Everolimus overcomes hormonal resistance in ER-positive breast cancer

The addition of everolimus to exemestane more than doubled progression-free survival in women with advanced breast cancer who became resistant to hormonal therapy.

A preplanned interim analysis of the phase III BOLERO-2 trial in women with advanced hormone-resistant, estrogen receptor–positive (ER+) breast cancer showed that everolimus (Afinitor) combined with the aromatase inhibitor exemestane increased progression-free survival (PFS), by local assessment, from a median of 2.8 months with exemestane alone to 6.9 months—a 57% risk reduction (hazard ratio [HR], 0.43; $P = 1.4 \times 10^{-15}$). The results were presented at the recent 2011 European Multidisciplinary Cancer Congress in Stockholm, Sweden.[1]

Based on central assessment, the everolimus-exemestane combination produced a 64% reduction in the risk of progression or death (10.6 months vs 4.1 months; HR = 0.36; $P = 3.3 \times 10^{-15}$), according to lead investigator José Baselga, MD, PhD, of the Massachusetts General Hospital Cancer Center in Boston.

The researchers evaluated everolimus because the mammalian target of rapamycin (mTOR) pathway is activated in hormone therapy–resistant advanced breast cancer. Phase II everolimus trials have suggested that the mTORC1 inhibitor could reverse resistance to endocrine therapy.[2]

The group enrolled 724 postmenopausal women (median age, 62 years) with advanced ER+, human epidermal growth factor receptor 2–negative (HER2–) breast cancer who were refractory to letrozole or anastrozole. Previous treatment also included chemotherapy for metastatic disease in roughly 68% of the patients, tamoxifen in 48%, and fulvestrant (Faslodex) in about 16%. The patients were randomized to treatment with everolimus 10 mg/d or placebo, with both arms receiving exemestane 25 mg/d. Treatment was continued until disease progression or unacceptable toxicity occurred. The primary endpoint was PFS, as assessed by the investigators; secondary endpoints included survival, response rate, and safety. The preplanned interim analysis was performed and reviewed by an independent data monitoring committee after observing 359 PFS events.

The overall response rate was 9.5% for the everolimus arm and 0.4% for the placebo arm ($P < 0.0001$). The clinical benefit rate was 33% and 18%, respectively ($P < 0.0001$). A subgroup analysis of PFS showed consistent results across all subpopulations of patients.

At the time of the interim analysis, 83 patients had died (10.6% in the everolimus arm, and 13.0% in the placebo arm), but those data are immature, according to Dr. Baselga.

Adverse events for the everolimus group and the placebo group were consistent with previous everolimus experience, with the most common grade 3/4 events including stomatitis (8% vs 1%, respectively), anemia (5% vs < 1%), dyspnea (4% vs 1%), hyperglycemia (4% vs < 1%), fatigue (3% vs 1%), and pneumonitis (3% vs 0%).

Novartis Pharmaceuticals, which manufactures everolimus, plans to

Report prepared by Patrice Wendling.

What's new, what's important

Breast cancer is the most common cancer among women and still the second leading cause of cancer death, killing nearly 40,000 women in the U.S. each year. Antiestrogen therapy is the first and most effective targeted therapy for breast cancer in postmenopausal women. But many patients develop resistance to hormonal therapy. Greater understanding of the pathogenesis of breast cancer continues to help scientists and clinical researchers find novel ways of treating this disease.

One of the mechanisms of estrogen resistance is an overactive mTOR (mammalian target of rapamycin) pathway. It is very promising to note that this preclinical finding is translating into a meaningful intervention for our patients. The BOLERO-2 trial has shown that the mTOR inhibitor everolimus (Afinitor) can reverse endocrine resistance and improve progression-free survival and overall response rate in patients with advanced estrogen receptor–positive breast cancer.

The dose of everolimus used in this trial was 10 mg/d and of exemestane, 25 mg/d; both drugs were taken by mouth once daily. Although the combination was well tolerated, adverse events were more common among the group that received everolimus. The most frequent grade 3/4 events included stomatitis, anemia, dyspnea, hyperglycemia, fatigue, and pneumonitis.

