Therapeutic Considerations in Metastatic HER2+ Breast Cancer

Expert Perspectives From Across the Nation
(Florida, Maryland, Massachusetts, New York, North Carolina, Pennsylvania, Virginia, and Washington, DC)
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INTRODUCTION


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. 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. 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 subtypes: 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 Over these subtypes, HR-negative/HER2-positive historically had the worst prognosis, but outcomes have improved with the development of ther-
APTERIES that target HER2. Three of these therapies include monoclonal antibodies, antibody-drug conjugates (ADCs), and oral tyrosine kinase inhibitors (TKIs). This is “an era of immense drug exploration for HER2-targeted therapy,” according to Denduluri.

**OVERVIEW OF HER2-POSITIVE BREAST CANCER**

Approximately 15% of all breast cancers are HER2-positive. 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 with the use of immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH).

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. 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). A newer term, HER2-low, describes breast cancer scored IHC 1+ or 2+ with a negative FISH or chromogenic assay.

**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. Several HER2-targeted therapies are approved in the metastatic setting, including the monoclonal antibodies trastuzumab and pertuzumab; the ADCs ado-trastuzumab emtansine (T-DM1) and fam-trastuzumab deruxtecan-nxki (T-DXd); and TKIs, such as lapatinib and the recently approved neratinib and tucatinib.

**Monoclonal antibodies**

In 1998, the FDA granted its first approval for a drug that targets HER2-positive breast cancers, trastuzumab. The therapy “revolutionized the care of HER2-positive breast cancer,” according to Denduluri. More than a decade 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. 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). 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. The median survival of these patients was very impressive, with 37% of patients living 8 years,” said Denduluri. Gradishar said, “With more than a year improvement in outcomes with the dual HER2-targeting with trastuzumab and pertuzumab, [this] became the go-to first-line therapy for the majority of patients with HER2-positive metastatic disease.” Denduluri similarly stated that “for recurrent stage 4 breast cancer that is HER2-positive, or even de novo metastatic breast cancer that is HER2-positive, [most clinicians] use the trastuzumab plus pertuzumab plus docetaxel or the trastuzumab plus pertuzumab plus paclitaxel because of the survival benefit.”

Regarding adverse events (AEs) in the CLEOPATRA trial, results from the safety analysis indicated that neutropenia was the most common grade 3 or higher 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.

Margetuximab, a monoclonal antibody, is “bioengineered to optimize the fragment crystallizable [Fc] region [to have] greater affinity for the activating domain and less for the inhibitory effect,” stated Gradishar. It is currently being investigated by the FDA for the treatment of metastatic or locally advanced HER2-positive breast cancer previously treated with anti-HER2–targeted therapy. According to Gradishar, there is “some optimism … that this will [become] an approved drug.” However, Brufsky pointed out that 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), the drug did not meet the coprimary end point of OS and only modestly met the progression-free survival (PFS) end point. “It will be interesting to see what the FDA does,” he said. “It would be really nice to have” margetuximab as a treatment option. When looking at the prespecified exploratory survival analysis of margetuximab, patients carrying the CD16A-158F allele (85% of the population) experienced a greater median OS with margetuximab than with trastuzumab (23.7 vs 19.4 months; P = .087). Patients who were homozygous for the CD16A-158VV allele (15% of the population) did not experience an advantage with margetuximab. "For the
future, it is very likely that, in addition to HER2, there will need to be a second biomarker to enhance and select the patients who would benefit most from the margetuximab compound,” said Anders.

**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. The ADC T-DM1, indicated for the treatment of patients with metastatic HER2-positive breast cancer who previously received trastuzumab and a taxane, separately or in combination, is typically used by Denduluri and Anders in the second-line setting. Based on results from the EMILIA and TH3RESA trials, T-DM1 “became the go-to therapy after progression on trastuzumab,” said Gradishar. T-DM1 received approval on the basis of results from the phase 3, randomized, open-label EMILIA trial (NCT00829166), 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). 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%).

