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NEWSLETTER

Clinician Update: Breast Cancer

In the Pipeline: New Targets for Breast Cancer

Several new breast cancer therapies were approved over the last year, but what lies ahead? PAGE 2

PAGE 5

Research News

What's New in Breast Cancer Research?

PAGE 8

For Your Patients: Where To Turn for Support

Breastcancer.org

In the Pipeline: New Targets for Breast Cancer

Several new breast cancer therapies were approved over the last year, but what lies ahead?

Breast cancer is the most common malignancy in the world, having supplanted lung cancer in 2020, with 2.3 million new cases each year. About 685,000 people die of breast cancer annually, and the burden of this disease appears destined to worsen in the coming decades. A study published last September in *The Breast* predicted that annual global breast cancer cases will rise to three million by 2040, an increase of 40 percent, with deaths increasing 50 percent, to more than one million.

That worrisome forecast does not diminish the accomplishments of investigators who have worked tirelessly to develop new treatments. The availability of targeted therapies, immunotherapies, and other innovative agents has contributed to positive trends: For instance, while rates of breast cancer have risen about 0.5 percent per year lately in the United States, the portion of older women dying of the disease has steadily declined by about 1 percent annually.

The availability of improved treatments has undoubtedly contributed to that decline, and new options keep arriving. This year, the U.S. Food and Drug Administration (FDA) approved two breast cancer drugs: elacestrant (Orserdu), for advanced-stage or metastatic, estrogen receptor-positive, HER2-negative breast cancer with an ESR1 mutation that has been treated with at least one hormonal therapy; and sacituzumab govitecan (Trodelvy) for treatment of HR-positive/HER2-negative breast cancer. Last year's approvals included trastuzumab deruxtecan (Enhertu), for patients with the new designation of HER2-low breast cancer; and olaparib (Lynparza), a much-needed addition to the arsenal for treating triple-negative breast cancer.

Yet, there can be little doubt that new biomarkers and therapeutics are needed to improve the diagnosis and treatment of breast cancer. Researchers are taking aim at these and other targets with the goal of finding new ways to save more lives.

EGFR: Epidermal growth factor receptor (EGFR) plays a role in controlling cancer progression, including proliferation, metastasis, and drug resistance. Treatments that target EGFR have been developed for several tumor types, including non-small cell lung, colon, and pancreatic cancers, as well as head and neck cancers. High expression of EGFR has been associated with more-aggressive forms of breast cancer (such as triple negative and inflammatory breast cancers). However, clinical trials have yet to find a benefit from EGFR inhibitors in these patient populations, though investigations continue.

FGFR: Cancer researchers have long known that the fibroblast growth factor receptor (FGFR) signaling pathway plays a role in cell survival, proliferation, migration, and angiogenesis. Alterations and amplification of FGFR have been implicated in a number of solid tumors, including breast cancer. Several FGFR inhibitors are being investigated for the treatment of breast cancer in clinical trials, including futibatinib (Lytgobi). In a phase 2, open-label, non-randomized, multicenter study that's currently recruiting, researchers are evaluating the efficacy and safety of futibatinib and futibatinib plus fulvestrant (Faslodex) in adult patients with locally advanced or metastatic breast cancer who have FGFR gene amplifications. Contact Massive Bio at (646) 867-7200 or referrals@massivebio.com if you have a patient whom you think could be a candidate for this trial.

Novel PARP and CDK4/6 inhibitors: The FDA has approved three PARP inhibitors and three CDK4/6 inhibitors for the treatment of recurrent ovarian cancer and advanced estrogen-receptor-positive breast cancer. However, both drugs benefit a relatively modest patient population, so efforts are underway to modify these agents to give them broader application. One intriguing treatment in development is a novel compound called ZC-22, which inhibited both PARP and CDK4/6 in recent lab and animal studies more effectively than the combination of the PARP inhibitor olaparib and the CDK4/6 inhibitor abemaciclib (Kisqali). It also sensitized breast and ovarian cells to cisplatin.

