Als Recommended for Breast Cancer Prevention

The U.S. Preventive Services Task Force (USPSTF) recently released, in draft format, updated recommendations for breast cancer prevention—namely that clinicians offer risk-reducing medications, including aromatase inhibitors (AI), to women with an increased risk of the disease and a low risk of side effects (available at www.uspreventiveservicestaskforce.org).

The statement makes a small but notable shift from the agency’s 2013 recommendation by adding the AIs anastrozole and exemestane to the list of acceptable risk-reducing medications, which already includes the selective estrogen receptor modulators tamoxifen and raloxifene (Ann Intern Med 2016;164:279–96).

Jack Cuzick, PhD, director of the Wolfson Institute of Preventive Medicine at Queen Mary University in London, UK, considers the USPSTF’s addition of AIs a positive development. He notes that this is the first time a U.S. government agency has recommended the drugs, which, unlike tamoxifen and raloxifene, are not FDA approved for preventive use. The USPSTF guidelines now align with those of the American Society of Clinical Oncology and the National Comprehensive Cancer Network, which already recommend AIs to postmenopausal women at increased risk.

As in the past, the USPSTF statement suggests that clinicians formally assess risk with the NCI Breast Cancer Risk Assessment tool or other algorithm, or consider risk factors such as family history and abnormal cells on a prior breast biopsy without using a formal tool.

Cuzick sees risk assessment as a major hurdle for prescribing preventive therapies. “Risk is a complicated business, based on more than just single factors, and increasingly people are using risk models to determine what the risk is, rather than just individual factors,” he says. The Tyrer-Cuzick Model, which Cuzick helped develop, combines individual factors and family history with information on breast density and genetic risk factors.

Additionally, the USPSTF continues to stress that the potential benefits of taking the medications must be balanced against possible side effects, which can include blood clots, hot flashes, and increased risk of endometrial cancer, among others. “We’d like drugs that have fewer side effects, but still, the balance looks quite favorable for most women at high risk,” Cuzick says.

Researchers are studying how to reduce side effects. For example, in a phase III trial presented at the 2018 San Antonio Breast Cancer Symposium in Texas, women with a noninvasive breast abnormality given a low dose (5 mg) of daily tamoxifen for 3 years reduced their risk of developing invasive breast cancer by 52% with no significant side effects; a typical regimen of 20 mg daily for 5 years seems to provide a comparable benefit with more side effects. An ongoing phase III trial is investigating the effectiveness of a tamoxifen gel applied directly to the breasts to prevent the disease.

Cuzick hopes that the USPSTF statement will boost prevention efforts. “There’s no doubt that preventive therapy is underused in breast cancer,” he says. “It’s a personal choice as to what a woman wants to do, but I think it’s a good option, and it’s certainly worth giving it a try.” —Catherine Cansio

BRCA Exchange Launches

Until recently, clinicians, researchers, and patients often found it difficult to determine whether a given BRCA variant was likely pathogenic. The Global Alliance for Genomics and Health (GA4GH), an international alliance including more than 500 healthcare, research, and patient advocacy organizations, seeks to rectify this situation with the BRCA Exchange, which has collected information on more than 20,000 unique, inherited BRCA variants (PLoS Genet 2018;14:e1007752).

“By having everything in one place, users can get information on more variants, more information about a given variant, and frequency information useful for classification,” says Amanda Spurdle, PhD, of the QIMR Berghofer Medical Research Institute in Australia, the article’s senior author. The website, www.brcaexchange.org, has had more than 10,000 visitors from around the world in the past year, with a big uptick since its official launch in January; a mobile app is also available.

Until now, much of the information needed to classify BRCA variants had been stored in individual testing laboratories around the world, where it was not easily accessible, notes Liying Zhang, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY, who was not involved in creating the database.

In addition to gaining access to this information by forging new data-sharing relationships, one of GA4GH’s biggest accomplishments has been determining how to combine such data and assess their quality, says Timothy Yap, MD, PhD, of The University of Texas MD Anderson Cancer Center in Houston, who was also not involved in creating the database. “We needed a central point to encourage data sharing between global centers, and to develop strategies suitable for using individual laboratory reports to assess genetic variation,” he explains. Using these strategies, GA4GH supplemented data available from some broader genetic databases, such as the Breast Cancer Information Core, ClinVar, and the Leiden Open Variation Database, with information from novel sources.

Steven Gallinger, MD, of the University of Toronto, Canada, another researcher not involved in the BRCA Exchange, notes that an increase in clinical genotyping and direct-to-consumer testing has created a pressing need for tools like this database. That’s because many healthcare providers are not genetics experts, yet they are called upon to help their patients interpret BRCA variant findings. “The Exchange will help fill this knowledge gap,” Gallinger says, which is essential given...
that many patients may be weighing life-changing decisions related to BRCA variants, such as whether to pursue prophylactic surgery.

In addition, the database will be helpful for researchers studying BRCA variants. Zhang says that bringing all of these data together will be especially helpful for investigators seeking to better understand the effects of the relatively rare, nontruncating BRCA variants, which will ultimately improve patient care and management.

To expand the BRCA Exchange’s reach, GA4GH is developing data-sharing relationships with labs worldwide. The group is also interested in incorporating additional types of data, such as the results of functional assays.

In addition, now that the BRCA Exchange has launched, GA4GH plans to use the methods and relationships it has developed in the past few years to create similar exchanges for other clinically important genes. –Kristin Harper

**Experts Question Recent Pharma Acquisitions**

The purchase of Celgene by Bristol-Myers Squibb (BMS) and Eli Lilly’s acquisition of Loxo Oncology may not boost drug development but will likely lead to higher prices, experts say. That means patients and shareholders might not gain much from the acquisitions.