Anders shared that she generally is a purist with her treatment approach for metastatic HER2-positive breast cancer: She follows the standard CLEOPATRA regimen of trastuzumab plus pertuzumab (plus docetaxel) and then usually moves on to the EMILIA regimen with T-DM1. “This has been [clinicians’] tried-and-true [approach] for so long,” she said. However, she might alter this sequence for patients with progressing central nervous system (CNS) metastases, for whom she might first consider the HER2CLIMB tucatinib regimen before T-DM1.

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. The phase 2, two-part, 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). 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 (95% CI, 53.4-68.0). 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).

In a subgroup analysis of patients with stable brain metastases in the DESTINY-Breast01 trial (n = 24), 58.3% of patients achieved an objective response (95% CI, 36.6%-77.9%), which was similar to the objective response for the full patient cohort, discussed earlier. The median duration of PFS was 18.1 months (95% CI, 6.7-18.1) for the brain metastases group. Among all patients, a decreased neutrophil count was the most common AE grade 3 or higher (20.7%).

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. “The problem [with ILD] is that it is idiosyncratic,” said Brufsky. “You never know what is going to happen; it is not predictable.” Women with metastatic breast cancer are often short of breath because of both the burden of disease and fatigue from their treatment regimen. Previously, clinicians may not have addressed the symptoms, but now they know they must be watchful for the potential development of ILD. Denduluri noted that care needs to be multidisciplinary. “When patients have a cough or shortness of breath, [it] is sometimes hard to differentiate [whether those are ILD symptoms] if they have pulmonary metastases,” she said, adding that pulmonologist consultation should be sought. Jahanzeb noted that the prescribing information for T-DXd recommends advising patients on the risk of ILD and the need to immediately report symptoms. T-DXd comes with a black box warning, stating that if patients develop grade 2 or higher pneumonitis, they should permanently discontinue T-DXd. 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.

Anders noted that the prescribing information for T-DXd says that the first dose of T-DXd should be withheld if patients develop ILD within 28 days of T-DXd initiation. T-DXd should be withheld if patients develop grade 2 or greater ILD within 28 days of T-DXd initiation. In a subgroup analysis of patients with stable brain metastases, grade 2 or greater ILD was seen in 5% of patients. The median duration of ILD was 18.3 months (range, 4.7-53.4).

**BREAST CANCER**

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selective, and it has greater permeability. So there is more of a bystander effect ... and there is significant activity in the HER2-low setting.” DESTINY-Breast04 will be a very interesting trial, said Gradishar, “because it may offer a therapeutic that would bridge different silos of breast cancer.”

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

**Tyrosine kinase inhibitors**

Lapatinib was the first TKI and second drug approved, after trastuzumab, for targeted treatment of metastatic HER2-positive breast cancer. Lapatinib is a dual HER2 inhibitor (targeting both EGFR and HER2) and 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

In terms of safety and efficacy, this treatment combination was compared with capecitabine alone in a phase 3, randomized, open-label trial (NCT00078572) for women with locally advanced or metastatic breast cancer who 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.15,16 Neratinib, a pan-HER inhibitor that also targets 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 who had been previously treated with 2 or more HER2-targeted therapies (N = 621).34,35 Patients were randomized to receive neratinib plus capecitabine or lapatinib plus capecitabine. The median follow-up duration was 29.9 months (IQR, 21.9-40.6). PFS, 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 the difference was 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 CNS metastases, according to results from an assessment of pooled data from NALA and two other phase 2, randomized trials (NEFERT-T [NCT00915018] and TBCRC 022 [NCT01494662]).36-38 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 “Like a lot of these TKIs that bind EGFR, diarrhea is a problem,” said Brufsky. This is the most challenging aspect of neratinib, shared Anders. Strategies to improve diarrhea associated with neratinib have included loperamide, budesonide plus loperamide, and colestipol plus loperamide. As these supportive measures are implemented, “the rates of grade 3 diarrhea go down quite a bit,” said Anders. In her practice with prophylactic and continued management of diarrhea with loperamide combined with another agent, she sees no more than 10% to 20% of her patients experience substantial problems with diarrhea.

Recently approved, the first HER2-specific 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, 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 end point 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 end point 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; \( P < .0001 \). For patients with active brain metastases, median OS was 20.7 months (95% CI, 15.1 to 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 The survival was “really quite striking in the patients with active metastases ... and not so much in the stable metastases,” according to Gradishar.

