

Practice-changing endocrine trials shed light on breast cancer treatment and management

At the 2016 San Antonio Breast Cancer Symposium, investigators presented findings on PFS benefits of adding an mTOR inhibitor to anti-hormonal therapy in advanced disease in postmenopausal women; the lack of clarity on the optimal duration of extended AI therapy, also in postmenopausal women; and using CTCs in helping predict breast cancer outcomes in the neoadjuvant setting.

Fulvestrant plus everolimus improves PFS in HR+, HER2- advanced breast cancer

Key clinical point This study provides further evidence of the benefits of adding an mTOR inhibitor to anti-hormonal therapy in postmenopausal women with advanced breast cancer resistant to aromatase inhibitors. **Major finding** Fulvestrant plus everolimus was associated with a PFS of 10.4 months, vs 5.1 months for fulvestrant alone. **Data source** Randomized phase 2 trial of 131 women with HR-positive, HER2-negative locally advanced or metastatic breast cancer resistant to aromatase inhibitors. **Disclosures** Sponsored by PrECOG with financial support from Novartis. Dr Kornblum reported having no conflicts of interest.

Adding everolimus to fulvestrant doubled median progression-free survival (PFS) among postmenopausal women with hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2-negative (HER2-negative) metastatic breast cancer resistant to therapy with an aromatase inhibitor (AI), Noah S Kornblum, MD, reported during his presentation at the meeting of the PrECOG 0102 trial findings.

In the randomized phase 2 trial, the combination of the mammalian target of rapamycin (mTOR) inhibitor everolimus with the selective estrogen receptor down-regulator (SERD) fulvestrant was associated with a median PFS of 10.4 months, compared with 5.1 months for fulvestrant plus placebo, said Dr Kornblum, of Montefiore Einstein Center for Cancer Care, New York. The findings provide additional evidence that adding everolimus to anti-estrogen therapy in AI-resistant disease improves clinical outcomes," he added.

Most women with HR-positive breast cancer who are treated with an AI will eventually develop resistance to those agents. Strategies for overcoming resistance include the addition of everolimus to a steroid AI, exemestane, as has been demonstrated

in the BOLERO-2 trial. "Another strategy for overcoming AI resistance is by more completely blocking estrogen-receptor signaling through the use of a selective estrogen receptor down-regulator, which may result in more complete blockade of the ER signaling pathway than a steroidal AI such as exemestane," Dr Kornblum said.

To test this hypothesis, the investigators enrolled 131 postmenopausal women with inoperable locally advanced or metastatic HR-positive, HER2-negative breast cancer resistant to AIs. AI resistance was defined as relapse while receiving adjuvant AI therapy, and/or progression after one or more AIs for metastatic disease. The patients could have had no more than one prior chemotherapy regimen for metastatic disease.

The patients were stratified by Eastern Cooperative Oncology Group performance status, presence of measurable disease, and previous chemotherapy status, and were then randomized to receive either high-dose fulvestrant (500 mg on day 1 and 15 of cycle 1, and then on day 1 of cycles 2-12) plus oral everolimus 10 mg/day, or fulvestrant and placebo. The trial had an induction phase, in which patients were treated until evidence of progressive disease or unacceptable toxicity for a maximum of 12 28-day cycles, and a continuation phase in which patients who had neither disease progression nor experienced unacceptable toxicities could have their data unblinded and could continue on the fulvestrant-everolimus combination.

The trial did not include the use of corticosteroid-containing mouthwash for prevention of treatment-associated stomatitis, because it was designed before



Dr Noah Kornblum

the evidence of the benefit of such prophylaxis became public, Dr Kornblum said.

The primary endpoint of PFS by investigator assessment was significantly better with the fulvestrant-everolimus group at 10.4 months, compared with 5.1 months for the fulvestrant-placebo group. The hazard ratio was 0.60 ($P = .02$).

There was no difference in overall survival (OS), however. Median OS in the combination group was 24.8 months, compared with not yet reached in the placebo arm (not statistically significant).

The combination therapy was associated with more grade 3 adverse events than the fulvestrant-placebo combination (48% vs 14%, respectively). The most common grade 3 adverse events occurring in more than 5% of patients were stomatitis, pneumonitis, fatigue, and hyperglycemia. Overall, the safety profile of the combination was consistent with that seen in BOLERO-2, Dr Kornblum said. In all, 10% of patients assigned to the combination and 12% assigned to placebo withdrew from the study because of adverse events; these patients were included in the analysis, which was by intention to treat.

