BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Cyclin-Dependent Kinase 4/6 Inhibition in the Treatment of Hormone Receptor–Positive Breast Cancer

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H&O Which CDK4/6 inhibitors are being used to treat advanced and metastatic HR-positive, HER2-negative breast cancer?

HR The cyclin-dependent kinase 4/6 (CDK4/6) inhibitors that are currently used to treat metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer are palbociclib (Ibrance, Pfizer), ribociclib (Kisqali, Novartis), and abemaciclib (Verzenio, Lilly). All 3 drugs are approved in combination with endocrine therapy, and abemaciclib is also approved as a single agent in heavily pretreated breast cancer.

H&O What have we learned recently regarding the role of CDK4/6 inhibitors in this type of breast cancer?

HR There have been significant recent advances in this area. Multiple trials have evaluated CDK4/6 inhibitors in combination with endocrine therapy, either an aromatase inhibitor or fulvestrant (Faslodex, AstraZeneca), and have shown at least a doubling of progression-free survival (PFS) when used in the first-line, second-line, or later-line settings. Another important finding in these trials is that the use of CDK4/6 inhibitors can delay the start of chemotherapy, which generally worsens patient quality of life compared with endocrine therapy. The use of CDK4/6 inhibitors has expanded rapidly because they are generally well tolerated in addition to being highly efficacious.

Several trials have evaluated the use of CDK4/6 inhibitors in the second-line setting in combination with fulvestrant: PALOMA-3 (Palbociclib Combined With Fulvestrant in Hormone Receptor-Positive HER2-Negative Metastatic Breast Cancer After Endocrine Failure), MONALEESA-3 (Study of Efficacy and Safety of LEE011 in Men and Postmenopausal Women With Advanced Breast Cancer), and MONARCH 2 (A Study of Abemaciclib Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer), which looked at palbociclib, ribociclib, and abemaciclib, respectively. Approximately one-third of the patients in PALOMA-3 had received prior chemotherapy for metastatic disease, vs none in the other 2 trials. Interestingly, the hazard ratios for improvement in PFS were identical across the trials, and PFS was shorter in patients who had received chemotherapy than in those who had not received chemotherapy. In other words, prior chemotherapy appeared to increase resistance to subsequent endocrine therapy, a finding that reinforced guidelines recommending sequential endocrine therapy before starting chemotherapy.

Three first-line trials have begun looking at an aromatase inhibitor backbone in postmenopausal women with HR-positive metastatic breast cancer: PALOMA-2 (A Study of Palbociclib + Letrozole vs. Letrozole for 1st Line Treatment of Postmenopausal Women With ER+/HER2-Advanced Breast Cancer), MONALEESA-2 (Study of Efficacy and Safety of LEE011 in Postmenopausal Women With Advanced Breast Cancer), and MONARCH 3 (A Study of Nonsteroidal Aromatase Inhibitors Plus Abemaciclib

in Postmenopausal Women With Breast Cancer), which is looking at palbociclib, ribociclib, and abemaciclib, respectively. Again, these studies demonstrated almost a doubling of PFS when the CDK4/6 inhibitor was added to endocrine therapy, with remarkably similar hazard ratios across trials.

Women who were premenopausal but were put into menopause with chemical ovarian suppression received a similar benefit from treatment—in this case CDK4/6 inhibition—as those who were postmenopausal.

Tolerability and dose schedule are different depending on the agent. The most common toxicity with ribociclib and palbociclib is neutropenia, without febrile neutropenia. These agents are given in a 3-weeks-on, 1-week-off schedule. Ribociclib also can cause elevated liver enzymes and is associated with a risk of a prolonged QT interval. Data have shown that the risk of a prolonged QT interval is heightened among patients receiving both ribociclib and tamoxifen, and therefore this combination is no longer given. Although the risk associated with ribociclib alone is quite small, electrocardiograms are mandated during use. The most common toxicity of abemaciclib is diarrhea, with much less frequent neutropenia, and this agent has also been associated with elevated liver enzymes and a small increase in the risk of venous thromboembolism. Abemaciclib is dosed continuously. In addition, the FDA recently warned that CDK4/6 inhibitors carry a rare risk of interstitial lung disease.