Circulating miRNAs: MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression and are involved in a variety of biological processes, including the development of cancer. Some recent research indicates that miRNAs may have a role as a non-invasive tool for early diagnosis of certain breast cancers, particularly estrogen-receptor negative tumors, as well as serve as targets for therapy. Certain miRNAs are associated with the onset and progression of triple-negative breast cancer, while others have been linked to tumor recurrence and reduced survival. In the short term, miRNAs likely hold the most promise as prognostic biomarkers, but some investigators are interested in targeting them for treatment.

HSPA8: Heat shock 70 kDa protein 8 (HSPA8) is part of a family of proteins associated with cancer proliferation and metastasis. HSPA8 is overexpressed in certain malignant tumor types, including triple-negative breast cancer, among others. In the case of triple-negative breast cancer, overexpression of HSPA8 is associated with poor prognosis. In animal models, absence of HSPA8 inhibits tumor growth and induces cell apoptosis. The potential value of HSPA8 as a biomarker and therapeutic target is being studied. One recent finding indicates that expression of HSPA8 in triple-negative breast cancer correlates with infiltration of certain immune cells (CD4+, CD8+ T cells, neutrophils, monocytes, and macrophages), which could serve as a biomarker for prognosis.

SIRT2: Mammalian sirtuins (SIRTs) are molecules known to regulate different stages of cancer development and metastasis, as well as multidrug resistance. Sirtuins have been shown to be tumor promoters as well as a tumor suppressors in different cancers. The role of one sirtuin, SIRT2, in carcinogenesis is complex and controversial. Compared to healthy tissue, malignant tissue in some cancers often has reduced expression of SIRT2. Under certain circumstances, SIRT2 has tumor-suppressive qualities. However, one study found that high levels of SIRT2 in breast cancer predicted increased risk for recurrence. Several synthetic and natural sirtuin modulators are being explored in preclinical work. A 2022 study in *Cells* found that the experimental SIRT2 inhibitor AGK2, combined with paclitaxel, controlled proliferation of breast cancer cells in vitro. AGK2 also appeared to improve the anti-tumor effect of paclitaxel.

Breast cancer stem cells: In what some are calling a paradigm shift, an evolving theory argues that cancer development and metastasis are driven by cancer stem cells (CSCs), which are now seen as a potential therapeutic target in breast cancer. Research indicates that CSCs can self-renew and differentiate, as well as promote resistance to chemotherapy and radiation. Mice xenografted with CSCs develop new tumors. Targeting breast CSCs is challenging, due to their many similarities to normal mammary stem and progenitor cells, though early-stage trials are underway.

Research News

Age Cutoffs Keep Some Breast Cancer Patients From Receiving Adjuvant Therapy

Should a patient with early-stage breast cancer receive different treatment than another patient with the identical diagnosis simply because she's one year older? Adjuvant therapy, in the form of radiation, is often recommended following lumpectomy in patients with high risk for recurrence. Clinicians frequently use age as a determining factor when making treatment decisions, but strict cutoffs may deprive some patients of receiving important therapies, according to a new study in the *International Journal of Radiation Oncology-Biology-Physics.*

In the study, researchers examined a database of 160,990 patients who underwent breast-conserving surgery and had higher-risk features, including estrogen-receptor negative cancer, positive margins, or tumor size greater than 3 centimeters, which made them appropriate candidates for radiation. Compared to patients who were age 69, those who were age 70 at diagnosis were 53 percent less likely to be recommended radiation therapy and 39 percent less likely to receive radiation. These stark drops in recommendation of adjuvant therapy did not occur with any other year-to-year comparisons. The authors argue that using chronologic age as a cutoff for treatment decision is a form of bias, and that clinicians should consider a patient's physiologic age, among other factors, instead.

Gene Mutations Linked to Contralateral Breast Cancer

Researchers have identified several gene mutations that increase the risk for contralateral breast cancer, which occurs when a patient with primary cancer in one breast develops a secondary tumor in the opposite breast. It has been known for several decades that mutations in the *BRCA1* and *BRCA2* genes significantly increase the risk for breast cancer and ovarian cancer. Less-common gene mutations are also known to increase breast cancer risk in a small number of women. However, less is known about how these mutations influence the risk for contralateral breast cancer.

