therapy,<sup>2</sup> whereas the Turkish Federation MF07-01 study showed an overall survival improvement of 17% with locore-

gional treatment,<sup>3</sup> Dr. Khan explained. The trial in India had a similar design to E2108, she added.

### E2108 Details

The phase III E2108 trial was conducted by the ECOG-ACRIN Cancer Research Group. E2108 enrolled 390 women (median age, 55 years) with de novo stage IV breast cancer. Approximately half had hormone receptor–positive HER2–negative tumors, 29% had HER2–positive tumors, and 10% had triple–negative disease. In the enrolled population, metastases in bone alone were observed in 31% of cases; in viscera alone, in 26%; and in both, in 27%. In the randomized population, the bone–plus–viscera percentage rose to 41%. The most frequently used systemic therapy was chemotherapy plus anti–HER2 agents.

Patients were treated with systemic therapy optimized according to patient and disease characteristics. The 256 patients who experienced no progression of distant disease after 4 to 8 months of therapy were then randomly assigned to continued systemic therapy alone ( $n = 131$ ) or early local therapy ( $n = 125$ ). In the local therapy arm, of the 125 patients, 109 underwent surgery, 87 achieved free surgical margins and required no additional treatment, and 74 were treated with radiotherapy as well. Patients were followed for 5 years to determine overall survival, the primary endpoint.

### No Survival Improvement With Local Therapy

At a median follow–up of 53 months, 121 patients had died. Median overall survival was 54 months, with no differences observed between the arms (hazard ratio [HR] = 1.09;  $P = .63$ ). “The survival curves overlap... They are completely superimposable, and there is no hint of an advantage in terms of survival with locoregional treatment to the primary intact tumor,” Dr. Khan reported.

Overall survival by tumor subtype also showed no significant differences for the 79 women in the HER2–positive subset (HR = 1.05) and the 137 women in the hormone receptor–positive HER2–negative subset (HR = 0.94). However, for the 20 women with triple–negative breast cancer, survival was worse with the addition of early local treatment (HR = 3.50), but this was not statistically significant given the small number of patients in this subset.

Locoregional treatment did, however, prevent better locoregional control in the early local therapy arm. Of the 43 locoregional disease progression events, 25.6% occurred in patients treated with systemic therapy alone, compared with 10.2% among patients receiving locoregional treatment as well (HR = 0.37,  $P = .003$ ).

### Unexpected Health-Related Quality-of-Life Outcomes

Health–related quality of life measured by the Functional Assessment of Cancer Therapy–Trial Outcome Index was significantly worse in the locoregional therapy arm than with systemic therapy alone at 18 months post randomization. However, Dr. Khan added, no difference was observed at 6 or 30 months, noting not all patients completed these surveys.

“Although we saw a 2.5–fold higher risk of local disease progression without locoregional therapy, the use of locoregional treatment for the primary site did not lead to improved quality of life,” Dr. Khan said. “This result was a little surprising, since one of the reasons for considering surgery and radiation is the idea that growth of the tumor will impair quality of life. Instead, we found the adverse effects of surgery and radiation appear to balance out the gains in quality of life that were achieved with better control of the primary tumor.”

### Moving Forward

“When combined with the results of an earlier trial in Mumbai, India,<sup>2</sup> these results of E2108 tip the scales against the possibility that local therapy to the breast tumor will help women live longer,” Dr. Khan concluded. Although she and her colleagues maintain that locoregional therapy has little benefit, it should be considered, however, “when systemic disease is well controlled with systemic therapy but the primary site is progressing,” she added.

Results are still pending for the ongoing Japan Clinical Oncology Group study JCOG–1017, which has a similar design as E2108. ●

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### The Advanced Practitioner Perspective

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Data from the E2108 randomized phase III trial shows that the survival outcome of women with newly diagnosed, metastatic breast cancer treated with or without surgery and radiation were the same. Therefore, the addition of local therapy did not improve overall survival.

The goal of the study was to determine whether surgery and radiation should be routine or standard of care therapy for patients with stage IV breast cancer. According to the results of this study, women with newly diagnosed stage IV breast should not be offered surgery and radiation with the goal of achieving

a survival benefit. The study included women with hormone receptor-positive, HER2-negative, HER2-positive, or triple-negative disease.