One question that remained unclear after the completion of these initial studies was the role of CDK4/6 inhibitors in premenopausal women who are rendered postmenopausal by gonadotropin-releasing hormone agonists. These patients were generally included in the second- or greater-line studies, where efficacy was similar to that in postmenopausal women. Younger patients tend to have more aggressive, less hormone-sensitive disease and are more likely to present with de novo metastatic breast cancer. Unfortunately, the first-line trials looking at CDK4/6 inhibitors excluded women who were premenopausal and taking chemical ovarian suppression agents. The American Society of Clinical Oncology (ASCO) guidelines note that patients who are premenopausal and able to use ovarian suppression should receive the same treatment as postmenopausal women. We have also anxiously been awaiting survival data from the phase 3 CDK4/6 inhibitor studies. MONALEESA-7 (Study of Efficacy and Safety in Premenopausal Women With Hormone Receptor Positive, HER2-Negative Advanced Breast Cancer) looked only at premenopausal women, and showed almost identical PFS benefit and hazard ratios compared with the postmenopausal trials. Survival data were recently presented by Dr Sara Hurvitz at the 2019 ASCO annual meeting.

H&O Could you discuss the available OS data?

HR At the 2019 ASCO meeting, we saw first-line survival data from CDK4/6 inhibitors in metastatic breast cancer, and data from a small phase 2 trial comparing endocrine therapy plus CDK4/6 inhibitors vs chemotherapy. Both trials focused on premenopausal women: MONALEESA-7, as I just mentioned, and Young-PEARL (A Study of Palbociclib With Exemestane Plus GnRH Versus Capecitabine in Premenopausal Women With HR+ MBC). MONALEESA-7 is a large, randomized phase 3 trial looking at 672 premenopausal women with metastatic breast cancer who were placed on ovarian suppression along with endocrine therapy in the first-line setting. One course of prior chemotherapy was allowed, which was necessary to address the bias of many investigators—especially outside the United States—in favor of induction treatment with chemotherapy.

Patients were randomly assigned in a 1:1 ratio to receive endocrine therapy, either an aromatase inhibitor or tamoxifen plus ovarian suppression with goserelin (Zoladex, AstraZeneca), combined with either ribociclib or a placebo. The primary endpoint was PFS. In results that were published in *Lancet Oncology* in 2018 by Tripathy and colleagues, PFS was significantly improved with the addition of ribociclib, from 13.0 to 23.8 months (hazard ratio, 0.55; 95% CI, 0.44-0.69; $P<.0001$).

As we suspected would be the case, women who were premenopausal but were put into menopause with chemical ovarian suppression received a similar benefit from treatment—in this case CDK4/6 inhibition—as those who were postmenopausal.

Only approximately 40% of these patients had received prior neoadjuvant or adjuvant endocrine therapy, and 40% had de novo metastatic disease. This is consistent with previous data suggesting that younger women are more likely than postmenopausal women to present with de novo metastatic disease. Fourteen percent had received chemotherapy for advanced disease, and approximately 57% had visceral disease.

At the second planned interim overall survival (OS) analysis, the stopping boundary was a *P* value of .01018, with at least 75% of the total 252 deaths required for the planned final OS analysis. At this analysis, OS was significantly longer in the ribociclib arm compared with placebo, with a 29% relative reduction in the risk of death (hazard ratio, 0.712 [95% CI, 0.535-0.948]), and a *P* value of .00973. Median OS was not reached in the ribociclib arm, and was 40.9 months in the placebo arm (95% CI, 37.8 to not evaluable). Two landmark analyses were performed to better understand the survival differences, given that the median had not been reached in the experimental arm. The estimated OS at 36 months was 71.9% (95% CI, 66.0-77.0) for ribociclib vs 64.9% (95% CI, 58.7-70.4) for placebo. At 42 months, the estimated OS was 70.2% (95% CI, 63.5-76.0) vs 46.0% (95% CI, 32.0-58.9), respectively.

