BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Update on CDK4/6 Inhibitors in Breast Cancer

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H&O Which breast cancer patients are eligible for treatment with a CDK4/6 inhibitor?

ST CDK4/6 inhibitors, which include palbociclib (Ibrance, Pfizer), ribociclib (Kisqali, Novartis), and abemaciclib (Verzenio, Lilly), are used for patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) breast cancer. Patients with metastatic HR+/HER2– breast cancer generally receive first-line treatment with endocrine therapy plus a CDK4/6 inhibitor. Patients with high-risk early-stage HR+/HER2– breast cancer, by contrast, generally receive 2 years of adjuvant abemaciclib with endocrine therapy.

H&O What are the side effects of these medications?

ST The side effect profiles vary somewhat among CDK4/6 inhibitors. The major side effect of palbociclib is neutropenia. Nearly two-thirds of patients who receive palbociclib develop grade 3 or 4 neutropenia, so patients who take this agent need regular monitoring of blood counts. Dose holds and modifications are sometimes needed in response to low blood counts.

The rate of neutropenia is similar with ribociclib as with palbociclib. Ribociclib can also lead to prolongation of the QT interval and elevation of liver function enzymes.

Abemaciclib is less likely than palbociclib and ribociclib to cause neutropenia, but it is more likely to cause gastrointestinal toxicity. Approximately 80% of patients receiving abemaciclib experience some level of diarrhea, but high-grade diarrhea is unusual.

Rare side effects that can occur with any of the CDK4/6 inhibitors include blood clots and interstitial lung disease.

H&O What strategies are used to manage these side effects or avoid them?

ST The best way to manage diarrhea related to abemaciclib is to tell patients in advance about the risk, advise them to have loperamide on hand, and instruct them on how to use it if symptoms develop. Patients need to inform their doctor if their diarrhea is not well controlled with loperamide because dose holds and reductions may be necessary.

For patients experiencing grade 3 or 4 neutropenia with palbociclib or ribociclib, we usually hold the drug until neutropenia levels decrease to grade 1. When we restart the drug, we often begin at a lower dose with the hope that the problem will not recur. Another important step for patients who receive ribociclib is regular electrocardiography over the first 2 months to determine whether QT prolongation is present. We also need to make sure that patients are avoiding medications that are known to interact with ribociclib or prolong QT.

H&O How do oncologists choose among CDK4/6 inhibitors?

ST Choosing which CDK4/6 inhibitor to use with endocrine therapy for first-line treatment of metastatic, HR+/HER2– breast cancer is still controversial. The most common choice at this point is ribociclib because it is the only CDK4/6 inhibitor that has been found to produce a statistically significant improvement in overall survival

(OS) in this setting. The final OS analysis of the phase 3 MONARCH 3 trial at 8 years of follow-up showed a trend toward an increase in OS with the addition of abemaciclib to aromatase inhibition, at 66.8 vs 53.7 months.[1] Although the difference was not statistically significant, a 13.1-month increase is very meaningful clinically. The PALOMA-2 trial, however, did not show an improvement in OS with palbociclib in the first-line setting (53.9 vs 51.2 months).[2] All 3 of the drugs have been shown to double progression-free survival (PFS) in this setting, however, so there is not a wrong or right answer here. We may have very good reasons to select to select one agent over another based on factors such as underlying comorbidities and concomitant medications.

In the adjuvant setting for early-stage HR+/HER2– breast cancer, abemaciclib is currently the only approved CDK4/6 inhibitor. This approval was based on data from the phase 3 monarchE trial, which showed a statistically significant improvement in invasive disease–free survival with the addition of abemaciclib to endocrine therapy.[3] Data from the phase 3 NATALEE trial showed that the addition of 3 years of adjuvant ribociclib to endocrine therapy also improved invasive disease–free survival.[4] We are currently waiting to see if the US Food and Drug Administration will approve the use of ribociclib in the setting of early-stage disease. Data from the PALLAS and PENELOPE-B studies did not support the use of adjuvant palbociclib in the early-stage disease setting.[5,6]

> Novel combinations are being tested in an effort to overcome resistance to CDK4/6 inhibition.

H&O What are the other important studies that have looked at CDK4/6 inhibitors?

ST In the metastatic setting, another important trial was the MONALEESA-7 study.[7] Patients in this trial were premenopausal and received the ovarian suppression agent goserelin in conjunction with endocrine therapy with or without ribociclib. This study showed that the PFS and OS benefits of ribociclib extended to premenopausal patients.

The phase 3 SONIA trial looked at using CDK4/6 inhibition in the first-line vs the second-line setting in metastatic disease.[8] The study was designed to show the superiority of first-line treatment, which it failed to do. Some have interpreted this to mean that first-line treatment can be endocrine monotherapy, with CDK4/6 inhibition added to endocrine therapy as second-line treatment after progression. However, the SONIA study was not designed to demonstrate noninferiority, so I do not think that it supports this approach. Furthermore, this study used palbociclib, and we do not know if the data are generalizable to the other CDK4/6 inhibitors. Although these are important data, I have not felt that the data from the SONIA trial change the fact that the standard of care is to give a CDK4/6 inhibitor upfront with endocrine therapy.

