How effective are existing endocrine agents at reducing breast cancer recurrence?

We use a variety of endocrine agents to reduce the risk for recurrence in women with newly diagnosed stage I, II, or III breast cancer that is hormone-dependent. Selective endocrine receptor modulators (SERMs), such as tamoxifen, are effective in both pre- and postmenopausal women because they work at the receptor level. Tamoxifen typically reduces breast cancer recurrence by approximately 40% to 50%.

A more effective option for postmenopausal women is the use of aromatase inhibitors, such as anastrozole, letrozole, and exemestane, which reduce recurrence by approximately 50% in postmenopausal women. Aromatase inhibitors work by preventing the conversion of male hormones to estrogen and therefore are suitable only for women whose ovaries are no longer producing estrogen.

What we have learned over the past couple of years, based on results from TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial), is that we can give premenopausal women the benefits of aromatase inhibitors by causing them to become postmenopausal. We can do that chemically, through the use of luteinizing hormone–releasing hormone (LHRH) agonists such as leuprolide and goserelin (Zoladex, AstraZeneca), which suppress ovarian function. Alternatively, we can achieve the same effect by surgically removing both ovaries.

How effective are the existing endocrine agents at reducing the progression of breast cancer?

When a patient has stage IV breast cancer, meaning that it has metastasized, the goal is no longer cure. At this point, our goal is to help patients live as long as they can, with a good quality of life, which includes addressing any symptoms caused by the cancer. For these patients, we can use the same SERMs and aromatase inhibitors that are given to patients with earlier-stage disease. However, other types of endocrine agents, such as the selective estrogen receptor downregulators (SERDs), also are very effective in these patients. The first of these agents is fulvestrant (Faslodex, AstraZeneca). Like tamoxifen, fulvestrant works at the receptor level, but it is just as effective or possibly slightly more effective than aromatase inhibitors. Clinical trials are currently comparing fulvestrant with aromatase inhibitors as first-line treatment. In the meantime, we do know that fulvestrant is more effective than tamoxifen, so it is an option for postmenopausal women (and also for premenopausal women when given in combination with an LHRH agonist).

Patients with advanced disease also can benefit from the addition of new, targeted agents that can act synergistically with endocrine therapy. Such targeted agents are used in an effort to overcome the resistance to endocrine therapy that cancer cells develop over time. For example, targeted agents may block cellular pathways that are sending signals to the DNA of cancer cells to continue to grow and survive independently of estrogen.
The 2 targeted agents that are currently approved for this use are everolimus (Afinitor, Novartis) and palbociclib (Ibrance, Pfizer). Everolimus is a phosphoinositide 3 kinase (PI3K) pathway inhibitor that works by blocking mammalian target of rapamycin (mTOR), whereas palbociclib works by blocking cyclin-dependent kinase 4/6 (CDK4/6), which is part of the cyclin D pathway.

A large clinical trial called BOLEORO-2 (Breast Cancer Trials of Oral Everolimus-2) showed that adding everolimus to endocrine therapy in patients whose metastatic disease has become resistant to treatment with endocrine therapy alone approximately doubles the time it takes for metastatic breast cancer to progress. So, the combination of an aromatase inhibitor and everolimus has been approved by the US Food and Drug Administration as a solid second- or third-line treatment for patients whose tumors no longer respond to endocrine therapy alone.

The addition of palbociclib to endocrine therapy also has been shown to improve progression-free survival in patients with metastatic disease. Palbociclib doubles the time to progression when used in first-line treatment, as shown in PALOMA-1 (Study of Letrozole With or Without Palbociclib for the First-Line Treatment of Hormone-Receptor Positive Advanced Breast Cancer). In addition, it nearly triples the time to progression when used in second-line treatment, as seen in PALOMA-3 (Palbociclib Combined With Fulvestrant in Hormone-Receptor-HER2-Negative Metastatic Breast Cancer After Endocrine Failure).

Resistance to endocrine therapy in combination with a targeted agent does eventually develop, but in some cases that can take years. What we have not been able to show so far with targeted agents is an improvement in overall survival. Everolimus has not been shown to improve overall survival significantly in clinical trials, possibly because of the large variation in treatments used after everolimus, and the answer to the question of whether palbociclib can improve overall survival is eagerly awaited. It will come with longer follow-up.

**H&O** Are researchers examining whether everolimus and palbociclib can reduce the risk for breast cancer recurrence?

**IM** Ongoing clinical trials are looking at whether adding these medications to endocrine therapy can reduce recurrence rates in patients with stage I, II, or III disease, but it will take years to learn the answer.