This information highlights the need for advanced practitioners to initiate and continue to have discussions with their patients about their goals of care. This study emphasizes that these conversations should include the lack of survival benefit with the addition of locoregional therapy when discussing treatment options. Informing patients of treatments and adverse events, survival outcomes, and a conversation regarding quality of life should be explored.

**Disclosure:** Ms. Anastasia has no conflicts of interest to disclose.

## Abstract 1005

### Study Indicates Effectiveness of Tucatinib Combination in Previously Treated HER2-Positive Metastatic Breast Cancer With Brain Metastases

By The ASCO Post Staff

Visit <https://meetinglibrary.asco.org/record/185141/abstract> to read the full abstract and view author disclosures.

**T**ucatinib, a small-molecule tyrosine kinase inhibitor that is highly selective for HER2, plus trastuzumab/capecitabine significantly improved central nervous system (CNS) progression-free survival, overall survival, and intracranial response rate vs placebo plus trastuzumab/capecitabine, as shown by the pivotal phase III HER2CLIMB trial.<sup>1</sup> The study population included patients with HER2-positive metastatic breast cancer and brain metastases at baseline.

The study was conducted by Nancy U. Lin, MD, and colleagues. Dr. Lin, who is Associate Professor of Medicine at Harvard Medical School and Clinical Director of the Breast Oncology

Center, Medical Oncology, Dana-Farber Cancer Institute, Boston, analyzed the findings at the ASCO20 Virtual Scientific Program. The report was published simultaneously in the *Journal of Clinical Oncology*.<sup>2</sup>

### HER2CLIMB Trial

The phase III trial supported the April 2020 approval of tucatinib in combination with trastuzumab/capecitabine in advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

In the double-blind trial, 612 patients with HER2-positive metastatic breast cancer who had prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine were randomly assigned 2:1 to receive oral tucatinib at 300 mg twice daily, plus trastuzumab and capecitabine (n = 410) or placebo plus trastuzumab and capecitabine (n = 202). Trastuzumab was given at a loading dose of 8 mg/kg on day 1 of cycle 1 if needed and then at a maintenance dose of 6 mg/kg on day 1 of 21-day cycles thereafter. (An alternative trastuzumab dosing regimen was 600 mg

subcutaneously on day 1 of every 21-day cycle.) Capecitabine was given at 1,000 mg/m<sup>2</sup> orally twice daily on days 1 through 14 of every 21-day cycle. Patients were treated until disease progression or unacceptable toxicity. All patients underwent baseline brain magnetic resonance imaging.

### Details of the Analysis

The current analysis included 291 patients (48% of trial population) with brain metastases at baseline, including 98 (48%) in the tucatinib group and 93 (46%) in the control group. The major outcome measures were CNS progression-free survival based on Response Evaluation Criteria in Solid Tumors, version 1.1, overall survival, and intracranial confirmed overall response rate and intracranial response duration in patients with measurable disease. Patients with isolated brain disease progression could continue study therapy after local treatment until second disease progression, with time from randomization to second disease progression or death being assessed.

### Key Findings

Median CNS progression-free survival was 9.9 months in the tucatinib group vs 4.2 months in the control group (hazard ratio [HR] = 0.32, 95% confidence interval [CI] = 0.22–0.48,  $P < .0001$ ). Median overall survival was 18.1 months vs 12.0 months (HR

= 0.58, 95% CI = 0.40–0.85,  $P = .005$ ). Intracranial overall response rate was 47.3% (95% CI = 33.7%–61.2%) vs 20.0% (95% CI = 5.7%–43.7%). Median duration of response was 6.8 months (95% CI = 5.5–16.4 months) vs 3.0 months (95% CI = 3.0–10.3 months).

Among a total of 30 patients with isolated brain disease progression who continued study therapy after local treatment, the median time from randomization to second disease progression or death was 15.9 months vs 9.7 months (HR = 0.33, 95% CI = 0.11–0.02).