Mahtani noted that of all the patients with brain metastases in the trial (n = 291), 66 (23%) had untreated brain metastases. They were also asymptomatic, according to Mahtani. With these data, she said “it is hard not to think of the possibility of doing screening brain MRIs, although they are not supported by the guidelines.” She said that when she sees “how many patients may potentially have brain metastases that we are not aware of, [it is] striking.”

Although TKIs are generally associated with some gastrointestinal toxicity, Tolaney stated that “tucatinib is a little different ... because [it] dial[s] in on turning off HER2 and tries to spare inhibiting EGFR.” In the HER2-CLIMB trial, grade 3 or higher diarrhea was experienced by 12.9% of those receiving tucatinib and 8.6% of those receiving placebo. Diarrhea was the most common AE in both groups. The other most common AEs of grade 3 or higher in the tucatinib group were palmar–plantar erythrodysesthesia syndrome, elevations in alanine aminotransferase and aspartate aminotransferase levels, and fatigue.40 “I have noticed that some of my colleagues have been hesitant [to prescribe tucatinib], thinking that the tolerability of tucatinib is the same as some of the other TKIs,” said Mahtani. “In my practice, it has not been that way. It has been a lot easier to tolerate for patients.”

Tolaney noted tucatinib’s approval for both second- and third-line settings, appreciating its flexibility as a therapy option. For a “patient who progressed on trastuzumab plus pertuzumab plus docetaxel up front, and possibly had CNS progression in addition to systemic progression,” she said, the tucatinib regimen offers an option that can potentially spare her from radiation. Jhaveri stated that she is “sticking with [tucatinib] as a third-line [option], unless there is compelling evidence to think about it in the second line ... This regimen is a slam dunk [when] dealing with an active brain metastasis patient.” She noted that the patients with brain metastases in the trial were asymptomatic, had tumors 2 cm or smaller, and did not require immediate local intervention. “We cannot use [tucatinib] for just any brain metastases that we might come across in our clinic,” she said.

CONCLUSIONS

Jahanzeb recalled participating in an empirical trial for trastuzumab approximately 23 years ago. At that time, she said, hitting the target and then designing a drug was “a quantum leap.” Today, “it is very heartening” to see that “real research is bearing fruit” for a patient group with a previously poor prognosis. “Now is the luckiest [time] to be [diagnosed with metastatic HER2-positive breast cancer] if you have access to these [therapies],” he said. Jhaveri agreed. “We are in a very exciting time,” she said. “We have 7 approved anti-HER2 therapies to offer our patients, which have made a big improvement for survival in the early stage and now also in the metastatic setting.” She acknowledged that there is still a lot of work to do, and with more and more unique classes of agents under development, she is looking forward to seeing how outcomes can be further improved.

PATIENT SPOTLIGHT.

The following case of a patient with metastatic HER2-positive breast cancer was presented during the regional broadcasts. Afterward, viewers were polled regarding the treatment strategy they would choose for this patient. The poll results are provided on the next page.

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 work-up 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.
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. Approximately 63% of those located in the DC/Pennsylvania/Maryland area, Virginia, and North Carolina selected T-DM1 as their second-line therapy preference. The tucatinib regimen was the second most popular choice. Of those located in Florida, 100% chose T-DM1. Brufsky said the choices were reasonable; he would use the tucatinib regimen if the patient were to have brain progression. He noted that there are trials comparing T-DXd with T-DM1, and although there are not yet answers, he believes T-DM1 will still be a good choice as second-line therapy.

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. Approximately 63% of those from Virginia and North Carolina chose the tucatinib regimen (with T-DXd at ~37%), whereas T-DXd was selected by nearly 64% of those from the DC/Pennsylvania/Maryland area (with tucatinib at ~30%). Of those located in Florida, 100% chose the tucatinib regimen. Jahanzeb acknowledged that beyond the second line, treatment sequencing is a “free-for-all.” Anders stated that making her selection between T-DXd and the tucatinib regimen for third-line therapy would depend on the status of the patient’s metastases to the brain as well as practical considerations to discuss with the patient, such as whether she feels comfortable taking oral medications at home, whether she is concerned about medication interactions or errors, and whether she wants to prioritize avoiding alopecia. Many patients also have insurance coverage with an oral drug co-pay that is much more exorbitant than the cost of an intravenous drug, so finances may also factor into therapy decision-making.