The BOLERO-2 trial is a potentially practice-changing study and offers new hope for our patients.

—Jame Abraham, MD, *Editor*

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submit the data for worldwide regulatory approval of the drug as a treatment for ER+ advanced breast cancer by year's end, although the medical oncology community is likely to embrace off-label use in this indication since both drugs are already available. Everolimus is approved in the United States for progressive neuroendocrine tumors of pancreatic origin, subependymal giant cell astrocytoma associated with inoperable tuberous sclerosis, and advanced renal cell carcinoma after sunitinib (Sutent) or sorafenib (Nexavar) treatment failure. Exemestane, an aromatase inhibitor, is approved as neoadjuvant therapy for hormone receptor–positive breast cancer in postmenopausal women.

Dr. Baselga reported consulting for several pharmaceutical companies, including the study sponsor, Novartis Pharmaceuticals.

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Commentary

The beginning of small molecule therapy for endocrine-resistant metastatic breast cancer?

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The natural history of estrogen receptor–positive (ER+) metastatic breast cancer (MBC), especially when limited to bone and soft tissue, is generally one of slow progression. As such, the management of ER+ low-volume MBC is one of slow changes in relatively nontoxic antihormonal agents. Multiple classes of such agents exist. The typical patient may progress from an aromatase inhibitor (AI) to a selective estrogen receptor modulator (SERM) such as tamoxifen, to an estrogen receptor downregulator (ERDR) such as fulvestrant (Faslodex), to a progestin such as megestrol acetate, and then possibly to an aromatase inactivator such as exemestane. Some of us even try androgens, although such compounds are not as readily available as they were in the past. Many patients enjoy years of relatively symptom-free life as they move on from one agent to another.

Unfortunately, at some point most patients with ER+ MBC progress through all available antihormonal agents. Much effort has been expended over the past 15 years to try to optimize the choice of agents and, potentially, the sequence in which those agents are given to maximize progression-free survival (PFS). AIs, for example, were found many years ago to be superior in terms of PFS to megestrol acetate in the second-line setting and to tamoxifen in the first-line setting. Findings from recent studies, such as EFECT, have demonstrated the equivalence of fulvestrant and exemestane in ER+ MBC that had progressed on AIs.[1]

Building on solid preclinical data, there have been several trials of insulin-like growth factor (IGF) and IGF receptor (IGF-R) modulation in patients with resistant ER+ MBC. However, despite a strong preclinical rationale, to date the results of these studies have been disappointing.[2]

Inhibition of the mammalian target of rapamycin (mTOR) pathway in endocrine-resistant breast cancer has a rational basis. The phosphatidylinositol-3 kinase/mTOR pathway is overactive in endocrine-resistant cell lines.[3] mTOR inhibitors such as everolimus (Afinitor) enhance the activity of letrozole in cell culture.[4] Everolimus combined with letrozole as neoadjuvant therapy had a higher

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response rate in ER+ breast cancer than letrozole alone.[5]

The BOLERO-2 study examined PFS in a trial of everolimus with exemestane versus exemestane alone in 724 women with progressive ER+ MBC after treatment with nonsteroidal aromatase inhibitors.[6] Median PFS was improved from 4.1 months (which is typical of exemestane in AI-resistant disease, as seen in the EFECT trial) to 10.6 months (hazard ratio [HR], 0.36; $P = 3.3 \times 10^{-15}$). All of the subgroups seemed to benefit. Overall survival (OS) data in this study are still immature (83 deaths, with an interim analysis expected at 173 deaths). Major toxicities were stomatitis (56%; 8% grade 3), fatigue (33%; 3% grade 3), dyspnea (18%; 4% grade 3), anemia (16%; 5% grade 3), hyperglycemia (13%; 4% grade 3), elevation in serum aspartate transaminase (AST) levels (13%; 3% grade 3), and pneumonitis (12%; 3% grade 3).