— Neil Osterweil

Still no clarity on duration of extended AI therapy

Key clinical point The optimal duration of aromatase inhibitor (AI) therapy following 5 years of endocrine therapy in postmenopausal women is still unknown. **Major finding** There were no significant differences in disease-free or overall survival in three studies investigating extended AI therapy.

Data source Randomized phase 2 NSABP B-42 with 3996 patients; randomized phase 3 DATA study with 1912 patients; randomized phase 3 IDEAL trial with 1824 patients.

Disclosures NSABP B-42 was sponsored by PrECOG with financial support from Novartis. Dr Mamounas reported having no conflicts of interest. The DATA trial was sponsored by the Dutch Breast Cancer Research Group and Novartis. Dr Tjan-Heijnen reported nothing to disclose. IDEAL was supported by the Dutch Breast Cancer Research Group and Novartis. Dr Blok reported nothing to disclose.

When does adjuvant therapy with an aromatase inhibitor become too much of a good thing? Or, put another way, what's the optimal duration of extended aromatase inhibitor therapy? That's the question that three clinical trials have tried – but largely failed – to answer.

For example, the randomized, double-blinded NSABP B-42 trial, comparing extended therapy with letrozole in postmenopausal women with hormone receptor-positive (HR-positive) breast cancer who have completed previous adjuvant therapy with an aromatase inhibitor (AI) showed no difference in disease-free survival (DFS) after 7 years of follow-up between women treated with extended letrozole or placebo.

“Our findings suggest that careful assessment of potential risks and benefits is required before recommending extended

letrozole therapy to patients with early-stage breast cancer, including patient and tumor characteristics such as age and nodal status, existing comorbidities, information on bone mineral density, and tolerance of the aromatase inhibitor in the initial years,” Eleftherios P Mamounas, MD, of NRG Oncology/NSABP, said at the symposium.



Dr Eleftherios Mamounas

DATA data

In the DATA study, also presented at the meeting, investigators from the Netherlands compared 6 years of anastrozole with 3 years of anastrozole after 2 or 3 years of adjuvant tamoxifen for postmenopausal women with estrogen receptor-positive (ER-positive), and/or progesterone receptor-positive (PR-positive) breast cancer. They found that “adapted” DFS (DFS starting 3 years after randomization) and adapted overall survival (OS) were similar between the two groups. “The findings of the DATA study do not support extended adjuvant AI use after 5 years of sequential endocrine therapy for all postmenopausal hormone receptor-positive breast cancer patients,” said Vivianne Tjan-Heijnen, MD, of Maastricht University Medical Center in the Netherlands.

Less than IDEAL

In the optimistically named IDEAL trial, a separate team of investigators, also from the Netherlands, looked at the relative merits of continuing adjuvant therapy with letrozole for 2.5 or 5 years after 5 years of adjuvant therapy with tamoxifen, an AI, or a combination in postmenopausal women with HR-positive breast cancer. They found no differences in either DFS or OS between patients treated for 5 years or those treated for only half that long. “We conclude that there is no benefit of extending AI-based therapy longer than two-and-a-half years,” said Erik Blok, MD, of Leiden University Medical Center in the Netherlands.

Give what, to whom, for how long?

Results of the trials raise more questions than they answer, said Michael Gnant, MD, of the Medical University of Vienna, the invited discussant. “Essentially, these three trials did not reach the necessary statistical significance levels to demonstrate a clear benefit for the respective AI extension,” he said, adding that he does not think that other agents used in luminal breast cancer would help. “Based on their tolerability profile, and in part also on financial toxicity, I don't think that the promising agents we explore in many situations for the treatment of hormone receptor-positive breast cancer will realistically be used in the extended adjuvant setting,” he said.

New strategies are needed for targeting the chronic part of luminal breast cancer recurrence risk, Dr Gnant noted. Using endocrine therapies in that setting would likely be ineffective. Instead, agents that could directly target dormant cancer stem cells would “eliminate the source of late metastases for good.”

The best evidence to date clearly points to individualized treatment plans for patients, Dr Gnant said. For example, for a patient who has had 2-5 years of tamoxifen, an AI for 2.5-5 additional years can help prevent recurrences, provided the patient has risk factors for recurrence and excellent bone health.

“Based on the trial results, it is more complex for a patient who comes off initial or sequential AI. There are factors favoring the extension of AI treatment, and other factors to speak against such extension. I suggest to start with patient features at this time,” he said.