The investigators concluded that in patients with heavily pretreated, HER2-positive metastatic breast cancer with brain metastasis, the addition of tucatinib to the combination of trastuzumab and capecitabine “doubled the [intracranial overall response rate], reduced risk of intracranial progression or death by two-thirds, and reduced risk of death by nearly half.” ●

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### The Advanced Practitioner Perspective

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In April 2020, the FDA approved tucatinib in combination with trastuzumab/capecitabine in advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

The HER2CLIMB trial had the remarkable inclusion criteria that allowed enrollment of patients with active, untreated, or progressing central nervous system (CNS) metastasis. Patients who developed isolated CNS progression while receiving treatment were not immediately taken off study. Instead, such patients were allowed to stay in the study and receive localized therapy (such as radio-

therapy). The presented results were from an updated analysis of patients with active CNS metastasis, in which the addition of tucatinib to the combination of trastuzumab and capecitabine doubled overall CNS response rate, reduced risk of intracranial progression or death by two-thirds, and reduced risk of death by nearly half.

These trial results will be practice-changing for clinicians who care for patients with relapsed/refractory, advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases.

Oncology advanced practitioners are often well-versed in single, doublet, and triplet drug combinations. It is important to educate patients and their caregivers about potential adverse events (AEs) that may occur with treatment, and that some AEs may be more

likely to develop with combination therapy. Common AEs included diarrhea, rash, and palmar-plantar erythrodysesthesia, which are also seen with capecitabine. Trastuzumab can also cause a decrease in ejection fraction, which did not appear to worsen with the addition of tucatinib. Capecitabine and tucatinib

may have some overlap with increased and reversible liver function tests. Some patients who develop AEs may need to have their capecitabine dose reduced or held until their AE resolves.

**Disclosure:** Ms. Anastasia has no conflicts of interest to disclose.

## Abstract 1006

### Alpelisib Deemed Effective in Advanced Breast Cancer After Treatment With CDK4/6 Inhibitor

By The ASCO Post Staff

Visit <https://meetinglibrary.asco.org/record/186927/abstract> to read the full abstract and view author disclosures.

The phase II BYLieve trial indicates the effectiveness of the PIK3CA inhibitor alpelisib in patients with PIK3CA-positive, hormone receptor-positive/HER2-negative advanced breast cancer previously treated with a cyclin-dependent kinase (CDK) 4/6 inhibitor plus an aromatase inhibitor. These results were announced at the ASCO20 Virtual Scientific Program.<sup>1</sup>

More than 50% of the 121 patients were alive without disease progression at 6 months, and the median progression-free survival was 7.3 months, according to Hope S. Rugo, MD, FASCO, Professor of Medicine and Director of Breast Oncology and Clinical Trials Education at the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center.

BYLieve is the first prospective trial to evaluate alpelisib and endocrine therapy with either fulvestrant or letrozole in patients with PIK3CA-mutated hormone receptor-positive advanced disease who have experienced disease progression on or after therapy with an inhibitor of CDK4/6. BYLieve met its primary endpoint, having exceeded the study-defined clinically relevant threshold of 30%, Dr. Rugo said.

“The combination of alpelisib and fulvestrant has demonstrated clinically meaningful efficacy” in this patient population, Dr. Rugo announced.

### Rationale for Study

Alpelisib is approved for use in combination with fulvestrant for hormone receptor-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer, following disease progression on or after an endocrine-based regimen, based on a 35% improvement in progression-free survival in the phase III SOLAR-1 trial.<sup>2</sup> For the small subset of 20 patients previously exposed to a CDK4/6 inhibitor in SOLAR-1, the median progression-free survival was 5.5 months vs 1.8 months in the control arm; 44.4% of patients were free of disease progression at 6 months.

As Dr. Rugo noted, the current standard of care in the first-line setting is endocrine therapy plus a CDK4/6 inhibitor, but resistance to these regimens typically develops. For patients with PIK3CA-mutated tumors, alpelisib plus fulvestrant could be a treatment option, although supportive clinical data were lacking.