**H&O** What other agents are being examined to reduce progression in patients with metastatic disease?

**IM** A number of different types of drugs are being explored for patients with metastatic disease. At the most recent San Antonio Breast Cancer Symposium, we saw the results of a large phase 3 trial called BELLE-2 (Phase III Study of BKM120/Placebo With Fulvestrant in Postmenopausal Patients With Hormone Receptor Positive HER2-Negative Locally Advanced or Metastatic Breast Cancer Refractory to Aromatase Inhibitor). This study looked at the experimental PI3K pathway inhibitor buparlisib in combination with fulvestrant for postmenopausal patients whose cancers had already progressed on previous endocrine therapies. We were hoping that buparlisib would be more effective than everolimus, which acts on the same pathway, but that did not turn out to be the case—the agent actually performed slightly worse than everolimus in patients who had already been exposed to endocrine therapies.

However, other PI3K inhibitors that are more alpha-specific (the active part of the PIK3CA gene) may hold promise for patients who carry a PIK3CA gene mutation in their tumors. Two large phase 3 trials are examining the use of the alpha-specific PI3K agents taselisib and alpelisib in patients with advanced breast cancer and a PIK3CA mutation: SANDPIPER (A Study of Taselisib + Fulvestrant Versus Placebo + Fulvestrant in Patients With Advanced or Metastatic Breast Cancer Who Have Disease Recurrence or Progression During or After Aromatase Inhibitor Therapy; NCT02340221) and SOLAR-1 (Study Assessing the Efficacy and Safety of Alpelisib Plus Fulvestrant in Men and Postmenopausal Women With Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor Treatment; NCT02437318). These agents seem to be effective in patients without the PIK3CA mutation, but we believe they may be more effective in patients with this mutation. We will have to wait for results for several years.

Another agent that is being studied is entinostat, which is a histone deacetylase (HDAC) inhibitor. A phase 2 trial of entinostat did not show much of an advantage in progression-free survival, but it did appear to improve overall survival. We will see in a few years what happens in the phase 3 trial of entinostat (Exemestane With or Without Entinostat in Treating Patients With Recurrent Hormone Receptor-Positive Breast Cancer That Is Locally Metastatic or Advanced; NCT02115282), which is being sponsored by the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network (ECOG-ACRIN) and funded primarily by the National Cancer Institute.

In addition to the targeted agents, newer forms of endocrine therapy that are more potent than the ones we have right now are being investigated. Two of the medications that are being looked at in phase 2 clinical trials are GDC-0810 (A Study of ARN-810 | GDC-0810) in Postmenopausal Women With Locally Advanced or Metastatic Breast Cancer (CDK4/6), which is part of the cyclin D pathway.

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Metastatic Estrogen Receptor Positive Breast Cancer; NCT01823835) and GDC-0927 (Study of SRN-927 in Postmenopausal Women With Locally Advanced or Metastatic Estrogen Receptor Positive Breast Cancer; NCT02316509). Like fulvestrant, these are selective estrogen receptor downregulators, but they are taken orally and possibly are more potent. They may prove to be helpful in halting disease progression in patients who have mutations in the ESR1 gene (estrogen receptor 1); such patients do not respond very well to conventional endocrine therapies such as aromatase inhibitors.

Although a number of other agents are being studied in the laboratory, these are the agents in phase 2 or 3 trials that we will learn the most about over the next few years.

**H&O In the meantime, should all patients with estrogen receptor–positive breast cancer receive targeted agents in addition to endocrine agents?**

**IM** That is difficult to answer. On the one hand, we have seen an impressive benefit in halting disease progression, so it might make sense to use these as part of first-line treatment in patients with extensive tumors in the liver, for example. On the other hand, we have not seen a survival benefit yet, and these agents always carry a risk for toxicity that can interfere with the patient’s quality of life. I think that the use of these agents is a reasonable option and I do use them, but they should not be considered mandatory for all patients who present with metastatic disease. Endocrine therapy by itself can be a great choice for patients with a very low burden of cancer and who want to avoid coming to the office for frequent blood draws, or who want to minimize side effects. Targeted agents can always be added at a later stage of the disease. Of course, this will all change should the phase 3 trials that are being conducted show that drugs such as palbociclib confer a survival advantage.

**H&O Are any other combinations being examined?**

**IM** A few trials are looking at the use of endocrine therapy in combination with 2 targeted agents instead of 1 (ie, triple combinations). It will take time to figure out whether 3 drugs are better than 2, or whether the various regimens should be given concomitantly or sequentially. In the meantime, our options are endocrine therapy alone or endocrine therapy plus a targeted agent, which may be followed by endocrine therapy plus a different targeted agent.

**Suggested Readings**


