Advances in the Management of Metastatic Breast Cancer
Presented by William J. Gradishar, MD

ABSTRACT

Recent advances in the understanding of the molecular underpinnings of metastatic breast cancer have led to the identification of novel therapeutic targets. The latest update to the NCCN Guidelines for Breast Cancer reflects a rapidly evolving treatment landscape, highlighting the growing importance of combination therapies and personalized medicine in managing estrogen-receptor (ER)–positive, HER2-positive, and triple-negative subtypes. For patients with ER-positive disease, the standard of care remains combination therapies involving cyclin-dependent kinase 4/6 inhibitors, endocrine therapy, and PI3 kinase. In patients with HER2-positive disease, the use of fam-trastuzumab deruxtecan-nxki and tucatinib have demonstrated improved outcomes. For those with triple-negative breast cancer, pembrolizumab, PARP inhibitors, and antibody–drug conjugates (eg, sacituzumab govetecan-hziy) have shown activity.

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Metastatic breast cancer remains a highly heterogeneous and complex disease, characterized by diverse molecular subtypes and clinical manifestations. The ongoing challenge for clinicians and researchers is to develop tailored therapeutic strategies to target the distinct biology of each subtype while minimizing toxicity and maintaining quality of life for patients.

During the NCCN 2023 Annual Conference, William J. Gradishar, MD, Betsy Bramsen Professor of Breast Oncology, Professor of Medicine, and Chief of the Division of Hematology and Medical Oncology at Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, discussed the latest update to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), highlighting the growing importance of combination therapies and personalized medicine in managing estrogen receptor (ER)–positive, HER2-positive, and triple-negative subtypes.

ER-Positive Metastatic Breast Cancer

As Dr. Gradishar reported, the treatment landscape for ER-positive metastatic breast cancer has evolved over the years, with a shift toward combination therapies over monotherapy options. The NCCN Guidelines now include multiple combination treatments involving cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, such as palbociclib, abemaciclib, and ribociclib, paired with endocrine therapy (Figure 1).

These combinations have consistently demonstrated improved progression-free survival (PFS) in both first- and second-line settings across various clinical trials: PALOMA, MONALEESA, and MONARCH. According to Dr. Gradishar, however, ribociclib has shown the most compelling data related to survival benefits. The recent addition of elacestrant (a selective estrogen receptor degrader) to the NCCN Guidelines offers another treatment option for patients with ESR mutations.

“While the traditional endocrine therapies, such as aromatase inhibitors, tamoxifen, and fulvestrant, have shown benefits in treating ER-positive breast cancer, they also present limitations, including the development of ER mutations and various toxicity issues,” said Dr. Gradishar. “The introduction of newer therapies and combination treatments has allowed for a more nuanced approach to treating breast cancer, leading to improved patient outcomes.”

Recent updates in the NCCN Guidelines for ER-positive metastatic breast cancer have focused on the use of sequential CDK4/6 inhibitors. The MAINTAIN trial, presented by Kalinsky et al at the 2022 ASCO Annual Meeting, studied the combination of fulvestrant and ribociclib in patients who had already received a CDK4/6 inhibitor. The trial suggested a modest improvement in PFS with sequential use of one CDK inhibitor followed by another, said Dr. Gradishar, although this evidence may be insufficient to establish it as a standard of care.

In contrast, the PACE trial did not show an improvement in PFS with the combination of fulvestrant and palbociclib. According to Dr. Gradishar, this discrepancy highlights the need for further data to determine whether sequential CDK4/6 inhibitor use should be routinely recommended, and ongoing trials, such as the post-MONARCH trial, are currently addressing these issues. For now, clinicians should exercise caution when considering sequential CDK4/6 inhibitor therapy for most patients, Dr. Gradishar added.
After CDK4/6 Inhibition

The first-line treatment of choice for patients with hormone receptor (HR)–positive, HER2-negative metastatic breast cancer remains the combination of CDK4/6 inhibitors with endocrine therapy (Figure 2). However, subsequent treatment options have expanded to include mTOR inhibitors, PI3 kinase inhibitors, and elacestrant for patients with ESR1 mutations.

The SOLAR-1 trial investigated the use of alpelisib, a PI3K inhibitor. The trial showed that in patients harboring PI3K mutations, adding alpelisib improved PFS by approximately 5.6 months.7

“It’s important to note that alpelisib can cause side effects, such as glucose management issues and rashes, which require close monitoring and management,” said Dr. Gradishar. Despite these side effects, he added, the BYLieve trial also demonstrated similar benefits when using alpelisib after CDK4/6 inhibitor therapy.8

The phase III EMERALD trial compared elacestrant with standard endocrine therapy in patients who had previously received CDK4/6 inhibitor treatment. The results showed modest improvements in PFS for all patients receiving elacestrant, with greater effects observed in patients with mutated ESR1.9 Based on these findings, elacestrant was approved for use in postmenopausal patients or men with ER-positive, HER2-negative breast cancer and an ESR1 mutation after at least one line of prior therapy. The drug is also being investigated in combination with CDK4/6 inhibitors and other targeted therapies in ongoing clinical trials.