### BYLieve Details

The ongoing, open-label, phase II noncomparative BYLieve trial enrolled premenopausal or postmenopausal women (or men) with hormone receptor-positive, HER2-negative advanced breast cancer and a PIK3CA mutation. Patients' last line of prior therapy was a CDK4/6 inhibitor plus an endocrine agent, systemic chemotherapy, or endocrine therapy. This population was allocated into one of three cohorts:

- Cohort A: Patients who received a CDK4/6 inhibitor plus an aromatase inhibitor as immediate prior therapy (results presented here)
- Cohort B: Patients who received a CDK4/6 inhibitor plus fulvestrant as immediate prior therapy (data pending)
- Cohort C: Patients who experienced disease progression on or after an aromatase inhibitor and received chemotherapy or endo-

crine therapy as immediate prior treatment (enrolled later).

Of the 127 patients in cohort A, 121 had centrally confirmed *PIK3CA* mutations. Seventy percent had received one prior metastatic regimen; the remainder had received at least two prior therapies or none in the metastatic setting. No patients had fulvestrant as a first-line metastatic agent. Most patients (60%) had secondary endocrine resistance.

Patients received oral alpelisib at 300 mg once daily plus 500 mg of fulvestrant on days 1 and 15 on cycle 1, followed by day 1 of each cycle thereafter. The primary endpoint was 6-month progression-free survival.

### Response and Stable Disease Rates

Among the 121 patients in cohort A with a confirmed *PIK3CA* mutation, the response rate was 17.4% (all partial responses). Almost half (45.5%) achieved stable disease, and 11.6% (n = 14) of patients had progressive disease as the best response. Among the 100 patients with measurable disease at baseline, the response rate was 21%, and the stable disease rate was 55.5%, Dr. Rugo reported.

Although BYLieve had no control arm, Dr. Rugo put the results in context with conventional treatment of patients with *PIK3CA*-mutated advanced breast cancer and previous treatment with a CDK4/6 inhibitor by comparing the data from BYLieve to data from 95 patients in the U.S. Flatiron Health–Foundation Medicine database. Patients had received a range of regimens, most frequently capecitabine monotherapy, fulvestrant monotherapy, fulvestrant plus palbociclib, everolimus plus exemestane, and fulvestrant plus letrozole and palbociclib.

### The Advanced Practitioner Perspective

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This is exciting news for patients who have progressed on prior therapy, because we now have another treatment that may offer benefit. Oncology advanced practitioners will note that the most common adverse events included hyperglycemia and rash. Prevention and identifying risk factors prior to treatment may help

Unadjusted results showed a median progression-free survival of 7.3 months in BYLieve cohort A vs 3.6 months in the real-world cohort. Similar outcomes were shown when data were weighted by odds, propensity score matching, and exact matching. “Matched analysis comparing BYLieve with real-world [data of] standard treatment in the post-CDK4/6 inhibitor setting further supports the use of alpelisib plus fulvestrant,” Dr. Rugo concluded.

### Safety Profile

The most common adverse events of all grades were diarrhea, hyperglycemia, and nausea. Grade  $\geq 3$  adverse events occurred in 66.9% of patients; they were primarily hyperglycemia (28.3%), rash (9.4%), diarrhea (5.5%), dyspnea (2.4%), stomatitis (1.6%), vomiting (1.6%), and pruritus (1.6%). Treatment-related grade  $\geq 3$  serious adverse events occurred in 14.2% of patients. Eighteen percent of patients discontinued treatment due to treatment-related toxicity, and 65% had doses reduced or interrupted.

Dr. Rugo said that generally, the adverse events were consistent with previous studies of alpelisib. Based on a small number of patients, it appears that prophylactic antihistamines may ameliorate the occurrence and severity of rash associated with the drug. ●

### References

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reduce or avert side effects. As an example, obtaining a baseline fasting glucose and/or hemoglobin A1C prior to starting therapy may identify who is at risk for hyperglycemia. Pre-medication with an antihistamine may mitigate development or decrease the severity of a rash. Education of patients and caregivers is important to recognize and manage adverse events.

