Updates in HR-Positive, HER2-Negative Metastatic Breast Cancer for the Advanced Practitioner

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Advances in the treatment of hormone receptor-positive, HER2-negative metastatic breast cancer continue to shape clinical practice. At JADPRO Live, presenters discussed the evolving therapeutic landscape, highlighting the role of CDK4/6 inhibitors, biomarker-driven targeted therapies, antibody-drug conjugates, and PARP inhibitors. With a focus on efficacy, patient selection, and the management of adverse events, they discussed the importance of personalized medicine in optimizing treatment outcomes. As resistance mechanisms become better understood, next-generation sequencing and emerging therapies offer new avenues for patients.

Recent advances in the treatment of hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (mBC) were highlighted at JADPRO Live 2024 by Kathryn Newlin, RN, MSN, ANP-BC, and Sanita Burgic, RN, MSN, AGNP-C, of the Siteman Cancer Center at the Washington University School of Medicine in St. Louis. Ms. Newlin and Ms. Burgic reviewed efficacy data and toxicity profiles of CDK4/6 inhibitors, targeted therapies like PI3K and PARP inhibitors, and antibody-drug conjugates. Emerging therapies and new classifications like HER2-low further expand options for this patient population.

TREATMENT LANDSCAPE

HR-positive, HER2-negative breast cancer represents the most common subtype, accounting for approximately 70% of breast cancer cases in the United States. Endocrine therapy has traditionally been the cornerstone of treatment; however, "Tumors can develop resistance to endocrine therapy. Therefore, we need novel treatment approaches to overcome this resistance," stated Ms. Burgic.

The treatment landscape for the disease now includes cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, PI3K inhibitors, AKT inhibitors, antibody-drug conjugates (ADCs), and PARP inhibitors.

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CDK4/6 INHIBITORS: FIRST-LINE STANDARD OF CARE

CDK4/6 inhibitors combined with endocrine therapy represent the standard first-line treatment for HR-positive, HER2-negative mBC. By inhibiting the CDK4 and CDK6 proteins that regulate cell cycle progression, these agents slow tumor growth and proliferation. Commonly used CDK4/6 inhibitors include palbociclib (Ibrance), ribociclib (Kisqali), and abemaciclib (Verzenio), each with distinct dosing regimens and toxicity profiles.

Palbociclib and ribociclib are administered on a 21-day-on/7-day-off cycle, while abemaciclib is given twice a day and dosed continuously. Hematologic effects, such as neutropenia, are associated with palbociclib and ribociclib, whereas abemaciclib is associated with gastrointestinal side effects like diarrhea. All of these agents can cause severe, life-threatening interstitial lung disease or pneumonitis in rare cases.

"When choosing a CDK4/6 inhibitor, consider factors such as dosing schedules, comorbidities, and patient adherence," said Ms. Burgic.

For example, abemaciclib penetrates the blood-brain barrier and is the only CDK4/6 inhibitor tested in patients with HR-positive brain metastases. However, if there is a small-volume bone-only disease that is largely asymptomatic, palbociclib can be considered. Ribociclib is the most studied CDK4/6 inhibitor in pre- and perimenopausal patients (MONALEESA-7). But in the case of cardiac issues, hepatic comorbidities, or polypharmacy, ribociclib should be avoided.

MOLECULAR TESTING

Once patients progress on first-line therapy, molecular testing should be performed to identify any potential actionable somatic mutations, including *ESR1, PIK3CA, AKT1, PTEN,* and *BRCA1/2*. "We do this to figure out which pathway alteration is seen and tailor individual treatment for the patient," explained Ms. Newlin.

Early and comprehensive biomarker testing is an important first step in diagnosing and treatment planning for metastatic breast cancer. Companion diagnostic tests such as FoundationOne or Guardant360 help identify actionable somatic mutations to guide personalized treatment selection.

TARGETED THERAPIES

ESR1 Mutations and Elacestrant

Most *ESR1* mutations will arise after progression on first-line therapy for mBC. Elacestrant (Orserdu) is an oral selective estrogen receptor degrader that binds to mutated ESR1 receptors, promoting degradation and inhibiting tumor growth. Data from the EMERALD trial demonstrated that elacestrant significantly improved progression-free survival (PFS) compared to standard-of-care therapies, particularly in patients with detectable *ESR1* mutations.

In clinical trials, GI toxicities (35%), increased AST and ALT (29%), and increased cholesterol (30%) and triglycerides (27%) were noted. "A lipid panel should be checked prior to starting elacestrant and then continued to be checked for dyslipidemia," noted Ms. Burgic. The patient can take it with or without food to help with the nausea, along with antiemetics if needed.

PIK3CA Mutations and PI3K Inhibitors

PIK3CA mutations, present in 40% of HR-positive, HER2-negative mBC cases, confer resistance to endocrine therapy. Alpelisib (Piqray), a PI3K-alpha inhibitor, paired with fulvestrant, has shown efficacy in patients with *PIK3CA*-mutated tumors. The SOLAR-1 trial revealed a doubling of median PFS with this combination in patients with a *PIK-3CA* driver mutation.