Currently, the main factor driving the choice of extended AI therapy will be how well the patient has tolerated AIs in the first years of therapy and whether she is at increased risk for fractures, suggesting younger age as a factor favoring extended AI use. Patients with higher clinicopathologic risk factors such as node positivity or more luminal type tumors, as well as higher risk according to genomic studies, might also benefit from extended AI therapy, he said.

Biomarkers needed

“What the data from these and other trials tell us is that endocrine therapy is not for everyone. We need biomarkers that can tell us who should be getting extended endocrine therapy, be it 10 years or even a longer duration of time, versus a subgroup that might do very well with 5 five years of AI,” Aditya Bardia, MBBS, MPH, of the breast cancer division at Massachusetts General Hospital Cancer Center in Boston, said in an interview.

There are several such biomarkers under investigation, but they need validation and testing in large scale clinical trials before they find their way into day-to-practice, said Dr Bardia, who was not involved in the studies.

— Neil Osterweil

CTCs help predict breast cancer outcomes in neoadjuvant setting

Key clinical point CTCs are a useful prognostic biomarker in early breast cancer patients treated with neoadjuvant chemotherapy. **Major finding** OS was associated with the presence of at least 2 CTCs at baseline (HR, 2.6 for 2 CTCs; 3.84 for 3-4 CTCs; and 6.25 for 5 or more CTCs). **Data source** Meta-analysis of data for 2156 patients. **Disclosures** Supported by a research grant from Janssen Diagnostics. Dr Bidard reported having no disclosures.

Circulating tumor cells (CTCs) are a useful prognostic biomarker in early breast cancer patients treated with neoadjuvant chemotherapy, according to findings from an interna-

tional meta-analysis of individual patient data. The cells, which can be measured using a Food and Drug Administration-approved assay, are known to seed distant metastases and to be prognostic before and during therapy for patients with metastatic breast cancer, and prognostic before adjuvant therapy for patients with nonmetastatic breast cancer.

However, findings in the neoadjuvant setting have been varied, Francois-Clement Bidard, MD, of Institut Curie, Paris, reported at the symposium.

In the IMENEO study, CTCs were useful, independent of pathologic complete response, for predicting overall survival and distant disease-free survival in the neoadjuvant setting. In addition, the findings showed for the first time that CTCs also predict locoregional relapse-free survival. Based on an analysis of data from 2156 patients from 21 studies at 16 centers in 10 countries, the CTC positivity rates using thresholds of one or more, two or more, and five or more, respectively, were 25%, 13%, and 6% in 1574 patients tested at baseline; 17%, 6%, and 3% in 290 tested after neoadjuvant chemotherapy; 15%, 5%, and 1% in 1,200 tested before surgery; and 11%, 4%, and 1% in 285 tested after surgery, Dr Bidard said.

Prior to neoadjuvant chemotherapy, at least one CTC was found in 19%, 22%, 24%, 29%, and 41% of cT1, T2, T3, T4a-c, and T4d breast cancers, respectively, and this was marginally associated with hormone receptor negativity, he said, noting that later CTC detection rates were not associated with any patient baseline characteristics.

Nearly one in four patients (24%) achieved pathologic complete response, but this was not associated at any time point with CTC count.

For the primary study endpoint of overall survival, a significant association was found with the presence of at least two CTCs at baseline (hazard ratio, 2.6 for two CTCs; 3.84 for three to four CTCs; and 6.25 for five or more CTCs). Similar associations were found for distant disease-free survival (hazard ratios, 2.4, 3.4, and 5.0, respectively) and for locoregional relapse-free interval with two CTCs and five or more CTCs (hazard ratios, 2.4 and 4.2, respectively).

Similar results were found using later time points, such as after the start of neoadjuvant chemotherapy or before surgery, he said.

On multivariate analysis, baseline CTC detection using any of the thresholds remained an independent predictor of overall and distant disease-free survival and locoregional relapse-free interval when considered together with pathologic complete response, cT, cN, and tumor subtype, suggesting that CTC measurement adds value to comprehensive prognostic models. That is, they complement rather than duplicate usual prognostic factors and pathologic complete response rates to better predict outcomes in patients with early breast cancer in the neoadjuvant setting, Dr Bidard said.

