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EXPERT PANEL DISCUSSION

Therapeutic Considerations in Metastatic HER2+ Breast Cancer

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Therapeutic Considerations in Metastatic HER2+ Breast Cancer

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INTRODUCTION

In fall 2020*, *OncLive*® hosted a series of 4 live regional broadcasts across the United States (California, Illinois, Texas, and Washington), each involving 2 medical oncologists specializing in the treatment of breast cancer.

The primary objective of the broadcasts was to review and evaluate data on recent therapeutic advances in treating metastatic HER2-positive breast cancer. The oncologists discussed factors that influence planning and treatment selection for their patients with this disease, and they reviewed clinical challenges and areas of uncertainty faced when selecting later lines of therapy. This manuscript summarizes the data presented during the broadcasts and captures key insights from the oncologists.

CONSIDERATIONS IN DISEASE STATE MANAGEMENT

Breast cancer is the second most common cancer¹ and the fourth leading cause of cancer deaths for women in the United States.² Women have a 12.9% chance of receiving a diagnosis of breast cancer during their lifetime, and in 2017, more than 3.5 million women received this diagnosis in the United States.² Most women, when diagnosed, are aged between 55 and 64 years.² Of newly diagnosed breast cancers, 6% are metastatic.³ To help determine optimal therapies and guide locoregional treatments, the American Joint Committee on Cancer recommends that all invasive breast cancers be tested for biomarkers, including molecular subtypes⁴: hormone receptor (HR)-positive/HER2-negative (termed luminal A); HR-negative/HER2-negative (triple negative); HR-positive/HER2-positive (luminal B); and HR-negative/HER2-positive (HER2-enriched).^{4,5} Of these subtypes, HR-negative/HER2-positive historically had the worst prognosis, but outcomes have improved with the development of therapies that target HER2.³ HER2-targeted treatment “has been a

rich area of investigation for the last couple of decades,” said **Gradishar**. The “explosion” in this therapeutic area has included trastuzumab and lapatinib, and, more recently, antibodies, such as pertuzumab; antibody-drug conjugates (ADCs), such as ado-trastuzumab emtansine (T-DM1) and fam-trastuzumab deruxtecan-nxki (T-DXd); and small molecules, such as neratinib and tucatinib. Treatment strategies “continue to evolve as [clinicians] learn how to incorporate new agents and improve use of established therapies,” said **Rugo**.

OVERVIEW OF HER2-POSITIVE BREAST CANCER

HER2-positive breast cancer accounts for approximately 15% of all breast cancers.³ Between 2012 and 2016, 4% of all invasive breast cancers were HR-negative/HER2-positive, and 11% were HR-positive/HER2-positive. The 5-year survival rates are 83% for HR-negative/HER2-positive and 89% for HR-positive/HER2-positive. HER2-positivity in breast cancer is identified by using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH).⁶ A tumor is considered HER2-positive if it receives an IHC score of 3+, which indicates strong staining of the cell membrane circumference of more than 10% of the tumor cells.⁷ A tumor is HER2-equivocal if it receives an IHC score of 2+, indicating weak-to-moderate complete membrane staining in more than 10% of tumor cells. A HER2-negative status involves light, incomplete membrane staining in more than 10% of tumor cells (IHC 1+) or no observable staining in 10% or fewer tumor cells (IHC 0).⁷ A newer term, HER2-low, describes breast cancer scored IHC 1+ or 2+ with a negative FISH or chromogenic assay.⁸

Tripathy said that some patients may have mixed clones and be diagnosed with HER2-negative breast cancer at initial diagnosis, but then diagnosed with HER2-positive cancer at recurrence or metastasis. He believes “those patients truly are biologically HER2-positive,” and so he would use an HER2-targeted treatment pathway. Although there are not enough data for clinicians to formally recommend this approach, these patients may be eligible for clinical trials.

STANDARD TREATMENTS FOR METASTATIC HER2-POSITIVE BREAST CANCER

Targeted therapies treat breast cancer cells that overexpress specific proteins on the cell surface and influence abnormal cell proliferation.⁹ Several HER2-targeted therapies are approved in the metastatic setting, including the monoclonal antibodies trastuzumab and pertuzumab; the ADCs T-DM1 and T-DXd; and the tyrosine kinase inhibitors (TKIs), lapatinib, neratinib, and tucatinib.¹⁰⁻¹⁶

Monoclonal antibodies

In 1998, the FDA granted its first approval for a drug targeting HER2-positive breast cancers, trastuzumab.^{9,10} Years later, in 2012, pertuzumab was approved, in combination

with trastuzumab and docetaxel, for treatment of patients with HER2-positive metastatic breast cancer who had not received prior anti-HER2 therapy or chemotherapy for metastatic disease.¹¹ For efficacy and safety, pertuzumab combined with trastuzumab and docetaxel was compared with placebo plus trastuzumab and docetaxel in patients 18 years or older with HER2-positive metastatic breast cancer (N = 808) in the phase 3, double-blind, randomized CLEOPATRA trial (NCT00567190).^{17,18} Final results demonstrated greater efficacy in the pertuzumab group than in the placebo group, with median overall survival (OS) of 57.1 months vs 40.8 months (hazard ratio, 0.69; 95% CI, 0.58-0.82). The median follow-up was more than 8 years: 99.9 months (interquartile range [IQR], 92.9-106.4) for pertuzumab and 98.7 months (IQR, 90.9-105.7) for placebo.¹⁸ **Rugo** says she believes that the most remarkable aspect of the trial results, after such prolonged follow-up, is that 25% of the patients are progression free. “Clearly there is a group of patients [who] just never have progression of their disease,” she said.

In CLEOPATRA, results from the safety analysis revealed that neutropenia was the most common grade 3 or higher adverse event (AE), experienced by 49% of the 408 patients in the pertuzumab group and 46% of the 396 patients in the placebo group. In the pertuzumab group, 1% of patients experienced treatment-related death from febrile neutropenia; less than 1% experienced treatment-related death from respiratory tract infection and somnolence. In the placebo group, 1% experienced treatment-related death from intestinal perforation, while less than 1% experienced treatment-related death from pneumonia, sepsis, myocardial infarction, and cerebrovascular accident.¹⁸

CLEOPATRA’s results increased the use of dual anti-HER2-targeting therapy for metastatic HER2-positive breast cancer, according to **Gradishar**. “For most [clinicians], this remains a standard first-line regimen,” he said. He noted that another taxane, paclitaxel, could potentially be substituted for docetaxel, with similar efficacy; however, **Tripathy** said that paclitaxel has not been tested in large randomized trials.