However, side effects such as hyperglycemia and skin rash require proactive management, such as baseline glucose monitoring and the use of antihistamines. "In my practice, I have seen severe episodes of the hyperglycemia leading to patients being admitted into the ICU. After that happened, we were more aggressive with our monitoring and checked glucose frequently," noted Ms. Newlin.

Capivasertib (Truqap), an AKT inhibitor, targets the PI3K/AKT/mTOR pathway, including alterations in *PIK3CA, AKT1,* and *PTEN*. It has a similar side effect profile, with both causing rash and diarrhea. It is also dosed differently at 400 mg orally twice daily for 4 days, followed by 3 off days.

BRCA Mutations and PARP Inhibitors

Patients with germline *BRCA1/2* mutations benefit from PARP inhibitors such as olaparib (Lynparza) or talazoparib (Talzenna). These agents

exploit defective DNA repair mechanisms in cancer cells, leading to cell death. Both drugs have demonstrated significant improvements in PFS and overall survival (OS) in clinical trials. For example, the OlympiAD trial highlighted a 3-year OS rate of 40.8% for olaparib compared to 12.8% for standard therapies.

The most common class-specific adverse events are fatigue, hematologic toxicities (cytopenia), and GI toxicities (nausea, vomiting, diarrhea). Routine monitoring includes CBCs at baseline and monthly thereafter, and also being on the lookout for symptoms of venous thromboembolic events.

Antibody-Drug Conjugates

Antibody-drug conjugates are composed of a monoclonal antibody (mAb) covalently attached to a cytotoxic drug via a chemical linker. They combine the advantages of specific targeting ability and potent killing effect of cancer cells. "In my opinion, ADCs are one of the most rapidly expanding treatment modalities in oncology," commented Ms. Newlin.

Clinical studies have shown that approximately 60% of patients previously classified as HER2-negative actually fall into the HER2-low category, defined as tumors with an IHC (immunohistochemistry) score of 1+ or 2+ without *HER2* gene amplification. This discovery expanded the potential treatment population for ADCs like trastuzumab deruxtecan (T-DXd). The DESTINY-Breast04 trial provided landmark data supporting its use, showing that T-DXd significantly reduced the risk of disease progression and improved overall survival when compared to standard chemotherapy.

The most common adverse effects of T-DXd include nausea, vomiting, diarrhea, myalgias, alopecia, and stomatitis. More severe complications include interstitial lung disease (ILD) and potential cardiotoxicity. Early detection through routine imaging and clinical monitoring is critical

"You're going to want to do physical examinations, frequent labs, and routine echocardiograms for these patients," said Ms. Newlin.

Another emerging area of research is HER2-ultralow, a category that includes tumors with faint or incomplete membrane staining (< 10% HER2 expression). This classification has fueled further investigation into whether HER2-targeted therapies, such as T-DXd, could benefit these patients.

Another ADC gaining attention is sacituzumab govitecan (Trodelvy). Originally approved for metastatic triple-negative breast cancer, it received FDA approval in February 2023 for HR-positive, HER2-negative mBC. The TROPiCS-02 study showed a statistically significant improvement in overall survival with sacituzumab govitecan.

Hematologic toxicities were seen in up to 70% of patients, with febrile neutropenia at about 5%. Gastrointestinal toxicities, particularly diarrhea, were also common, occurring in 57% of patients and leading to a black box warning.

Supportive care measures, including growth factors for neutropenia and anti-diarrheal medications, are important for management.

"We want to consider growth factors for a secondary prophylaxis for patients with neutropenia," Ms. Burgic mentioned.

EMERGING THERAPIES

In addition to ADCs, new targeted therapies continue to emerge for HR+, HER2- mBC. Inavolisib, a PI3K inhibitor, was FDA approved for use in combination with palbociclib and fulvestrant in endocrine-resistant, *PIK3CA*-mutated breast cancer. The INAVO120 trial demonstrated the efficacy of inavolisib, showing that patients treated with the inavolisib-palbociclib-fulvestrant triplet had a median progression-free survival of 15 months, compared to 7.3 months in the control arm.

Beyond inavolisib, research into next-generation estrogen receptor-targeting agents is ongoing, with multiple clinical trials investigating novel approaches such as selective estrogen receptor degraders (SERDs), selective estrogen receptor covalent antagonists (SERCAs), and proteolysis-targeting chimeras (PROTACs).

CONCLUSION

Breast cancer can develop resistance to endocrine therapy, making it essential to check for somatic mutations with each disease progression. Incorporating companion diagnostic testing into practice for patients with HR-positive, HER2-negative

metastatic breast cancer enables better treatment personalization. Targeted therapies are available for mutations in *ESR1, PIK3CA, AKT1, PTEN*, and *BRCA1/2*, and the classification of HER2-low has introduced new treatment options for HR+, HER2- mBC. Real-world studies, such as those comparing the efficacy of CDK4/6 inhibitors, are emerging and promise future insights. For further guidance, resources like the ONS Biomarker Database are valuable clinical tools.

Disclosure

Ms. Newlin has served on an advisory board for Biotheranostics, Inc., a Hologic Company. Ms. Burgic has no relevant financial relationships to disclose.