The two deals, announced in quick succession in early January, involve companies that make some widely used cancer treatments and some innovative new compounds. BMS, which manufactures the checkpoint inhibitors nivolumab (Opdivo) and ipilimumab (Yervoy), is paying $74 billion for Celgene, whose biggest seller for cancer is lenalidomide (Revlimid), a thalidomide derivative. Eli Lilly, producer of, among others, the EGFR antagonist cetuximab (Erbitux), will pay about $8 billion for Loxo Oncology. The FDA recently approved Loxo’s larotrectinib (Vitrakvi) for patients with advanced or inoperable soft-tissue sarcoma (STS), olaratumab’s (Lartruvo; Eli Lilly) potential has not held up in the phase III ANNOUNCE trial. At least for now, the company has no plans to continue promoting the anti-PDGFRα antibody.

“The sarcoma community is reeling from this outcome,” says Gary Schwartz, MD, chief of hematology and oncology at NewYork-Presbyterian/Columbia University Irving Medical Center, who participated in the trial. “We’d had great confidence that this combination was here to stay and ANNOUNCE’s findings would merely confirm what we’d already seen with the phase II trial.”

In that study, for which Schwartz was an author, 133 patients were randomly assigned to receive olaratumab plus doxorubicin, or doxorubicin alone (Lancet 2016;388:488–97). The difference in median overall survival (OS) between the arms was sizeable: 26.5 months versus 14.7 months. Olaratumab showed particularly impressive activity in patients with leiomyosarcoma, a common form of STS originating in smooth muscle; responses were also seen across all other subtypes evaluated. This prompted the FDA to grant accelerated approval to olaratumab in December 2016—a much-cheered

Kevin Schulman, MD, of Stanford University School of Medicine in California, says these deals are part of a continued pattern of acquisitions, but the timing isn’t necessarily significant because purchases are usually a matter of opportunity. “All large companies are constantly looking for acquisitions to fill gaps in their pipelines,” he notes.

The two most recent acquisitions, however, are unlikely to pay off as business deals, asserts Bernard Munos, MBA, a biomedical consultant with the Milken Institute who is based in Indianapolis, IN. (Munos previously worked for Eli Lilly but retired from the company in 2010.) Shareholders have often suffered losses after similar mergers, he says. Moreover, Loxo may not be the prize it appears to be, he adds, because Bayer shares the rights to larotrectinib and another compound in the Loxo pipeline, LOXO-195. “I am frankly not very optimistic that the shareholders of BMS or Lilly will see much benefit from the acquisitions.”

Whether the deals will speed drug development or spark innovation is another issue. In principle, combining companies can increase the efficiency of R&D, says Anupam Jena, MD, PhD, of Harvard Medical School in Boston, MA. Still, some researchers have argued that mergers and acquisitions impede drug development because the united companies face less competition and have less motivation to create new products.

To evaluate that idea, in 2017, Schulman and colleagues analyzed the effects of pharmaceutical mergers and acquisitions between 1985 and 2009 (see http://scholarship.law.duke.edu/faculty_scholarship/3749/). The researchers found that companies that took part in more mergers and acquisitions did tend to spend less on R&D. However, those companies were also more likely to get their drugs into clinical trials.

Schulman thinks that “the mergers will potentially decrease internal R&D at the acquiring firms but might spur more investment in early-stage biotechnology companies that will hope to be similarly acquired.”

Another consideration for R&D, Munos says, is how the acquisitions will affect innovation. “The jury is still out” on whether Loxo can continue to innovate as a part of Lilly, he says. BMS and Celgene, on the other hand, have had mixed records with their return on R&D in recent years, Munos says, and he predicts that they won’t do any better together.

He and Schulman agree that the acquisitions will probably lead to increases in drug prices. “That $8 billion [for Loxo] has to come from somewhere,” Schulman says.

Jena says that the effect on prices is harder to predict and will depend on how much competition the combined companies encounter that might eventually curtail cost increases. “There may be an impact on prices in the short term—although the size of that impact is unknown,” he says. –Mitch Leslie

**Olaratumab for STS Disappoints in Phase III**

Two years after receiving accelerated approval from the FDA as a first-line therapy with doxorubicin for patients with advanced or inoperable soft-tissue sarcoma (STS), olaratumab’s (Lartruvo; Eli Lilly) potential has not held up in the phase III ANNOUNCE trial. At least for now, the company has no plans to continue promoting the anti-PDGFRα antibody.

“The sarcoma community is reeling from this outcome,” says Gary Schwartz, MD, chief of hematology and oncology at NewYork-Presbyterian/Columbia University Irving Medical Center, who participated in the trial. “We’d had great confidence that this combination was here to stay and ANNOUNCE’s findings would merely confirm what we’d already seen with the phase II trial.”

In that study, for which Schwartz was an author, 133 patients were randomly assigned to receive olaratumab plus doxorubicin, or doxorubicin alone (Lancet 2016;388:488–97). The difference in median overall survival (OS) between the arms was sizeable: 26.5 months versus 14.7 months. Olaratumab showed particularly impressive activity in patients with leiomyosarcoma, a common form of STS originating in smooth muscle; responses were also seen across all other subtypes evaluated. This prompted the FDA to grant accelerated approval to olaratumab in December 2016—a much-cheered
BRCA Exchange Launches


Updated version Access the most recent version of this article at: doi:10.1158/2159-8290.CD-NB2019-008