In the study, reported in the *Journal of Clinical Oncology,* researchers compared the medical re-

cords of more than 32,000 women diagnosed with breast cancer with those of roughly 32,000 women who did not have the disease. Both cohorts included a diverse group of women, according to demographics (age and race), diagnosis (75.5 percent had hormone-receptor positive disease), and treatments received. All women included in the study underwent genetic testing. The analysis found that women with mutations in the *BRCA1*, *BRCA2*, and *CHEK2* genes had a significantly increased risk for contralateral breast cancer. Furthermore, women who had hormone-receptor negative breast cancer and a mutation in the *PALB2* gene were about three times more likely to develop contralateral breast cancer than women who lacked the mutation. The gene-linked heightened risk for contralateral breast cancer was increased among Black women. These findings should be considered as part of monitoring patients with select gene mutations.

Many Women Unaware of Breast Density as Risk Factor

Breast density is an established risk factor for breast cancer—women who have 50 percent or higher breast density on a mammogram are three times more likely to be diagnosed with breast cancer over a 15-year period than others with less than 10 percent density. Yet, the importance of breast density as a risk factor is not recognized by many women, according to a recent study in *JAMA Network Open*.

In the study, researchers conducted a telephone survey of a racially diverse group of 2306 women aged 40 to 76 in the United States. In the survey, women were asked a series of questions about their perceptions of breast cancer risk. The survey found that about half of the respondents believed that breast density is a greater risk factor than not having children, having more than one alcoholic drink per day, and having undergone a prior breast biopsy. On the other hand, most felt that breast density increased the risk for cancer less than having a first-degree relative with breast cancer or being overweight or obese. Among the participants, 61 women who had been informed about their breast density took part in a qualitative interview; just six, or 10 percent, were aware that breast density is a risk factor for cancer. Overall,

women displayed low knowledge about lifestyle changes that can decrease their risk. This suggests that new approaches to educating the public about breast cancer risk factors and prevention may be necessary.

Study Probes Why Chemo-Resistant Breast Cancer Cells Don't Respond to Immunotherapy

It's a frustrating reality: Breast tumors that resist treatment with chemotherapy usually fail to respond to immunotherapy, too. That includes immune checkpoint inhibitors, a class of drugs that has revolutionized the treatment of some other cancers. A team led by researchers at Tulane University in New Orleans, Louisiana, wanted to know why breast cancer cells don't respond to these innovative treatments.

To find out, the Tulane team studied breast cancer cells that had been treated with chemotherapy. They also examined how breast cancer cells in mice respond to chemotherapy and immune checkpoint inhibitors that target PD-L1, a protein that allows malignant cells to evade attack by the immune system, as well as another checkpoint protein, CD80. In a study published in *Nature Cancer*, the team reported that tumor cells that resist chemotherapy enter a dormant state, called cellular senescence, and are transformed in a way that makes them harder to treat with immunotherapy. "The tumor completely changes after chemotherapy treatment into this thing that is essentially built to block the immune system," said James Jackson, PhD, an associate professor of biochemistry and molecular biology at Tulane and a coauthor of the study, in a statement. The senescent breast cancer cells developed multiple checkpoint proteins on their surfaces, which allows them to elude protective T cells. Jackson argued that chemo-resistant breast cancer will require immunotherapy tailored to treat the specific checkpoints expressed by residual malignancies.

For Your Patients:
Where To Turn for Support

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Finding out you have breast cancer can be an upsetting, confusing experience. Finding Breastcancer.org can feel like discovering an oasis of calm and support. Breastcancer.org's stated goal is "to help people make sense of the complex medical and personal information about breast health and breast cancer, so they can make the best decisions for their lives." In pursuit of that goal, Breastcancer.org offers a wealth of information about breast cancer for patients, presented in an easy-to-navigate format and in plain language that doesn't require an advanced degree to understand.

Founded by oncologist Marisa C. Weiss, MD, of Lankenau Medical Center in Wynnewood, Pennsylvania, Breastcancer.org also features news about breast cancer and, importantly, an online support community. The latter allows people coping with this diagnosis to share thoughts on a variety of topics, ranging from treatments to diet tips, and share their feelings with a sympathetic group. As the site states, "no one should face breast cancer alone." Learn more at www.breastcancer.org.