The FAKTION trial investigated the combination of the AKT inhibitor capivasertib with endocrine therapy. Initial findings suggested that patients with a mutated AKT pathway derived benefits from the addition of capivasertib to fulvestrant.10 These results led to the CAPTello-291 trial, which further evaluated the combination in a larger patient

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**Figure 1.** Systemic for ER- and/or PR-Positive Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 4.2023 [BINV-P]. ©2023 National Comprehensive Cancer Network, Inc. All rights reserved. These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN®. To view the most recent and complete version of these NCCN Guidelines, go to www.nccn.org.

**Figure 2.** Roadmap for HR+/HER2– metastatic breast cancer.
population. The trial showed improved PFS when partnering endocrine therapy with capivasertib in both the overall population and those with an AKT-altered pathway.11

“Interestingly, the same incremental improvement was observed in patients without AKT pathway abnormalities, indicating that capivasertib may not be limited to patients with specific AKT alterations,” noted Dr. Gradishar.

**HER2-Positive Disease**

In HER2-positive disease, long-term follow-up data from the CLEOPATRA trial support the effectiveness of the dual HER2-targeting approach, improving median overall survival (OS) by more than 1.5 years.12

Ado-trastuzumab emtansine (T-DM1), the first antibody–drug conjugate, was previously considered as a second-line therapy based on the EMILIA trial. However, better treatment options are still needed because patients continue to experience recurrence.13

Fam-trastuzumab deruxtecan-nxki (T-DXd) has emerged as perhaps a more effective second-line treatment option due to its results in DESTINY-Breast03. This trial directly compared T-DXd and T-DM1 in patients previously treated with trastuzumab and a taxane. T-DXd demonstrated an improved objective response rate, PFS, and OS compared with T-DM1.14 Updated data showed sustained and enhanced effects, with a median PFS of 28 months with T-DXd versus 7 months with T-DM1.

According to Dr. Gradishar, interstitial lung disease is a notable concern associated with T-DXd; however, with increased experience and patient monitoring, most cases are relatively low grade and manageable. The sequential use of antibody–drug conjugates has shown activity in the DESTINY-Breast02 trial compared with alternative HER2-directed therapy.

The DESTINY-Breast09 trial is currently underway to evaluate whether T-DXd could replace the CLEOPATRA regimen as a first-line treatment option. This large trial, involving more than 1,000 patients, compares the CLEOPATRA regimen with T-DXd alone or T-DXd + pertuzumab. Results from this trial could potentially influence future NCCN Guidelines and clinical practice, predicted Dr. Gradishar.

In addition, tucatinib (a small-molecule tyrosine kinase inhibitor) has shown potential in treating HER2-positive breast cancer, especially because of its low off-target effect in comparison with lapatinib or neratinib. The HER2-CLIMB trial compared the combination of capecitabine, trastuzumab, and tucatinib with capecitabine and trastuzumab alone. The addition of tucatinib improved survival rates, including in patients with brain metastases.15

Antibody–drug conjugates such as T-DXd have also shown objective evidence of response in patients with brain metastases. The DESTINY-Breast04 trial showed improvements in survival rates for patients with HER2-low breast cancer treated with T-DXd, sparking interest in exploring the efficacy of T-DXd in patients with ultra-low HER2-expressing disease.

**Triple-Negative Breast Cancer**

Triple-negative breast cancer (TNBC) guidelines now consider various factors, including patients’ eligibility for immunotherapy, BRCA mutation status, and HER2 levels (Figure 3). The KEYNOTE-355 study provides evidence for using pembrolizumab in combination with chemotherapy in metastatic TNBC.

The ongoing DESTINY-Breast06 trial is comparing T-DXd with chemotherapy in patients with ultra-low HER2–expressing breast cancer, which may help to determine the effectiveness of this treatment in this population, said Dr. Gradishar.
as a first-line treatment of PD-L1–positive TNBC. The study compared pertuzumab and chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) with chemotherapy alone in patients who had not received prior treatment of metastatic disease. Although the entire population showed an incremental improvement in PFS, said Dr. Gradishar, the benefit was much greater for patients with a combined positive score (CPS) >10.16 Furthermore, the combination led to a clinically relevant improvement in OS of about 7 months for patients with higher CPS scores.

PARP inhibitors olaparib and talazoparib have shown activity in TNBC with BRCA mutations. The EMBRACA and OlympiAD trials reported improvements in PFS of about 2 months in both studies, with emerging data suggesting potential OS benefits.17,18

“Although there is preclinical evidence to support combining PARP inhibitors with checkpoint inhibitors, this approach is not yet recommended outside of clinical trials, as the addition of immunotherapy has not significantly enhanced objective response rates,” said Dr. Gradishar.

The antibody–drug conjugate sacituzumab govitecan-hzjy has proven effective in patients with TNBC who have received at least one chemotherapy regimen. The ASCENT trial demonstrated significant improvements in PFS and a doubling of OS from 6 to 12 months with sacituzumab govitecan-hzjy compared with physician’s choice of chemotherapy.19

Finally, datopotamab deruxtecan (Dato-DXd), a humanized antitrope IG1 monoclonal antibody conjugated to a topoisomerase payload, is an emerging treatment option for TNBC. According to Dr. Gradishar, preliminary data suggest its activity in TNBC and HER2-low disease, both as monotherapy and in combination with checkpoint inhibitors.

References