“I sometimes use [paclitaxel] when patients have gotten docetaxel in the adjuvant or neoadjuvant setting before that,” said **Tripathy**. For some patients who respond after several cycles of chemotherapy, **Rao** will “drop the taxane backbone and then continue the 2 antibodies to maintain the response.” This was also how the trial was designed and is a practice that most clinicians follow once “patients have achieved a response or stable disease after 8 cycles,” said **Rugo**.

The FDA is currently investigating margetuximab for the treatment of metastatic or locally advanced HER2-positive breast cancer previously treated with anti-HER2-targeted therapy.¹⁹ The Fc portion of this HER2-binding monoclonal antibody is “engineered [for] increased affinity for the activating Fc gamma receptor and decreased affinity for an inhibitory Fc gamma receptor when compared with trastuzumab,” according to **McArthur**. The safety and efficacy of margetuximab were

“Treatment strategies continue to evolve as [clinicians] learn how to incorporate new agents and improve use of established therapies.”

—HOPE S. RUGO, MD, FASCO
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explored in the phase 3, randomized, open-label SOPHIA trial (NCT02492711), in which patients with HER2-positive breast cancer who had received 2 or more prior HER2-targeted therapies were randomized to receive either margetuximab with chemotherapy or trastuzumab with chemotherapy (N = 536).^{20,21} “The most interesting thing about this trial was that they looked at the prespecified exploratory OS in these patients,” said **Rao**. Patients carrying the CD16A-158F allele (85% of the population) experienced a greater median OS with margetuximab than with trastuzumab (23.7 months vs 19.4 months; $P = .087$).²⁰ Patients who were homozygous for the CD16A-158V allele (15% of the population) did not experience an advantage with margetuximab.²⁰ The drug is “as well tolerated as trastuzumab,” said **Gradishar**, other than “infusion-related reactions” (13% margetuximab vs 3% trastuzumab), noted **McArthur**. The infusion-related reactions did not limit the therapy, according to **McArthur** and **Rugo**. Margetuximab takes advantage of precision medicine. If the carriers of the CD16A-158F allele can be identified, margetuximab seems to have an advantage over trastuzumab, said **Gradishar**. However, it is still unknown whether the FDA will approve margetuximab as a rescue treatment.

Antibody-drug conjugates

Each ADC consists of a recombinant monoclonal antibody molecularly bound to a cytotoxic drug (known as the drug payload) with a synthetic linker, and they combine the antibody’s high specificity for a target with the chemotherapy drug’s cytotoxicity.²² The ADC T-DM1, indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination,¹³ is the standard second-line therapy that **Rao** and **Rugo** use for patients after they have progressed on a regimen of a taxane + dual antibody therapy (trastuzumab + pertuzumab). T-DM1 received approval on the basis of results from the phase 3, randomized, open-label EMILIA trial (NCT00829166),^{23,24} which involved patients with HER2-positive, unresectable, locally advanced or metastatic breast cancer who experienced progression during or after treatment for metastatic or locally advanced disease or within 6 months of early-stage treatment (N = 991).²⁴ Patients were randomized to receive either T-DM1 (n = 495) or

capecitabine plus lapatinib (n = 496). T-DM1 as second-line therapy for metastatic breast cancer was associated with a longer median OS than was capecitabine plus lapatinib (29.9 months [95% CI, 26.3-34.1] vs 25.9 months [95% CI, 22.7-28.3]; hazard ratio, 0.75 [95% CI, 0.64-0.88]). In the safety analysis, grade 3 or higher AEs were experienced by 60% of those in the control group and 48% of those in the T-DM1 group. The most common grade 3 or higher AEs in the T-DM1 group were diarrhea (2%), fatigue (2%-3%), and vomiting (1%).²⁴

Based on these results, **Rugo** remarked that T-DM1 “quickly replaced capecitabine and lapatinib as standard second-line therapy, with an improvement not only in progression-free survival (PFS) but [also] in OS.” She noted that most of her patients on T-DM1 eventually regress with brain metastases, although T-DM1 does cross the blood-brain barrier. According to **McArthur**, historically, it was thought that antibodies could not cross the barrier; however, growing data indicate that either the antibody conjugates or the payload in ADCs can cross the barrier.

The ADC T-DXd is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting.¹⁴ The 2-part, phase 2, open-label, single-group DESTINY-Breast01 trial (NCT03248492) explored the optimal recommended dosing of T-DXd and then analyzed safety and efficacy of the recommended dose in patients 18 years or older with HER2-positive, unresectable or metastatic breast cancer who had received previous treatment with T-DM1 (N = 253).^{25,26} The recommended dose was identified at 5.4 mg per kg of body weight. Of the patients who received the recommended dose (n = 184), 60.9% achieved an objective response rate (95% CI, 53.4-68.0),²⁶ which was the highest response rate that **Pegram** had ever seen for any single HER2-targeted therapy in any line, calling it “a remarkable achievement.” With a median follow-up of 11.1 months (range, 0.7-19.9), the median PFS for all patients was 16.4 months (95% CI, 12.7 to not reached [NR]), and median OS was not reached. Median duration of response was 14.8 months (95% CI, 12.7-NR).²⁶

In a subgroup analysis of patients with stable brain metastases in the DESTINY-Breast01 trial (n = 24), 58.3% of

patients reached an objective response rate (95% CI, 36.6%-77.9%), which was similar to the objective response for the full patient cohort, discussed earlier.^{26,27} The disease control rate was close to 92% for patients with brain metastases and 97% for all patients, which was “the most remarkable thing from this trial,” said **Rao**. The median duration of PFS was 18.1 months (95% CI, 6.7-18.1) for the brain metastases group.²⁶ Among all patients, a decreased neutrophil count was the most common AE of grade 3 or higher (20.7%).²⁶