September 15, September 24, October 7, and October 26, 2020.

REFERENCES


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Combined Study Analysis Determines Best Drug Choices for Patients With Advanced Breast Cancer

Detection of ESR1 mutations in baseline circulating tumor DNA is associated with inferior progression-free survival (PFS) and overall survival (OS) in patients with advanced hormone receptor (HR)–positive breast cancer treated with exemestane vs fulvestrant, according to a combined analysis of the phase 3 SoFEA (NCT00253422) and EFECT (NCT00065325) trials published in Clinical Cancer Research. 1

Of the 30% of patients with detected ESR1 mutations, PFS was 2.4 months (95% CI, 2.0–2.6) on exemestane and 3.9 months (95% CI, 3.0–6.0) on fulvestrant (HR, 0.59; 95% CI, 0.39–0.86; P = .01). Patients without detected ESR1 mutations had PFS of 4.8 months (95% CI, 3.7–6.2) on exemestane and 4.1 months (95% CI, 3.6–5.5) on fulvestrant (HR, 1.05; 95% CI, 0.81–1.37; P = .69).

Further, patients with detected ESR1 mutations had 1-year OS of 62% (95% CI, 45.5%–75%) on exemestane and 80% (95% CI, 68%–87%) on fulvestrant (P = .04; restricted mean survival analysis). Patients without detected ESR1 mutations had 1-year OS of 79% (95% CI, 71%–85%) on exemestane and 81% (95% CI, 74%–87%) on fulvestrant (P = .69).

Notably, the investigators emphasized that patients treated with fulvestrant in both trials were given a dose half that in current use (250 mg of fulvestrant vs 500 mg of fulvestrant in the CONFIRM study; NCT00099437). Although there was no difference found between exemestane and fulvestrant in the ESR1-undetected group, this may reflect the lower dose of fulvestrant used. Therefore, they concluded that it is reasonable to speculate that such patients treated with fulvestrant may have had improved PFS on a 500-mg dose of fulvestrant compared with exemestane.

REFERENCE

Abemaciclib Reduces the Risk of Recurrence in High-Risk Early Breast Cancer

The addition of abemaciclib to endocrine therapy led to a significant reduction in the risk of invasive disease vs endocrine therapy alone in patients with high-risk early hormone receptor–positive, HER2-negative breast cancer, according to the results of a study presented at the European Society for Medical Oncology Virtual Congress 2020, held September 19-21.

In the patient population, abemaciclib reduced the risk of invasive disease by 25.3% vs endocrine therapy alone (HR, 0.747; 95% CI, 0.598-0.932; 2-sided P = .0096). Additionally, the 2-year invasive disease-free survival rates were 92.2% in the abemaciclib arm vs 88.7% in the endocrine-alone arm, reflecting an absolute improvement of 3.5%.

Abemaciclib is an oral, continuously dosed CDK4/6 inhibitor that is approved in hormone receptor–positive, HER2-negative advanced breast cancer in combination with endocrine therapy. Based on the overall survival advantage abemaciclib has shown in combination with fulvestrant in the metastatic setting, investigators evaluated adjuvant abemaciclib in combination with endocrine therapy.

The international monarch© trial (NCT03155997) included 5637 men and women with pre- and postmenopausal high-risk, early, hormone receptor–positive, HER2-negative breast cancer.

After completing primary therapy, patients were randomized 1:1 to 150 mg of abemaciclib twice daily for up to 2 years plus 5 to 10 years of endocrine therapy (n = 2808) as clinically indicated vs endocrine therapy alone (n = 2829).

Further results demonstrated that the addition of abemaciclib to endocrine therapy also had a significant impact on distant recurrence-free survival (DRFS) across all prespecified subgroups, reducing the risk of distant recurrence by 28.3% (HR, 0.717; 95% CI, 0.559-0.920; P = .0085). The 2-year DRFS rates were 93.6% with abemaciclib vs 90.3% with endocrine therapy alone, reflecting an absolute improvement of 3.3%.