— Sharon Worcester

PI3K inhibitor gives slight PFS edge at high cost for advanced breast cancer

Key clinical point The PI3K inhibitor buparlisib plus fulvestrant slightly prolonged progression-free survival of HR+/HER2- breast cancer pretreated with an aromatase inhibitor and mTOR inhibitor. **Major finding** The combination met its primary endpoint of better PFS than fulvestrant/placebo, but with high liver toxicity and mood disorders. **Data source** Randomized phase 3 trial of 432 women with HR-positive, HER2-negative, AI-pretreated breast cancer that progressed on or after mTOR inhibitor therapy. **Disclosures** Novartis sponsored the study. Dr Di Leo disclosed consulting and lecture fees from the company, and Dr O'Regan disclosed contracted research support. Dr Arteaga reported no disclosures relevant to the study.

A combination of a PI3K inhibitor and selective estrogen receptor down-regulator (SERD) met its primary endpoint of 2.1 months better progression-free survival (PFS) in postmenopausal women with locally advanced or metastatic breast cancer who were quickly running out of other treatment options, but the small gain in PFS came at a very high price in terms of toxicities, including mood disorders that may have led to patient suicide attempts, according to investigators.

The BELLE-3 trial looked at the combination of the SERD fulvestrant and an experimental inhibitor of the PI3 kinase, buparlisib, in postmenopausal women with hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2-negative (HER2-negative) breast cancer treated with an aromatase inhibitor (AI) who experienced disease progression either on or after receiving therapy with an inhibitor of the mammalian target of rapamycin complex 1 (mTORC1).

The combination of fulvestrant and buparlisib was associated with a median PFS of 3.9 months, compared with 1.8 months for fulvestrant and placebo (*P* less than .001), Angelo Di Leo, MD, of Ospedale Misericordia e Dolce in Prato, Italy, reported at the symposium.

Objective response rates (ORR) were low, at 7.8% in the combination arm, and 2.1% in the fulvestrant-plus-placebo arm. Although the PFS difference was statistically significant, “the higher rate of toxicity in patients receiving buparlisib and fulvestrant, including transaminase elevations and mood disorders, may represent a clinically relevant challenge for future development of this compound in this particular group of patients,” Dr Di Leo said.

Blocks AKT pathway

The preclinical rationale for the use of a P13K inhibitor after disease progression on mTORC1 inhibitor is that current mTOR inhibitors such as everolimus have a feedback mechanism that activates the AKT pathway, and that the use of P13K inhibitors can “abrogate or attenuate this activation, potentially blocking that pathway,” explained

coinvestigator Ruth O'Regan, MD, head of the division of hematology and oncology at the University of Wisconsin-Madison School of Medicine and Public Health. Dr O'Regan discussed the BELLE-3 findings in a briefing before Dr Di Leo's presentation of the data in general session.

In BELLE-3, 432 postmenopausal women with HR-positive, HER2-negative, AI-pretreated, locally advanced or metastatic breast cancer that had progressed on or after treatment with an mTOR inhibitor as the last line of therapy were enrolled. The patients were stratified by the presence or absence of visceral disease and then randomized on a 2:1 basis to fulvestrant 500 mg daily plus either buparlisib 100 mg/day (289 patients) or placebo (143).



Dr Ruth O'Regan

The primary endpoint of investigator-assessed PFS favored the addition of buparlisib, with a hazard ratio for progression of 0.67 (*P* less than .001). PFS results by independent central review were similar (HR 0.57, *P* less than .001).

The ORR for the buparlisib-fulvestrant combination, 7.6%, consisted of 0.3% complete responses and 7.3% partial responses. The ORR for the placebo-fulvestrant combination, 2.1%, was composed entirely of partial responses. The respective clinical benefit rates, defined as a combination of complete and partial responses and stable disease, were 24.6% and 15.4, respectively.

The benefit of buparlisib was evidently entirely among patients with visceral disease, with a PFS of 3.1 months, compared with 1.5 months. In contrast, PFS among patients with no visceral disease was 4.2 months, compared with 4.1 months, respectively, and was not significant.

In addition, the P13K inhibitor seemed to benefit patients with PIK3CA mutations detected in either the primary tumor or in circulating DNA samples, but not patients with wild-type PIK3CA.

Depression, anxiety with combination

Patients assigned to buparlisib-fulvestrant group had substantially higher proportions of alanine aminotransferase and aspartate aminotransferase elevations compared with patients in the placebo-fulvestrant group, as well as more reported depression and anxiety. Three patients in the buparlisib arm attempted suicide. There were no reported suicide attempts in the placebo arm.

Dr O'Regan said at the briefing that mood disorders are known adverse events associated with buparlisib, and that patients with psychiatric disorders were excluded from the trial.

— Neil Osterweil