Interstitial lung disease (ILD) of any grade (resulting from T-DXd use) was experienced by 13.6% of patients and led to 4 deaths. ILD onset occurred between 42 and 535 days following treatment initiation.²⁶ **Cairo** found the timing of onset for ILD interesting. “ILD is not necessarily an early event... or a late event. It is something to remain alert to throughout the course of treatment,” she said. In reviewing treatment recommendations for ILD, **Pegram** noted that for grade 2 or higher ILD, T-DXd should be permanently discontinued, and corticosteroid treatment should be initiated promptly. In the case of grade 1 ILD, the current dose of T-DXd should be paused until the ILD reaches grade 0; it can be resumed if that occurs within 28 days of the date of onset. If the ILD takes longer than 28 days to resolve, the T-DXd dose level should be reduced. Steroid treatment should be considered as soon as ILD or pneumonitis is suspected.¹⁴ Grade 1 disease can be difficult to detect, as patients are asymptomatic, and it is presumably detected via radiograph. **Rugo** said she typically scans patients every 12 weeks; however, she will order a chest x-ray [outside of the 12 weeks] for any patients with signs of a possible respiratory infection. **Rao** said she has increased the frequency of scanning during the coronavirus disease 2019 pandemic, although both **Rao** and **Gradishar** shared that the pandemic has not prevented them from using T-DXd. **Tripathy** said that regardless of ILD risk, he would use T-DXd in a patient with bulky life-threatening disease and either lymphangitic spread to the lungs, prehepatic failure (eg, 60% to 70% of the liver), or progression right after first-line therapy.

The evaluation of T-DXd continues in the ongoing DESTINY-Breast02 (NCT03523585), -Breast03 (NCT03529110), and -Breast04 (NCT03734029) trials.²⁸⁻³⁰ Investigators are reviewing T-DXd in pretreated (with T-DM1), HER2-positive, unresectable and/or metastatic breast cancer (Breast02); T-DXd vs T-DM1 for HER2-positive, unresectable and/or metastatic breast cancer previously treated with trastuzumab and taxane (Breast03); and T-DXd vs physician’s choice in previously treated HER2-low breast cancer that has spread and/or cannot be surgically removed (Breast04). Data from Breast04 are not yet available, but the results “could very well open up another silo of breast cancer,” said **Gradishar**. “There may be opportunities for combination strategies as well.”

The phase 3, randomized TULIP trial (NCT03262935) is currently investigating the ADC trastuzumab duocarmazine (SYD985) in patients with locally advanced or metastatic,

unresectable HER2-positive breast cancer (N = 436), with an estimated primary completion date of July 2021. Eligible patients had experienced disease progression during or after 2 or more HER2-targeting treatment regimens in the locally advanced or metastatic disease setting, and they are being randomized to receive either SYD985 or treatment of physician’s choice.³¹ **Gralow** noted that SYD985 effectively targets and kills lower-expressing HER2 (1+) cells and also kills HER2-0 cells through the bystander effect. “This is why there is enthusiasm for the activity of this drug,” she said.

Tyrosine kinase inhibitors

Lapatinib was the first TKI and second drug approved, after trastuzumab, for targeted treatment of metastatic HER2-positive breast cancer. It is indicated in combination with either (1) capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab; or (2) letrozole, for the treatment of postmenopausal women with HR-positive metastatic breast cancer that overexpresses the HER2 receptor, for whom hormonal therapy is indicated.¹² Before T-DM1 was approved, “capecitabine plus lapatinib had been the best second-line therapy [and] was generally used by many people,” said **Gradishar**. In terms of safety and efficacy, this treatment combination was compared with capecitabine alone in a randomized, phase 3, open-label trial (NCT00078572) for women with locally advanced or metastatic breast cancer that had not responded to previous therapy (N = 399). By independent assessment, lapatinib plus capecitabine lowered risk of progression by 43% in the intent-to-treat population (hazard ratio, 0.57; 95% CI, 0.43-0.77; $P = .00013$) compared with capecitabine alone.^{32,33}

In 2020, the FDA approved 2 new TKIs: neratinib and tucatinib. Neratinib, a very potent inhibitor of both HER2 and EGFR, is indicated in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting.¹⁵ This combination was explored in the phase 3, randomized NALA trial (NCT01808573), which involved patients with metastatic HER2-positive breast cancer that had been previously treated with 2 or more HER2-targeted therapies (N = 621).³⁴ Patients were randomized to receive neratinib plus capecitabine or lapatinib plus capecitabine.³⁵ The median follow-up duration was 29.9 months (IQR, 21.9-40.6). PFS, which was assessed by central review, was significantly improved in the neratinib group (hazard ratio, 0.76; 95% CI, 0.63-0.93; stratified log-rank $P = .0059$). OS was numerically better in the neratinib group, but not statistically significant (hazard ratio, 0.88; 95% CI, 0.72-1.07; stratified log-rank $P = .2086$).³⁵ Neratinib also had noteworthy activity against central nervous system (CNS) metastases, according to results from an

assessment of pooled data from NALA and two other phase 2, randomized trials (NEFERT-T [NCT00915018]³⁶ and TBCRC 022 [NCT01494662]³⁷).³⁸ Across the 3 studies, patients with CNS objective responses experienced improved PFS (hazard ratio, 0.58; 95% CI, 0.31-1.10; $P = .087$) and OS (hazard ratio, 0.43; 95% CI, 0.24-0.76; $P = .003$).³⁸

In NALA's safety analysis, the most-frequently experienced AEs of grade 3 or higher in the neratinib group were diarrhea, nausea, palmar-plantar erythrodysesthesia, hypokalemia, and vomiting. Diarrhea of all grades was experienced by 252 (83.2%) and 206 (66.2%) of patients receiving neratinib and lapatinib, respectively.³⁵ "The biggest issue with neratinib is diarrhea. [It] starts immediately," said **Rugo**. "These patients can get explosive diarrhea in the first 24 hours, so there has been a lot of effort to try and figure out how to control it." Treatment options include as-needed loperamide in high doses, which, **Rugo** noted, patients do not care for because it leads to constipation. Colestipol plus loperamide or budesonide plus loperamide can also serve as effective combination agents for diarrhea prophylaxis. In addition, rates of diarrhea can be substantially reduced with a dose-escalation protocol. Both **Gradishar** and **Rao** initiate neratinib through dose escalation, which "has resulted in greater tolerability than starting out at the full dose," **Gradishar** noted.