REFERENCE

Mortality Higher Among Women With Interval vs Screening-Detected Breast Cancers

Results from a study of Canadian women who did and did not participate in a population-based breast cancer screening program show that interval breast cancers (IBC) are more aggressive and deadlier than screening-detected breast cancers (SBCs).

The patient population consisted of 69,025 women who did and did not participate in the population-based screening program during the January 2004 to June 2010 study period. They accounted for 212,579 screening mammograms and were aged 50 to 64 years.

Tumor and patient characteristics of both cancer types were compared via multinomial logistic regression analysis to assess tumor and patient characteristics associated with a diagnosis of IBC compared with SBC, while mortality risk for each was assessed using competing risk analysis.

Results from the analysis indicated that 1687 invasive breast cancer diagnoses were made, equating to a 2.4% positivity rate among the women in the study.

The overall mortality rate was 13.3%, for 225 deaths. Of these deaths, the breast cancer–specific mortality rate was 75.5%, for 170 deaths; most (94) happened among screening program nonparticipants, and 20, 27, and 29 occurred among women in the SBC, noncompliant, and IBC groups, respectively.

Compared with SBC, IBC had greater odds of being both grade 3 (odds ratio [OR], 6.33; 95% CI, 3.73-10.75; P < .001) vs grade 1, and estrogen receptor–negative disease (OR, 2.88; 95% CI, 2.01-4.13; P < .001).

Breast cancer–specific mortality remained higher in the IBC group vs SBC group after a 7-year follow-up (HR, 3.55; 95% CI, 2.01-6.28), including a 2-year sojourn. However, non-breast cancer mortality was similar (HR, 1.33; 95% CI, 0.43-4.15).

REFERENCE

Gut Microbiota May Influence pCR in Early-Stage Breast Cancer

The results of a study presented at the 12th European Breast Cancer Conference, held virtually October 2-3, 2020, has linked levels of 2 short-chain fatty acids (SCFAs) in women with early-stage breast cancer to pathological complete response (pCR) to neoadjuvant chemotherapy (NACT).

The 2 SCFAs are propionate and butyrate, and their levels were shown to be lower in the gut bacteria of patients achieving pCR compared with those not achieving pCR after surgery.

Patients were placed into 1 of 2 cohorts: the study group, composed of women with early-stage breast cancer (n = 21), and a healthy control group (n = 24). In the study group, 42.9% had HER2-positive disease, 38.1% had triple-negative disease, and 19% had estrogen receptor–positive,
HER2-negative disease. Their treatments consisted of FEC-T chemotherapy (42.9%), FEC-TH chemotherapy (28.6%), and other (28.6%).

The patients in the study group had a median age of 56 years (range, 33-72) and a median body mass index (BMI) of 28.6 kg/m² (range, 19.6-55.6 kg/m²). Patients in the control group had a median age of 46 years (range, 31-61) and a median BMI of 25.9 kg/m² (range, 18.0-42.4 kg/m²).

Results were available for 20 participants in each cohort. Overall, pCR was seen in 25% of evaluable patients, and there were no significant differences in SCFA levels for the healthy controls and study patients before the first NACT cycle. However, significantly lower mean concentrations (µmol/g) of the SCFAs were seen after the final NACT cycle for propionate (P = .027) and butyrate (P = .024) in patients who achieved a pCR compared with those who did not.

The investigators hope their results lead to additional investigations of how to increase chemotherapy’s effectiveness, and they are planning larger studies on the influence of gut microbiota in breast cancer subtypes and on anticancer immune responses.

REFERENCE

Single-Dose Radiotherapy Is as Effective as Conventional Therapy for Patients With Breast Cancer

For women with early breast cancer, a single dose of targeted radiotherapy is just as effective as conventional radiotherapy, which requires several visits to the hospital after surgery, according to the results of a study published in BMJ.

Intraoperative radiotherapy, the combination of targeted therapy given after surgery, is associated with an approximately 80% chance of avoiding a full course of conventional therapy, fewer adverse effects, and no difference in survival or likelihood of cancer recurrence.

