BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

Section Editor: Hope S. Rugo, MD

Sequencing Therapies: Optimal Treatment for HR+/HER2– Metastatic Breast Cancer

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H&O What are the options for first-line treatment of patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) metastatic breast cancer?

VK The typical standard of care is CDK4/6 inhibition plus endocrine therapy. The 3 CDK4/6 inhibitors that are available are palbociclib (Ibrance, Pfizer), ribociclib (Kisqali, Novartis), and abemaciclib (Verzenio, Lilly). Studies on all 3 of these agents have shown positive results on their primary endpoint of progression-free survival, and ribociclib has shown a survival benefit in this setting.

The choice of endocrine therapy depends on what endocrine therapy the patient received previously. For a patient who previously received an aromatase inhibitor—letrozole, anastrozole, or exemestane—we would use the selective estrogen receptor degrader (SERD) fulvestrant (Faslodex, AstraZeneca). For a patient who had not received a prior aromatase inhibitor or had stopped taking one more than 24 months prior to the development of metastatic disease, we would likely start with an aromatase inhibitor.

H&O What are the options for second-line treatment?

VK Second-line treatment tends to be more complicated, with the choice of therapy based on several factors. First is the question of how long the first-line therapy was effective. If a patient was on a CDK4/6 inhibitor for at least 12 months before disease progression, we consider the tumor to still be endocrine-sensitive and generally use some sort of endocrine therapy. The optimal choice of therapy depends on the molecular characteristics of the tumor, so we perform next-generation sequencing with either tumor or liquid biopsy to evaluate the tumors for mutations in *PIK3CA* and *ESR1*. If the tumor has a *PIK3CA* mutation, the best option is usually targeted therapy with the PI3K inhibitor alpelisib (Piqray, Novartis) plus endocrine therapy. If the tumor has an *ESR1* mutation, a good option is the SERD elacestrant (Orserdu, Stemline) monotherapy. If the tumor does not have either of these molecular changes, we typically use a combination of the mammalian target of rapamycin (mTOR) inhibitor everolimus and endocrine therapy.

If the duration of CDK4/6 inhibition before disease progression was less than 12 months, we consider the tumor endocrine-resistant. Our first choice in that setting is usually chemotherapy with capecitabine. An alternative to chemotherapy in this setting is an antibody-drug conjugate (ADC)—either sacituzumab govitecan (Trodelvy, Gilead), or trastuzumab deruxtecan (also known as T-DXd; Enhertu, Daiichi-Sankyo/AstraZeneca) if the tumor is HER2-low. However, if the patient has a germline *BRCA1/2* mutation, then I would favor the use of a PARP inhibitor.

H&O What are the options for third-line or later treatment?

VK As with second-line treatment, the approach to third-line and later treatment depends on how endocrine-

sensitive the tumor is at that time, plus the molecular backbone of the tumor. If the tumor has a *BRCA* mutation, a PARP inhibitor will be incorporated at some point. If the tumor does not have a *BRCA1/2* mutation and the relevant targeted agents for *PIK3CA* and *ESR1* mutations have already been used, we typically move on to chemotherapy with capecitabine. Following this, we generally use an ADC. Additional options for later-line treatment are chemotherapeutic agents, such as gemcitabine, vinorelbine, eribulin, docetaxel, and paclitaxel.

> Capivasertib was able to benefit patients regardless of the mutations their tumor had.

H&O How do you decide on the optimal treatment sequence for individual patients?

VK This is a tough question because the treatment landscape is evolving quickly. We expect US Food and Drug Administration approval of the AKT inhibitor capivasertib over the next few months. The phase 3 CAPItello-291 trial, which was published in the *New England Journal of Medicine* earlier this year, showed that the addition of capivasertib to fulvestrant improved median progression-free survival in patients with HR+/HER2– metastatic breast cancer. Patients had experienced recurrence or progression on or after endocrine therapy, with or without a CDK4/6 inhibitor. Capivasertib was able to benefit patients regardless of the mutations their tumor had.

In summary, when developing a treatment plan for a patient, my first step is to determine whether the tumor is likely to be endocrine-sensitive or endocrine-resistant. If the tumor is endocrine-sensitive, I want to give endocrine-based therapy. This will be combined with targeted therapy or a SERD if a relevant mutation is found. If no such mutation is found, I use everolimus. If the tumor is endocrine-resistant, I move on to chemotherapy or an ADC.

The choice of therapy can be difficult and is highly patient-dependent. For example, one of the potential side effects of alpelisib is hyperglycemia, so this agent is usually not the best choice for a patient who has diabetes or insulin resistance. Another factor that plays a role in decision-making is the patient's tumor burden. If a patient would normally be a candidate for endocrine therapy alone but has a large burden of disease, we may use chemotherapy because it begins to work faster than endocrine therapy. In this case, we can use a short course of chemotherapy and then switch to endocrine therapy, or we can simply stick with a full course of chemotherapy.

H&O What are the most important studies that have looked at the use of these agents?

VK So far, the most important studies that have been conducted have looked at optimal therapies rather than sequencing. For example, the MONALEESA, MONARCH, and PALOMA trials have looked at the first-line and second-line use of CDK4/6 inhibitors; the SOLAR-1 trial looked at alpelisib; and the BOLERO-2 trial looked at everolimus. The EMERALD trial looked at elacestrant in patients who had previously received a CDK4/6 inhibitor, the TROPiCS-02 trial looked at sacituzumab govitecan, and the DESTINY-Breast04 trial looked at T-DXd in patients with HER2-low breast cancer.

H&O What studies are looking specifically at the sequence of treatment?

VK Three phase 2 trials have looked specifically at sequencing after CDK4/6 inhibition. The MAINTAIN trial looked at ribociclib after progression on a CDK4/6 inhibitor, and the PACE and PALMIRA trials looked at palbociclib (Ibrance, Pfizer) after progression on a CDK4/6 inhibitor. The MAINTAIN trial was the only one of these to show positive results, leaving unclear the question of how best to treat patients with metastatic breast cancer and CDK4/6 inhibitor resistance. The phase 3 postMONARCH trial, which is evaluating the use of abemaciclib after CDK4/6 progression, should be able to definitively answer this question (NCT05169567).

H&O What changes do you expect to see in the next year or so?

VK The area was stagnant until recently, with the approval of elacestrant in early 2023 and the recent positive data with capivasertib. The good news is that we expect to see even more options soon to change the landscape further, including more oral SERDs and ADCs.

Disclosures

Dr Kaklamani has served as a speaker for Pfizer, Gilead, Genentech, Novartis, AstraZeneca, Daiichi Sankyo, and Seagen; has served as a consultant for Puma, AstraZeneca, Gilead, TerSera Therapeutics, Daiichi Sankyo, Lilly, and Menarini; and has conducted research for Eisai.

Suggested Readings

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