The most recently approved TKI, tucatinib, is indicated in combination with trastuzumab and capecitabine for adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including those with brain metastases, after receiving 1 or more HER2-targeted regimens in the metastatic setting.¹⁶ Tucatinib is the first HER2-specific TKI. "Most of its activity is against HER2, with very little activity against EGFR or HER1," said **Rugo**. "Some of the toxicities with other oral TKIs are thought to be related to their anti-EGFR effect." Tucatinib, in combination with trastuzumab and capecitabine, was explored in patients 18 years or older with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1 (N = 612) in the phase 2, randomized, double-blind HER2CLIMB trial (NCT02614794).^{39,40} All patients received trastuzumab and capecitabine and were randomized to also receive either tucatinib (n = 410) or placebo (n = 202). At year 1, the risk of disease progression or death in the primary endpoint population was 46% lower in the tucatinib group than the placebo group (hazard ratio, 0.54; 95% CI, 0.42-0.71; $P < .001$). At year 2, in the total trial population, it was 34% lower (hazard ratio, 0.66; 95% CI, 0.50-0.88; $P = .005$) in the tucatinib group than the placebo group. For those receiving tucatinib in the primary endpoint population, the estimated 1-year PFS was 33.1% (95% CI, 26.6-39.7) and the median duration of PFS was 7.8 months (95% CI, 7.5-9.6); for those receiving placebo, these results were 12.3% (95% CI, 6.0-20.9) and 5.6 months (95% CI, 4.2-7.1), respectively.⁴⁰

For patients with both active and stable brain metastases (who experience poorer PFS than the overall population of those with breast cancer), tucatinib was associated with a 68% lower risk of disease progression in the brain and death than placebo at year 1 (hazard ratio, 0.32; 95% CI, 0.22-0.48; $P < .0001$).⁴¹ For patients with active brain metastases, median OS was 20.7 months (95% CI, 15.1-not estimable [NE]) in the tucatinib arm (n = 118) and 11.6 months (95% CI, 10.5-13.8) in the placebo arm (n = 56). For those with stable brain metastases, median OS was 15.7 months (95% CI, 13.8-NE) in the tucatinib group (n = 80) and 13.6 months (95% CI, 10.2-22.0) in the placebo group (n = 37).⁴¹ **Gradishar** noted that in terms of OS, "those with stable brain metastases did not seem to receive as much of a gain, but the gain experienced by those with active brain metastases is quite striking."

Rugo noted that the "cool [aspect of] this triplet [combination from HER2CLIMB] is that an antibody-based therapy has the ability to impact [overall] survival even when PFS is not as great." **Gradishar** said that this triplet therapy is more active and possibly more reliable [than older therapies], particularly in this population of patients with HER2-positive disease. He said that in a patient with brain metastases, this triplet therapy would be his first choice.

Better and more durable responses could potentially be achieved for active brain metastases when combining this systemic triplet treatment with local treatment, such as radiation and sometimes surgery, according to **Gralow**. Regarding prevention of brain metastases, Pegram shared that data from a retrospective study of the HER2CLIMB trial suggest that tucatinib may help prevent the spread of cancer to the brain. This topic "is an active area of interest," she said.

The most common AEs of grade 3 or higher in HER2CLIMB's tucatinib group were palmar-plantar erythrodysesthesia syndrome, diarrhea, elevations in alanine aminotransferase and aspartate aminotransferase levels, and fatigue.⁴⁰ Diarrhea was the most common AE in both groups, and grade 3 or higher diarrhea was experienced by 12.9% of those receiving tucatinib and 8.6% of those receiving placebo. The modest increase in diarrhea with tucatinib, compared with other TKIs, was because of "the lack of the intense EGFR blockade," according to **Rugo**. She also noted stomatitis as an AE with tucatinib treatment, for which she strongly recommends treatment with a steroid dental paste. **Rugo** said as well that the elevation of liver enzymes "seems very easy to control in this triplet combination." However, she advised that tucatinib should not be combined with paclitaxel, as this increases liver enzymes at a greater rate.

Comparing the T-DXd regimen with the tucatinib regimen, **Gralow** said that it is easier to administer tucatinib because of its AE profile. When treating metastatic disease, efficacy is important, she pointed out, but so are tolerability and quality of life, especially if patients are going to be on a regimen for a long time. Additionally, **Gralow** does not restrict tucatinib to patients with brain metastases. "This is a drug that works no matter where the cancer is," she said.

CONCLUSIONS

A multitude of excellent targeted treatment options exist for patients with HER2-positive breast cancer, according to **McArthur**, and these are not the end of the story. “Additional small molecules are in development, there are other ADCs, and there are fancy antibodies,” said **Gradishar**. “This area remains a rich source of clinical investigation.” **Tripathy** said that, looking ahead, he sees 2 branches of opportunities for metastatic HER2-positive breast cancer: moving the best drugs, such as T-DXd, to first-line treatment; and personalizing treatment based on genomics. “Getting that first remission is going to be really important,” he said. He indicated interest in seeing results from trials on first-line immunotherapies.

Pegram noted that with new drugs, it is critical to ensure that

clinicians are armed with the information they need to make good decisions. For example, the prescribing information documents for T-DXd and tucatinib offer very clear guidelines for dose modifications and other approaches for every AE a patient could encounter. He carries a laptop in his own clinic and refers to the prescribing information frequently. The panelists also follow trade journals, publications, continuing medical education programs, and social media for the most recent information on treatment options. During meetings, they said, Twitter can be a great resource for information and discussion, offering quick access to the large amounts of new data. By staying abreast of recent news and research regarding new and novel therapies, clinicians can help optimize the treatment approaches and outcomes for their patients with metastatic HER2-positive breast cancer. ■



PATIENT SPOTLIGHT.

The following case of a patient with metastatic HER2-positive breast cancer was presented during the regional broadcasts. Afterwards, viewers were polled to learn the treatment strategy they would choose for this patient. The poll results are provided below the case.

CASE

On a routine gynecologic visit, a postmenopausal woman (PM), aged 58 years, was found to have a palpable mass in the left breast and axillary lymphadenopathy. She was referred for mammography and further testing. Her past medical history involved hypertension (well controlled on lisinopril) and hypercholesterolemia (controlled on atorvastatin). She had no family history of cancer. PM was a nonsmoker and occasionally consumed alcohol.

Results from imaging showed a 2.3-cm mass in the left breast that appeared irregular; results from a PET/CT and bone scan showed pulmonary nodules and lesions in the spine. Results from the brain MRI were negative. Additional workup confirmed estrogen-receptor-negative, progesterone receptor-negative, HER2-positive (3+ by immunohistochemistry) breast cancer. PM was initially treated with docetaxel, trastuzumab, and pertuzumab. Eighteen months later, she presented with a worsening cough and pain. Imaging results showed progressive bone disease, multiple new pulmonary nodules, and metastases to the liver.



POLL RESULTS.

Which therapy would you select after docetaxel, trastuzumab, and pertuzumab?