Investigators analyzed 2298 women, 45 years or older, who were eligible for breast conservation surgery. Between March 2000 and June 2012, 1140 women were randomized to receive targeted intraoperative radiotherapy (TARGIT-IORT) and 1158 received external beam radiotherapy (EBRT).

Study results indicated that after 5 years of monitoring, local recurrence risk was 2.11% for TARGIT-IORT compared with 0.95% for EBRT, but the difference was not considered statistically significant.

In the first 5 years after surgery, the data showed 13 additional local recurrences (24 of 1140 vs 11 of 1158) and 14 fewer deaths (42 of 1140 vs 56 of 1158) with TARGIT-IORT compared with EBRT. Deaths from other causes were significantly lower with TARGIT-IORT than with EBRT (45 vs 74 events, respectively; HR, 0.59; 95% CI, 0.40-0.86; P = .005).

REFERENCE
Vaidya JS, Bilsara M, Baum M, et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. BMJ. 2020;370:m2836. doi:10.1136/bmj.m2836

Age Plays a Leading Role in COVID-19 –Related Breast Cancer Treatment Delays

Results from a questionnaire distributed within the first weeks of the coronavirus disease 2019 (COVID-19) pandemic show that 44% of breast cancer survivors experienced treatment delays for their disease.

According to the study, published in Breast Cancer Research and Treatment, these disruptions happened more often for younger vs older women (HR, 0.97; 95% CI, 0.95-0.99; P < .001) and were typically related to ovarian suppression hormone therapies.

Disruptions included injection delays from clinic closure, treatment protocol changes, and alternative therapies for which clinic visits were deemed unnecessary.

A 50-item questionnaire was developed on care delays and was distributed via social media and emailed to breast cancer survivor groups in the United States. A total of 609 responses were received during the study period (April 2-27, 2020).

Among the 44% of respondents who reported care delays, most (79%) were from delayed follow-up appointments, with the others related to breast reconstruction surgery (66%), diagnostic imaging (60%), and lab testing (50%). Thirty percent of respondents also reported hospital- and clinic-based treatment delays of radiation (30%), infusion therapies (32%), and surgical tumor removal (26%). The mean (SD) age at diagnosis was 43 (10.84) years.

A majority (63%) of the respondents were receiving care for their breast cancer at the time of the survey, with the mean age of the younger vs older women being 45.94 (10.31) years and 48.98 (11.10) years, respectively. Respondents identified as White (78%), Black (17%), and Asian (3%). There was 1 male respondent.

The authors hope their results are used in the aftermath of the pandemic to aid in how health care services are distributed and used, as well as to support future potential disaster planning for care disruptions.

REFERENCE

pCR Put Forth as a Surrogate Marker for Improved Survival in Early HER2+ Breast Cancer

Women with early-stage HER2-positive breast cancer who achieved a pathologic complete response (pCR) to neoadjuvant HER2-directed therapy experienced prolonged event-free survival (EFS) and overall survival (OS) vs those who did not, according to final results from the phase 3 NeoALTTO trial (NCT00553358). The likelihood of achieving a pCR was highest (51.3%) among patients who received the combination of lapatinib and trastuzumab vs those who received trastuzumab (29.5%) or lapatinib (24.7%) alone.

A total of 455 women with invasive, HER2-positive cancer were randomized to receive 1 of 3 neoadjuvant treatments for 6 weeks: intravenous trastuzumab, with a 4 mg/kg loading dose followed by 2 mg/kg weekly (n = 149); 1500 mg of lapatinib (n = 154); or 1000 mg of lapatinib daily plus the same trastuzumab regimen that was given in the trastuzumab-alone arm (n = 152). All patients received 80 mg/m² of paclitaxel starting at week 6 and continued on neoadjuvant therapy for another 6 weeks. Following surgery, patients received 34 weeks of adjuvant therapy according to their initial randomization to complete 1 year of HER2-targeted therapy.

At a median follow-up of 9.7 years, 77% of patients who achieved a pCR had improved EFS and OS was 88%; of those who did not achieve pCR, 61% did not have improved EFS, and the OS was 72%. The EFS rate was 69% in the combination arm, 65% in the trastuzumab-alone arm, and 63% in the lapatinib-alone arm. The OS rates were 80%, 76%, and 77%, respectively.

REFERENCES