**Disclosure:** Ms. Anastasia has no conflicts of interest to disclose.

**Abstract 1007****When Paired With Palbociclib, Fulvestrant and Letrozole Yield Comparable Results in PARSIFAL Trial**

By Caroline Helwick

Visit <https://meetinglibrary.asco.org/record/184813/abstract> to read the full abstract and view author disclosures.

**W**hen paired with palbociclib in the first-line treatment of metastatic breast cancer, fulvestrant and letrozole performed comparably, with no statistical superiority in progression-free or overall survival shown for either endocrine agent, in the phase II PARSIFAL study presented during the ASCO20 Virtual Scientific Program.<sup>1</sup>

The study's hypothesis was that fulvestrant would be the superior partner to the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, but "no major efficacy differences were observed by the two stratification factors, visceral or de novo metastatic disease," said Antonio Llombart-Cussac, MD, PhD, of Universidad Catolica Valencia and Medica Scientia Innovation Research, Spain.

"PARSIFAL was inconclusive in establishing superiority between the two endocrine backbone agents when combined with palbociclib. The final treatment decision must balance patients' and clinicians' preferences as well as subsequent treatment strategies," he added.

Breast cancer highlights speaker Erika Hamilton, MD, Director of the Breast Cancer and Gynecologic Cancer Research Program at Sarah Cannon Research Institute at Tennessee Oncology, noted that PARSIFAL's findings differed from those of the FALCON trial, which showed progression-free survival to be superior with fulvestrant vs anastrozole.<sup>2</sup> Dr. Hamilton noted: "How do we reconcile these findings? If we assume the results of both trials are accurate, it seems that just because SERD may be better than AI when they are given alone, this superiority doesn't necessarily hold true when the endocrine agents are in combination with a second drug."

**PARSIFAL Details**

In metastatic breast cancer resistant to endocrine therapy, a CDK4/6 inhibitor plus fulvestrant has improved survival in several trials. In patients with endocrine-naive metastatic breast cancer, fulvestrant conveyed a progression-free survival benefit over anastrozole in the FALCON trial,<sup>2</sup> as previously mentioned. "PARSIFAL wanted to explore the optimal endocrine agent to combine with palbociclib in the first-line -endocrine-sensitive scenario," Dr. Llombart-Cussac said.

PARSIFAL enrolled 486 women with endocrine-sensitive metastatic breast cancer and no prior therapy for advanced disease. The arms were well balanced in terms of baseline characteristics and prior treatment. Patients were randomly assigned to palbociclib at 125 mg daily on a 21-day schedule plus fulvestrant at 500 mg on days 1, 14, 29, and monthly thereafter or letrozole at 2.5 mg once daily, continuously.

The study assumed a 22-month median progression-free survival with letrozole plus palbociclib. The two-sided log-rank test had 80% power to detect a 0.70 hazard ratio (HR) for fulvestrant, equating to a median progression-free survival of 31.3 months. If superiority was not achieved, the plan was to switch to a noninferiority analysis whose margin was a hazard ratio of 1.21.

**No Differences Observed**

At a median follow-up of 32 months, in the investigator-assessed intent-to-treat analysis, median progression-free survival was 32.8 months with letrozole/palbociclib and 27.9 months with fulvestrant/palbociclib (HR = 1.13;  $P = .321$ ). "At this point, we failed to see a significant difference. As the superiority of fulvestrant was not achieved, we proceeded with the noninferiority analysis. Those results were inconclusive," Dr. Llombart-Cussac reported.

No differences were seen according to the presence of visceral disease (in both arms, nonvisceral disease was associated with notably longer remission), by disease presentation (recurrent vs de novo), or by prespecified subgroup. With 21% of deaths having occurred at the time of analysis, 3-year overall survival also did not differ: 77.1% with letrozole and 79.4% with fulvestrant (HR = 1.00;  $P = .986$ ).

Objective response rate, clinical benefit rate, and relative dose intensity were also similar between the arms. Adverse events, whether related to treatment or not, were similar as well, although more patients receiving fulvestrant discontinued therapy because of toxicity or other reasons.