H&O What agents are being tested in combination with CDK4/6 inhibitors?

ST Many trials are looking at combination strategies. One especially interesting study that Dr Komal Jhaveri presented at the 2023 San Antonio Breast Cancer Symposium was the phase 3 INAVO120 study.[9] In this study, which enrolled 325 patients with *PIK3CA*-mutated, HR+/HER2– advanced breast cancer that had relapsed within a year of adjuvant endocrine therapy, patients were randomly assigned in a 1:1 ratio to either the phosphoinositide 3-kinase alpha (PI3Kα) inhibitor inavolisib or placebo in addition to palbociclib and fulvestrant until disease progression or toxicity. At a median follow-up of 21 months, PFS was significantly longer in the inavolisib group than in the placebo group, at 15.0 vs 7.3 months (hazard ratio, 0.43; 95% CI, 0.32-0.59; $P<.0001$). There was also a trend toward improved OS with inavolisib. This was an interesting finding because it represents the first time we have been able to safely administer a PI3K inhibitor in combination with a CDK4/6 inhibitor and endocrine therapy. In addition, the difference in PFS was striking—the use of inavolisib doubled PFS. This combination appears to be very effective in this patient population. I look forward to seeing results with newer investigational PI3K inhibitors that may have even less toxicity.

The phase 3 CAPItello-292 study, which is recruiting patients, is looking at the addition of the novel AKT inhibitor capivasertib (Truqap, AstraZeneca) to CDK4/6 inhibition and endocrine therapy (NCT04862663).

Other studies are looking at the use of an oral selective estrogen receptor degrader (SERD) instead of an aromatase inhibitor as the endocrine backbone for CDK4/6 inhibition.

H&O What other studies are looking at CDK4/6 inhibition in breast cancer?

ST The ongoing phase 3 postMONARCH study is exploring the addition of abemaciclib to fulvestrant for patients with HR+/HER2– advanced or metastatic breast

cancer following progression on a CDK4/6 inhibitor and endocrine therapy. Recent data from this study, which were presented at the 2024 ASCO Annual Meeting, revealed that the addition of abemaciclib to fulvestrant improved PFS compared with fulvestrant alone in patients who had progression on endocrine therapy and a prior CDK4/6 inhibitor. This suggests that there are some patients who can benefit from continuation of CDK4/6 inhibition beyond progression. There are many choices for treatment in the post–CDK4/6 inhibitor setting, so I think we will carefully select patients for this approach, likely selecting those patients without a PI3K pathway alteration and those with prolonged benefit to upfront CDK4/6 inhibition.

Other phase 3 trials of interest include SERENA-4 and SERENA-6. SERENA-4 is comparing camizestrant plus palbociclib vs anastrozole plus palbociclib as first-line treatment for patients with HR+/HER2– advanced or metastatic breast cancer (NCT04711252), whereas SERENA-6 is comparing camizestrant plus a CDK4/6 inhibitor vs an aromatase inhibitor plus a CDK4/6 inhibitor for patients with HR+/HER2– metastatic breast cancer with an *ESR1* mutation detected while on first-line therapy (NCT04964934).

In addition, novel combinations are being tested in an effort to overcome resistance to CDK4/6 inhibition. For example, one approach is to add CDK2 inhibition to CDK4/6 inhibition and endocrine therapy, aiming to reverse CDK4/6 inhibitor resistance.[11] Researchers are also developing novel CDK4 inhibitors that do not include CDK6 inhibition. Dr Timothy Yap presented encouraging phase 1/2a data on that agent at the 2023 American Society of Clinical Oncology Annual Meeting, with activity seen even in patients who have progressed on CDK4/6 inhibition.[12] Another benefit of CDK4 without CDK6 is fewer cytopenias.

Disclosures

Dr Tolaney has served in a consulting or advisory role to Novartis, Pfizer, Merck, Lilly, AstraZeneca, Genentech/Roche, Eisai, Sanofi, Bristol Myers Squibb, Seagen, CytomX Therapeutics, Daiichi Sankyo, Gilead, OncXerna, Zymeworks, Zentalis, Blueprint Medicines, Reveal Genomics, ARC Therapeutics, Infinity Pharmaceuticals, Sumitovant Biopharma, Umoja Biopharma, Artios Pharma, Menarini/Stemline, AADI Bioscience, Bayer, Incyte, Jazz Pharmaceuticals, Natera, Tango Therapeutics, SystImmune, eFFECTOR Therapeutics, and Hengrui; has received institutional research funding from Genentech/Roche, Merck, Exelixis, Pfizer, Lilly, Novartis, Bristol Myers Squibb, Eisai, AstraZeneca, NanoString Technologies, Gilead, Seagen, OncoPep, Daiichi Sankyo; and has received travel support from Lilly, Sanofi, Gilead, and Jazz Pharmaceuticals.

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