It is interesting that a previous large phase III trial of a putative mTOR inhibitor (temsirolimus [Torisel]) combined with letrozole in the first-line treatment of ER+ MBC showed no PFS benefit compared with letrozole alone.[7] Another trial (TAMRAD), which was presented at the recent European Multidisciplinary Cancer Congress in Stockholm, Sweden, examined the use of tamoxifen and everolimus versus tamoxifen alone in the AI-resistant subgroup of a larger randomized phase II trial of women with ER+ MBC.[8] In exploratory analyses, this AI-resistant subgroup who received tamoxifen and everolimus had a better median PFS than the group receiving tamoxifen alone (8.6 months vs 4.5 months, respectively) and a better median OS (NR vs 32 months).

So what do we make of this result, and is it practice changing? On the one hand, the improvements in median PFS in the AI-resistant setting are the first to be seen with any nonhormonal small molecule, and they are substantial. On the other hand, we must now consider the not insignificant side effect profile of everolimus and prepare ourselves for treatment-related side effects that have perhaps not previously been seen in this population. Mature OS data from the BOLERO-2 trial would make the case for using everolimus stronger. However, the substantial PFS benefit, with a manageable side-effect profile, should likely lead to the adoption of everolimus with exemestane as a standard of care for AI-resistant ER+ MBC.

There are numerous unanswered questions at this point. Does the benefit of everolimus and exemestane extend to first-line treatment? Does the benefit of everolimus combinations extend to other AIs and/or fulvestrant? Could adjuvant therapy with antihormonal agents and everolimus be considered for ER+ breast cancer?

Like many important clinical

How I treat estrogen receptor–positive metastatic breast cancer after first-line antihormonal therapy fails

As I have noted in the accompanying commentary, the treatment of estrogen receptor–positive (ER+) metastatic breast cancer (MBC), especially when limited to the bone and soft tissue, is one of gradual changes. The pace of this disease tends to be relatively indolent. When deciding on which therapy to choose in progressive ER+ MBC in the second-line setting or beyond, the same factors that determine the choice of first-line therapy still apply. Performance status, patient desires, extent and location of metastases, time to progression on first-line therapy, time to distant disease, previous chemotherapy type and antihormonal therapy, and tumor characteristics are all considered in the decision for second-line therapy.

Aside from protection of bone complications of metastases with bisphosphonates or denosumab (Xgeva), I tend to progress from one antihormonal class to another when resistance to the first agent is demonstrated, as long as the patient remains asymptomatic or mildly symptomatic (bone pain, for example, that is manageable by low-dose opiates or anti-inflammatory agents).

Generally, in women with ER+ MBC limited to bone and soft tissue, with a decent progression-free interval on first-line therapy (eg, 4–6 months or longer), I tend to use fulvestrant (Faslodex) or exemestane if the first-line therapy had been a nonsteroidal aromatase inhibitor. Tamoxifen is also reasonable in this setting, although I tend to use it as third- or fourth-line therapy after fulvestrant and/or exemestane. Megestrol acetate tends to be a fifth-line therapy, if hormonal therapy is still desired or chemotherapy is not feasible. An interesting question that has yet to be answered is whether women with ER+ MBC regain sensitivity to antihormonal therapies used previously. Often, the interval between the use of one class of antihormonal agent and consideration of repeat use is more than 18–24 months. If the time to completion of adjuvant therapy and development of metastatic disease were this long, then we would consider reusing the initial therapy. Why not do the same in slowly progressive MBC?

For women with ER+ MBC who experience disease progression with signs of rapid progression, severe symptoms, or numerous space-occupying lesions in visceral organs, I tend to switch to chemotherapy. The choice of chemotherapy again depends on the status of the patient. Capecitabine (Xeloda) is a reasonable choice at this point, as are multiple single agents, including taxanes, epothilones, gemcitabine (Gemzar), vinorelbine, eribulin (Halaven), or anthracyclines.

The new data emerging about everolimus and exemestane are compelling and will likely change this current practice in the coming year.

—Adam Brufsky, MD, PhD

advances, the BOLERO-2 trial raises these and many other interesting therapeutic questions that will be tested and answered in the near future.

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