The options presented to the audiences were: (1) ado-trastuzumab emtansine (T-DM1), (2) tucatinib plus trastuzumab plus capecitabine, (3) fam-trastuzumab deruxtecan-nxki (T-DXd), and (4) lapatinib plus capecitabine. The majority of those in the **Texas (83.3%)** and **Seattle/Northern California (75%)** audiences chose **T-DM1**. Those in **Southern California** chose **T-DXd (37.5%)**, with **T-DM1 and tucatinib + trastuzumab + capecitabine tied for close seconds (25% for each)**.

The panelists uniformly chose T-DM1. **Cairo** said that when choosing between the ADCs T-DM1 and T-DXd, she considers the fact that T-DM1 has 4 chemotherapy molecules per trastuzumab backbone, whereas T-DXd has 8 molecules; additionally, T-DM1 has strength of evidence for efficacy and tolerability through a phase 3 trial. **Gralow** noted that she may consider forgoing T-DM1 as second-line treatment and selecting tucatinib instead if a patient has already received T-DM1 as an adjuvant therapy. If the tumor has already been exposed to an agent, she is more enthusiastic about moving up the line of therapy options.

What is the next regimen you would select for this patient?

The options presented to the audiences were: (1) T-DXd, (2) tucatinib plus trastuzumab plus capecitabine, (3) neratinib plus capecitabine, and (4) clinical trial. **T-DXd was chosen by the majority of all the audiences (60%-76%)**. **McArthur** said that no perfect answer exists among the options; in the third-line setting, all of them were good. When choosing a therapy, clinicians should consider patient needs and preferences. **Pegram** said this is the single time during the management of metastatic breast cancer in which a brain MRI is useful: The results can help guide the decision between T-DXd and tucatinib. If the patient has brain metastases, he favors tucatinib.

FOOTNOTE

*September 29, October 7, October 13, and October 15, 2020.

REFERENCES

- Breast cancer statistics. CDC. Updated June 8, 2020. Accessed October 27, 2020. <https://www.cdc.gov/cancer/breast/statistics/index.htm#:~:text=Breast%20cancer%20is%20the%20second,higher%20rate%20than%20white%20women>
- Cancer stat facts: female breast cancer. National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER) Program. Accessed July 23, 2020. <https://seer.cancer.gov/statfacts/html/breast.html>
- Breast cancer: facts & figures, 2019-2020. American Cancer Society. 2019. Accessed July 23, 2020. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf>
- AJCC Cancer Staging Manual*, 8th edition. Breast. The American College of Surgeons. November 10, 2017. Updated March 13, 2018. Accessed July 24, 2020. cancerstaging.org/references-tools/deskreferences/Pages/Breast-Cancer-Staging.aspx
- Cancer stat facts: female breast cancer subtypes. National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER) Program. Accessed October 8, 2020. <https://seer.cancer.gov/statfacts/html/breast-subtypes.html>
- Schramm A, De Gregorio N, Widschwendter P, Fink V, Huober J. Targeted therapies in HER2-positive breast cancer – a systematic review. *Breast Care (Basel)*. 2015;10(3):173–178. doi:10.1159/000431029
- Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline focused update. *J Clin Oncol*. 2018;36(20):2105–2122. doi:10.1200/JCO.2018.77.8738
- Tarantino P, Hamilton E, Tolane SM, et al. HER2-low breast cancer: pathological and clinical landscape. *J Clin Oncol*. 2020;38(17):1951–1962. doi:10.1200/JCO.19.02488
- Masoud V, Pagès G. Targeted therapies in breast cancer: new challenges to fight against resistance. *World J Clin Oncol*. 2017;8(2):120–134. doi:10.5306/wjco.v8.i2.120
- Herceptin. Prescribing information. Genentech; 2018. Revised November 2018. Accessed July 27, 2020. https://www.gene.com/download/pdf/herceptin_prescribing.pdf
- Perjeta. Prescribing information. Genentech; 2020. Revised January 2020. Accessed July 27, 2020. https://www.gene.com/download/pdf/perjeta_prescribing.pdf
- Tykerb. Prescribing information. Novartis; 2018. Revised December 2018. Accessed July 27, 2020. <https://www.novartis.us/sites/www.novartis.us/files/tykerb.pdf>
- Kadcyla. Prescribing information. Genentech; 2019. Revised September 2020. Accessed July 16, 2020. https://www.gene.com/download/pdf/kadcyla_prescribing.pdf
- Enhertu. Prescribing information. Daiichi Sankyo; 2019. Revised December 2019. Accessed July 18, 2020. <https://dsi.com/prescribing-information-portlet/getPIContent?productName=Enhertu&inline=true>
- Nerlynx. Prescribing information. Puma Biotechnology; 2020. Revised July 2020. Accessed July 27, 2020. <https://nerlynx.com/pdf/full-prescribing-information.pdf>
- Tukyasa. Prescribing information. Seattle Genetics; 2020. Revised April 2020. Accessed October 8, 2020. https://seagendocs.com/TUKYSA_Full_Ltr_Master.pdf
- A study to evaluate pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer (CLEOPATRA). ClinicalTrials.gov. Updated December 13, 2019. Accessed November 10, 2020. <https://clinicaltrials.gov/ct2/show/NCT00567190>
- Swain SM, Miles D, Kim S-B, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(4):519–530. doi:10.1016/S1470-2045(19)30863-0
- Margetuximab (anti-HER2). Macrogenics. Accessed October 27, 2020. <https://www.macrogenics.com/margetuximab-anti-her2/>
- Phase III SOPHIA trial evaluates margetuximab/chemotherapy vs trastuzumab/chemotherapy for HER2-positive breast cancer. The ASCO Post. March 10, 2020. Accessed October 10, 2020. <https://ascopost.com/issues/march-10-2020-supplement-conference-highlights-sabcs-2019/margetuximab-plus-chemotherapy-vs-trastuzumab-plus-chemotherapy-for-her2-positive-breast-cancer/>
- Margetuximab plus chemotherapy vs trastuzumab plus chemotherapy in the treatment of HER2+ metastatic breast cancer (SOPHIA). ClinicalTrials.gov. Updated September 23, 2020. Accessed November 4, 2020. <https://clinicaltrials.gov/ct2/show/NCT02492711>
- Rinnerthaler G, Gampenrieder SP, Greil R. HER2 directed antibody-drug-conjugates beyond T-DM1 in breast cancer. *Int J Mol Sci*. 2019;20(5):1115. doi:10.3390/ijms20051115
- A study of trastuzumab emtansine versus capecitabine + lapatinib in participants with HER2-positive locally advanced or metastatic breast cancer (EMILIA). ClinicalTrials.gov. Updated October 31, 2016. Accessed November 10, 2020. <https://clinicaltrials.gov/ct2/show/NCT00829166>
- Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(6):732–742. doi:10.1016/S1470-2045(17)30312-1
- A study of DS-8201a in metastatic breast cancer previously treated with trastuzumab emtansine (T-DM1). ClinicalTrials.gov. Updated August 18, 2020. Accessed November 10, 2020. <https://clinicaltrials.gov/ct2/show/NCT03248492>
- Modi S, Saura C, Yamashita T, et al; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382(7):610–621. doi:10.1056/NEJMoa1914510
- Jerusalem G, Park YH, Yamashita T, et al. CNS metastases in HER2-positive metastatic breast cancer treated with trastuzumab deruxtecan: DESTINY-Breast01 subgroup analyses [abstract 138O]. *Ann Oncol*. 2020;31(suppl 2):S63–S64. doi:10.1016/j.annonc.2020.03.239
- DS-8201a in pre-treated HER2 breast cancer that cannot be surgically removed or has spread (DESTINY-Breast02). ClinicalTrials.gov. Updated September 30, 2020. Accessed October 14, 2020. <https://clinicaltrials.gov/ct2/show/NCT03523585>
- DS-8201a versus T-DM1 for human epidermal growth factor receptor 2 (HER2)-positive, unresectable and/or metastatic breast cancer previously