Focusing on toxicities of special interest, Dr. Llombart-Cussac noted that the rate of thromboembolic events was low in both arms (4.5% with letrozole, 5.8% with fulvestrant), although two grade 4 events were observed with fulvestrant. Interstitial lung disease and pneumonitis of any

grade were seen in six patients in each arm; grade 3 events occurred in three patients receiving letrozole and two patients receiving fulvestrant. ●

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### The Advanced Practitioner Perspective

Wendy H. Vogel, MSN, FNP, AOCNP®  
Harborside

The results of this abstract regarding the PARSIFAL trial help to answer a question many patients and advanced practitioners have asked: “Should I pair palbociclib, a CDK4/6 inhibitor, with letrozole or fulvestrant?” Letrozole is an aromatase inhibitor and fulvestrant is an estrogen receptor antagonist. Both are approved in metastatic hormone receptor-positive breast cancer.

PARSIFAL did not show superiority in efficacy (progression-free survival) for either agent in visceral or de novo metastatic dis-

ease. The median progression-free survival was 27.9 months with fulvestrant and 32.8 months with letrozole, and the difference was not statistically significant. The objective response rate, clinical benefit rate, and relative dose intensity were similar in both arms. Therefore, the advanced practitioner must examine patient-specific needs and health issues as well as preferences for an oral agent vs. an injectable agent. It is noted that more patients discontinued fulvestrant in the trial for reasons other than progression. Overall, both drugs were well tolerated.

**Disclosure:** Ms. Vogel has no conflicts of interest to disclose.

### Abstract 1010

#### Phase III PADA-1 Trial Examines the Impact of *ESR1* Mutations in Metastatic Breast Cancer

By Caroline Helwick

Visit <https://meetinglibrary.asco.org/record/185414/abstract> to read the full abstract and view author disclosures.

**E***SR1* mutations are known to confer resistance to endocrine therapy in the metastatic breast cancer setting. These mutations herald a poor prognosis, so their clearance early in the treatment course may greatly reduce the risk of recurrence, according to the early results of the prospective phase III PADA-1 trial, reported during the ASCO20 Virtual Scientific Program.<sup>1</sup>

The study involved 1,017 patients with metastatic, hormonally sensitive breast cancer treated in the first-line setting with an aromatase inhibitor plus palbociclib. It found that patients with *ESR1* mutations at baseline, compared with those who had *ESR1* wild-type tumors, had double the odds of disease progression. However, if those mutations were cleared early during treatment, this risk diminished to roughly that of their wild-type peers. Of note, PADA-1 also found the mutation was more than twice as prevalent—7% vs 3%—among patients who received an aromatase inhibitor in the adjuvant setting.

“*ESR1* mutation screening before starting first-line treatment with an AI plus palbociclib could be considered for patients at higher risk of *ESR1* mutations,” stated lead investigator François-Clément Bidard, MD, PhD, of the Institut Curie, Paris.



### Study Rationale

The question of which is the best endocrine partner to cyclin-dependent kinase 4/6 (CDK4/6) inhibitors as first-line treatment has remained unanswered. *ESR1* mutations are detected in between 1% and 5% of patients upon first relapse but in up to 40% of patients who become resistant to an aromatase inhibitor.

“*ESR1* mutations might be of paramount importance, as they confer resistance to aromatase inhibitors but not to selective estrogen receptor degraders such as fulvestrant,” Dr. Bidard noted.

In patients treated with first-line palbociclib plus an aromatase inhibitor, the PADA-1 trial determined the rate of *ESR1* mutations at study inclusion and shortly after therapy was initiated as well as looked at the association between mutation and prognosis. PADA-1 also evaluated the utility of monitoring the onset of *ESR1* mutations in cell-free DNA. Dr. Bidard presented the early results for the first part of this study.

### PADA-1 Details

This trial included 1,017 patients with estrogen receptor-positive, HER2-negative, metastatic breast cancer who had received no prior therapy for metastatic disease and had no overt resistance to aromatase inhibitors. Sensitivity was assumed based on no prior treatment with an aromatase inhibitor or a disease-free interval of more than 12 months from adjuvant treatment with one.