treated with trastuzumab and taxane (DESTINY-Breast03). ClinicalTrials.gov. Updated September 25, 2020. Accessed October 14, 2020. <https://clinicaltrials.gov/ct2/show/NCT03529110>

30. Trastuzumab deruxtecan (DS-8201a) versus investigator's choice for HER2-low breast cancer that has spread or cannot be surgically removed (DESTINY-Breast04). ClinicalTrials.gov. Updated October 20, 2020. Accessed October 14, 2020. <https://clinicaltrials.gov/ct2/show/NCT03734029>
31. SYD985 vs. physician's choice in participants with HER2-positive locally advanced or metastatic breast cancer (TULIP). ClinicalTrials.gov. Updated October 5, 2020. Accessed October 14, 2020. <https://clinicaltrials.gov/ct2/show/NCT03262935>
32. Kaufman B, Stein S, Casey MA, Newstat BO. Lapatinib in combination with capecitabine in the management of ErbB2-positive (HER2-positive) advanced breast cancer. *Biologics*. 2008;2(1):61-65. doi:10.2147/btt.s1713
33. Capecitabine (XELODA) with or without lapatinib (GW572016) for women with refractory advanced or metastatic breast cancer. ClinicalTrials.gov. Updated December 13, 2010. Accessed October 14, 2020. <https://clinicaltrials.gov/ct2/show/NCT00078572>
34. A study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ metastatic breast cancer who have received two or more prior HER2 directed regimens in the metastatic setting (NALA). ClinicalTrials.gov. Updated March 18, 2020. Accessed October 14, 2020. <https://clinicaltrials.gov/ct2/show/NCT01808573>
35. Saura C, Oliveira M, Feng Y-H, et al; NALA Investigators. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol*. 2020;38(27):3138-3149. doi:10.1200/JCO.20.00147
36. Study evaluating neratinib plus paclitaxel vs trastuzumab plus paclitaxel in ErbB-2 positive advanced breast cancer (NEFERTT). ClinicalTrials.gov. Updated August 22, 2018. Accessed October 14, 2020. <https://clinicaltrials.gov/ct2/show/NCT00915018>
37. HKI-272 for HER2-positive breast cancer and brain metastases. ClinicalTrials.gov. Updated November 4, 2020. Accessed November 10, 2020. <https://clinicaltrials.gov/ct2/show/NCT01494662>
38. Awada A, Brufsky A, Saura C, et al. Impact of neratinib on development and progression of central nervous system metastases in patients with HER2-positive metastatic breast cancer: findings from the NALA, NEFERTT, and TBCRC 022 trials [poster P2-20-01]. Presented at: 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, Texas. https://pumabiotechnology.com/docs/121219_Awada_CNS_SABCS_2019_poster_10_Dec_2019_FINAL.pdf
39. A study of tucatinib vs. placebo in combination with capecitabine & trastuzumab in patients with advanced HER2+ breast cancer (HER2CLIMB). ClinicalTrials.gov. Updated September 28, 2020. Accessed November 10, 2020. <https://clinicaltrials.gov/ct2/show/NCT02614794>
40. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382(7):597-609. doi:10.1056/NEJMoa1914609. Published correction appears in *N Engl J Med*. 2020;382(6):586.
41. Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. 2020;38(23):2610-2619. doi:10.1200/JCO.20.0077

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FDA Approves FoundationOne Liquid CDx for New Indications in NSCLC, Advanced Ovarian, Breast Cancers

On October 27, 2020, the FDA approved the FoundationOne Liquid CDx for use as a companion diagnostic for 3 targeted therapies: alpelisib in advanced or metastatic breast cancer, rucaparib in advanced ovarian cancer, and alectinib in a specific type of metastatic non-small cell lung cancer (NSCLC). The regulatory agency also gave the green light to a label expansion for the diagnostic to report additional select copy number alterations and genomic rearrangements, according to an announcement from Foundation Medicine, Inc.¹

FoundationOne Liquid CDx is a companion diagnostic that evaluates guideline-recommended genes from a blood sample; the test is capable of evaluating more than 300 genes.² The blood-based biopsy also reports blood tumor mutational burden, microsatellite instability, and tumor fraction values. The goal of the test is to help inform treatment approaches and predict benefit of certain targeted therapies in patients across several cancer indications.

The FoundationOne Liquid CDx was previously approved by the FDA for all solid tumors with multiple companion diagnostic indications in August 2020. The decision was based on data from analytical and clinical validation studies that collected more than 7500 samples and 30,000 unique variants spanning more than 30 tumor types. The test was shown to have high sensitivity and specificity, even at the low allele frequencies observed in the blood samples that were collected for analysis.^{3,4}

REFERENCES

1. FDA approves new FoundationOne Liquid CDx companion diagnostic indications for three targeted therapies that treat advanced ovarian, breast, and non-small lung cancer. News release. Foundation Medicine; October 27, 2020. Accessed October 27, 2020. <https://www.foundationmedicine.com/press-releases/d7f17f4f-ab71-4c2b-9b98-bb12df081de1>
2. FoundationOne Liquid CDx. Foundation Medicine. Accessed October 27, 2020. <https://www.foundationmedicine.com/test/foundationone-liquid-cdx>
3. FDA approves FoundationOne Liquid CDx to serve as Rubraca (rucaparib) companion diagnostic to identify eligible patients with BRCA1/2-mutant, metastatic castration-resistant prostate cancer (mCRPC). News release. Clovis Oncology; August 26, 2020. Accessed October 27, 2020. <https://www.businesswire.com/news/home/20200826005806/en/FDA-Approves-FoundationOne%2CAE-Liquid-CDx-Serve-Rubraca%2CAE>
4. FDA approves Foundation Medicine's FoundationOne Liquid CDx, a comprehensive pan-tumor liquid biopsy test with multiple companion diagnostic indications for patients with advanced cancer. News release. Foundation Medicine; August 26, 2020. Accessed October 27, 2020. <https://www.foundationmedicine.com/press-releases/445c1f9e-6cbb-488b-84ad-5f133612b721>

Breast Cancer Incidence Rates Increase for Racial/Ethnic and Age Groups Between 2010 to 2016

Incidence rates for hormone receptor-positive breast cancer subtypes increased for a number of racial/ethnic and age groups in the United States between 2010 and 2016, according to the results of a cross-sectional study published in *JAMA Network Open*.

Using data from 18 cancer registries in the Surveillance, Epidemiology and End Results database to determine breast cancer molecular subtype-specific incidence rates by age at diagnosis and race/ethnicity, investigators identified 320,124 women of Hispanic and non-Hispanic White, Black, and Asian/Pacific Islander descent who received a diagnosis of breast cancer between 2010 and 2016. Participants were stratified by race/ethnicity, and incidence rates were age-standardized and stratified by 15-year age groups at time of diagnosis.

More than half (67.5%) of the women included in the study were non-Hispanic White (n = 216,092) and 41.5% of these women were between 55 and 69 years at diagnosis (n = 132,986). The majority of tumors (72.6%) were found to be luminal A, followed by triple-negative (11.3%), luminal B (11.2%), and *ERBB2*-enriched (4.8%).

Study results revealed that incidence rates for luminal B breast

cancer increased in all age groups (25-84 years) among non-Hispanic white women and Hispanic women.

Incidence rates of luminal A breast cancer also increased in non-Hispanic White women aged 40 to 54 years from 2010-2014 (annual percentage change [APC], 2.3%; 95% CI, 0.3%-4.2%) and in non-Hispanic Asian/Pacific Islander women from 2010-2016 in the same age group (APC, 2.5%; 95% CI, 0.6%-4.5%), as well as among non-Hispanic Black women aged 55 to 69 years (APC from 2010-2012, 4.9%; 95% CI, 4.0%-5.7%).

Conversely, incidence of triple-negative breast cancer decreased among non-Hispanic White women aged 40 to 54 years (APC, -2.3%; 95% CI, -3.8% to -0.7%) and 55 to 69 years (APC, -3.6%; 95% CI, -5.1% to -2.1%), as well as among non-Hispanic Black women aged 55 to 69 years (APC, -1.4%; 95% CI, -2.2% to -0.7%).

Study authors concluded that further surveillance of breast cancer trends by clinically relevant subgroups may help guide breast cancer prevention and control efforts.

REFERENCE

- Acheampong T, Kehm RD, Terry MB, Argov EL, Tehranifar P. Incidence trends of breast cancer molecular subtypes by age and race/ethnicity in the US from 2010 to 2016. *JAMA Netw Open*. 2020;3(8):e2013226. doi:10.1001/jamanetworkopen.2020.13226

COVID-19 Delays in Breast Cancer Surgery Could Mean More Deaths Over Next Decade

The coronavirus disease 2019 (COVID-19) pandemic has caused widespread delays and cancellations in cancer care. For breast cancer patients facing delays in surgery, this could result in close to 3000 additional deaths over a 10-year period, according to an analysis based on Kantar Health's CancerMPact Patient Metrics database.¹

This database estimates that there will be 335,779 new breast cancer cases in the United States in 2020, 319,700 of which will be nonmetastatic.¹ According to authors of a study published in *JAMA Oncology*, a 60-day delay in breast cancer surgery will lead to a 4% increase in the number of deaths after 5 years and 7% at 10 years.²

The database also estimates that 79,925 new nonmetastatic breast cancer cases were diagnosed in the first 3 months of the pandemic when elective surgery was temporarily suspended in hospitals overwhelmed by patients with COVID-19. That suspension would lead to 1598 deaths 5 years after diagnosis and 2797 deaths at 10 years.¹

The results of a questionnaire published in *Breast Cancer Research and Treatment* in August 2020 found that although age was a leading factor in care delays (eg, younger women faced more postponements), 44% of all breast cancer survivors reported delays in treatment due to COVID-19.³

According to the Kantar Health analysis, the cost of cancer treatment is also expected to rise, with estimates indicating that breast cancer care will cost an additional \$215.2 million 5 years post COVID-19 and \$376.7 million 10 years post pandemic.¹

REFERENCES

1. COVID-19 related breast cancer surgery delays could result in nearly 3,000 additional deaths over a 10 year period. News release. Businesswire; October 19, 2020. Accessed October 19, 2020. <https://www.businesswire.com/news/home/20201019005633/en/COVID-19-Related-Breast-Cancer-Surgery-Delays-Could-Result-in-Nearly-3000-Additional-Deaths-Over-a-10-Year-Period>
2. Bleicher RJ, Ruth K, Sigurdson ER, Beck JR, Ross E, Wong YN, et al. Time to surgery and breast cancer survival in the United States. *JAMA Oncol*. 2016;2(3):330-339.
3. Papautsky EL, Hamlish T. Patient-reported treatment delays in breast cancer care during the COVID-19 pandemic. *Breast Cancer Res Treat*. 2020;184(1):249-254. doi:10.1007/s10549-020-05828-7

Most Patients With De Novo Metastatic Breast Cancer Harbor Regional Lymph Node Disease

According to the results of study published in *JAMA Network Open*, the majority of patients with de novo metastatic breast cancer harbor regional lymph node disease at presentation.