Patients had cell-free DNA tested for *ESR1* mutations at inclusion and during treatment with an aromatase inhibitor plus palbociclib (step 1). Some 565 patients developed progressive disease and were eliminated from the study. For 135 patients, an emerging *ESR1* mutation was detected, although disease was not progressing; these patients were randomly assigned to continue the same treatment or switch to fulvestrant plus palbociclib (step 2, n = 135). (These data will be reported at a later date.)

At inclusion, testing identified 33 patients with mutations (3.2%). The presence of this mutation at baseline was associated with prior exposure to an aromatase inhibitor in the adjuvant setting, with a prevalence of 7.1% among patients with at least 3 years of adjuvant treatment vs 3.2% in the overall population (odds ratio

[OR] = 3.0). *ESR1* mutations were also more likely among patients with bone metastases (4.0%; OR = 3.4) and among postmenopausal women (4.1%; OR = 5.4).

### Worse Prognosis Associated With *ESR1* Mutation

At a median follow-up of 21.2 months, median progression-free survival for the 33 mutation-positive patients was 11.0 months, but it was 26.7 months for patients with *ESR1* wild-type disease (HR = 2.3;  $P < .001$ ).

“No multivariate analysis was done, as many patients are still being followed in step 1,” Dr. Bidard explained. “However, a sensitivity analysis found no impact of the type of adjuvant endocrine therapy on progression-free survival.”

### Clearance of *ESR1* Mutations

For 23 of the 33 patients (69%), *ESR1* mutations were cleared after 4 weeks of treatment. However, 15 of these patients experienced a later “resurgence” of the mutation. A smaller subgroup of 10 patients experienced no mutational clearance at 4 weeks.

In addition, clearance of *ESR1* mutations heralded a better prognosis. The median progression-free survival was 24.1 months in the cleared group vs 7.4 months in those with still-detectable *ESR1* mutations (Table 1).

In closing, Dr. Bidard said *ESR1* mutation at baseline is a prognostic marker for patients treated with an aromatase inhibitor and palbociclib. However, “both the 11-month median progression-free survival in patients with *ESR1*-mutated disease and the frequent clearance of the mutation after one cycle suggest an aromatase inhibitor plus palbociclib retains some activity despite the *ESR1* mutation,” he commented.

New oral selective estrogen receptor degraders are of increasing interest as a means of further improving the outcomes of patients with *ESR1* mutations, said Dr. Bidard. ●

### Reference

1. Bidard FC, Callens C, Dalenc F, et al: Prognostic impact of *ESR1* mutations in ER+ HER2- MBC patients with prior treatment with first-line AI and palbociclib: An exploratory analysis of the PADA-1 trial. ASCO20 Virtual Scientific Program. Abstract 1010.

**The Advanced Practitioner Perspective**

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**Harborside**

The phase III PADA-1 trial examined the prognostic influence of *ESR1* mutations. *ESR1* mutations are frequently found in patients with newly diagnosed metastatic breast cancer or in locoregional recurrences of breast cancer. They are rare in primary tumors. These mutations may be found during adjuvant endocrine therapy, after adjuvant endocrine therapy, or during neoadjuvant endocrine therapy.

This study validated the theory that an *ESR1* mutation may cause resistance to endocrine therapy, thus negatively affecting prognosis. This study examined patients who were receiving aromatase inhibitor (AI) therapy with palbociclib in patients with estrogen receptor-positive, HER2-negative metastatic breast

cancer. Upon the onset of an *ESR1* mutation noted in circulating tumor DNA, study participants' therapy was randomly assigned to continue the same therapy or to change from an AI to fulvestrant, an estrogen receptor antagonist, still combined with palbociclib.

Safety and efficacy are being evaluated and reported at a later date. PADA-1 noted that early clearance of the mutation (within 1 month of treatment) improved prognosis. It was also noted that patients in this study who received an AI as adjuvant therapy and again in the metastatic setting were more likely to have an *ESR1* mutation. For the advanced practitioner, sequencing of hormonal therapy from the neoadjuvant/adjuvant setting into the metastatic setting may be impacted by the presence or emergence of an *ESR1* mutation.

**Disclosure:** Ms. Vogel has no conflicts of interest to disclose.