In the cohort study, researchers evaluated patients who presented with de novo stage IV breast cancer at the Memorial Sloan Kettering Cancer Center from 2006 to 2018. Medical records of each patient were reviewed to determine clinicopathological parameters, and pretreatment PET-CT imaging was also reviewed to validate the extent of regional nodal involvement at metastatic diagnosis. Only those patients with de novo metastatic breast cancer and evaluable pretreatment PET-CT images were included (about half of all patients). Those patients without such images were excluded.

A subset of patients underwent regional lymph node biopsy for diagnostic confirmation; this group served to validate the radiographic nodal assessment.

Among 597 women with untreated metastatic breast cancer, 512 (85.8%) showed regional lymph node involvement by PET-CT or nodal biopsy: 509 (85%) had involvement of axillary level I, 328 (55%) of axillary level II, 136 (23%) of axillary level III, 101 (17%) in the supraclavicular fossa, and 96 (16%) in the internal mammary chain.

Overall, lymph node involvement was found to be more prevalent among estrogen receptor (ER)-negative tumors (92.4%) compared with ER-positive tumors (83.6%). However, nodal involvement at the time of metastatic diagnosis was not associated with overall survival.

Although the exclusion of patients with unevaluable pretreatment PET-CT images may have introduced selection bias into the subsequent analyses, all contemporary patients who presented to the cancer center at initial evaluation underwent a PET-CT.

REFERENCE

Bitencourt A, Saccarelli CR, Morris EA, et al. Regional lymph node involvement among patients with de novo metastatic breast cancer. *JAMA Network Open*. 2020;3(10):e2018790. doi:10.1001/jamanetworkopen.2020.18790

Ductal Carcinoma in Situ Is Associated With Higher Breast Cancer Death Risk

Women with ductal carcinoma in situ (DCIS) were more than 3 times as likely to die of breast cancer than women without DCIS, according to results of a large cohort study published in *JAMA Network Open*.¹

DCIS represents about 1 in 5 new breast cancer cases but can almost always be cured.² Standard courses of treatment to prevent invasive recurrence include surgery, radiation, and hormone therapy.

Researchers from the Women's College Research Institute in Toronto, Ontario, used data from the Surveillance, Epidemiology and End Results (SEER) database to compare the number of breast cancer deaths in 144,524 women treated for DCIS vs women in the general population. Women in the DCIS cohort were first diagnosed between 1995 and 2014. All underwent surgical treatment and 47.1% received radiation therapy. Follow-up data were available up to 2016 and analyzed in 2020. Women in the cohort were followed from diagnosis until death from breast cancer or the date of their last follow-up. Women in the general population were analyzed as a control group.¹

Ideally, treatment for DCIS would eliminate the risk of invasive ipsilateral recurrence; however, the data suggest a different scenario. Based on the SEER data, investigators expected 458 deaths in the DCIS cohort, assuming that each woman was cancer-free at the time of DCIS diagnosis. Instead, of the 144,524 women treated for DCIS, 1540 died of breast cancer in the 20 years following diagnosis—a standardized mortality ratio (SMR) of 3.36 (95% CI, 3.20-3.53). The findings suggest that the current treatment focus, which is preventing invasive recurrence, is not effective in eliminating breast cancer death after DCIS.¹

In addition, certain populations saw significantly higher SMRs: women diagnosed with DCIS before age 40 years (SMR, 11.95; 95% CI, 9.66-14.39), Black women (SMR, 7.56; 95% CI, 6.76-8.42), and Black women diagnosed with DCIS before age 50 years (SMR, 12.10; 95% CI, 9.94-14.54).¹

The study authors noted that the investigation was not meant to inform clinical management of DCIS and that the cumulative breast cancer-specific death rate (3.3%; 95% CI, 3.1%-3.7%) in the 20 years after diagnosis is not enough to recommend chemotherapy. But they acknowledge that chemotherapy may be a consideration in those populations that saw an increased risk percentage.¹

REFERENCES

1. Giannakeas V, Sopik V, Narod SA. Association of a diagnosis of ductal carcinoma in situ with death from breast cancer. *JAMA Netw Open*. 2020;3(9):e2017124. doi:10.1001/jamanetworkopen.2020.17124
2. Ductal carcinoma in situ (DCIS). American Cancer Society. Updated September 20, 2019. Accessed October 12, 2020. <https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/types-of-breast-cancer/dcis.html>

Data Collection Method for Benign Breast Disease Can Provide Insight on Cancer Development

The way in which benign breast diseases (BBD) are detected can give insight on which are most likely to become cancerous, according to research presented at the 12th European Breast Cancer Conference, October 2-3, 2020.¹

A team of investigators found that for women attending breast screenings, BBD found on the first visit is considered “prevalent” BBD while disease found on subsequent visits is classified as “incident” BBD. Typically, screenings are done for women after age 50 years in Spain and many other European countries with national screening programs.^{1,2}

Data were collected from almost 630,000 women who underwent a total of 2,327,384 screening mammograms between 1995 and 2015. Investigators determined that women diagnosed with incident BBD saw a 2.67-fold increased chance of developing breast cancer compared with women with no BBD. Women with prevalent BBD saw a 1.87-fold increased risk compared with women with no BBD.¹

The investigators classified BBD as either proliferative or nonproliferative, depending upon whether the breast tissue showed an increase in specific cell growth. Using this categorization, the team determined that women with proliferative BBD had a 3.28-fold increased chance of breast cancer compared with women with no BBD. Women with nonproliferative BBD saw a 1.96-fold increased risk.^{1,2}

Among women with an incident, nonproliferative BBD, the team found a 2.39-fold increased chance of developing breast cancer compared with women with no BBD. For women with prevalent, proliferative BBD, the increased risk was 2.85-fold, and women with prevalent, nonproliferative BBD had a 1.63-fold increased risk.¹

The investigators hope these data can help in the design of personalized breast screening strategies to improve screening effectiveness. They believe these findings will help clinicians understand the different risks associated with BBD to improve predictions for accuracy of breast cancer risk.^{1,2}

REFERENCES

1. Louro J, Román M, Posso M, et al. Differences in breast cancer risk after a benign breast cancer disease according to the screening type. *Eur J Cancer*. 2020;138(suppl 1):S11. doi:10.1016/S0959-8049(20)30552-9
2. Researchers reveal which benign breast disease is most likely to develop into cancer. News release. European Organisation for Research and Treatment of Cancer; October 1, 2020. Accessed October 26, 2020. https://www.eurekalert.org/pub_releases/2020/10/eofrrw092920.php