The toxicity profile remained consistent with longer follow-up, with neutropenia being the most common finding. One of the toxicities that is unique to ribociclib among CDK4/6 inhibitors is prolongation of the QT interval, which occurred in 1.8% of patients in the ribociclib group vs 1.2% of those taking placebo. The original study reported a further increase in QT prolongation in patients taking tamoxifen, with an increase of more than 60 milliseconds from baseline in the corrected QT interval in 16% of patients receiving tamoxifen vs 7% of those receiving an aromatase inhibitor. For this reason, tamoxifen should not be given in combination with ribociclib. Most of the patients in MONALEESA-7—approximately 73% to 74%—received letrozole or anastrozole, and the hazard ratio for OS in this group was 0.699.

The study also looked at time to first-time subsequent chemotherapy, which was longer in patients receiving ribociclib. PFS2, which was defined as the time to progression from randomization to progression following the first therapy used after ribociclib or placebo, also was longer in patients who had received ribociclib than in those who had received placebo. The choice of subsequent therapies after treatment discontinuation was similar between the 2 groups; subsequent CDK4/6 inhibition was used in 19% of patients in the placebo arm and 10% of those in the ribociclib arm. These data, also shown in PALOMA-2 and other CDK4/6 inhibitor trials, are encouraging because they show that use of targeted therapy does not cause resistance to the next agent—patients still respond similarly to the next line of therapy.

These exciting data from MONALEESA-7 suggest that differences in OS may appear earlier in younger patients—who have more relatively endocrine-resistant disease than older women—when effective targeted therapy is added to endocrine therapy.

In July 2019, 2 additional trials reported OS results by press release. MONARCH 2 reported an OS benefit in postmenopausal and pre/perimenopausal women with second-line abemaciclib combined with fulvestrant, and MONALEESA-3 showed an OS benefit in postmenopausal women with first- and second-line ribociclib in a preplanned interim analysis. These data will be reported at the 2019 European Society for Medical Oncology annual meeting. Additional data from the other first-line trials will be forthcoming.

PALOMA-3 also has OS data, which Turner and colleagues published in the *New England Journal of Medicine* in 2018. The PALOMA-3 population is unique among the studies combining a CDK4/6 inhibitor with fulvestrant, because one-third of the patients had received chemotherapy for advanced disease. The difference in OS among the overall population was not statistically significant based on the prespecified *P* value threshold of .235, although there was an absolute improvement in OS of 6.9 months between palbociclib and placebo (34.9 vs 28.0 months, respectively; hazard ratio, 0.791; 95% CI, 0.626-0.999; *P*=.0246). However, among the 79% of patients classified as sensitive to prior endocrine therapy, OS was significantly better with palbociclib than with placebo (39.7 vs 29.7 months, respectively; hazard ratio, 0.721; 95% CI, 0.551-0.942; *P*=.0081). Interestingly, the hazard ratio for improved OS in PALOMA-3 was similar to that seen in MONALEESA-7, with a relative benefit of approximately 30%.

H&O What other studies have looked at the use of CDK4/6 inhibitors in premenopausal women?

HR The other important trial in premenopausal women that was presented at the 2019 ASCO meeting was the phase 2 Young-PEARL trial from Korea that I mentioned earlier. This trial was intriguing because it addressed the efficacy of chemotherapy vs endocrine therapy in young women. Park and colleagues randomly assigned 184 premenopausal women who had received prior tamoxifen to receive either palbociclib combined with ovarian suppression with leuprolide and exemestane or capecitabine given at the standard dose of 2500 mg/m^2. Enrolled patients could have received 1 prior line of chemotherapy. The primary endpoint was investigator-assessed PFS. The median age of the patients was 44 years, half had visceral disease, and between 40% to 47% of patients had 2 or more sites of metastases.

The study found that after a median follow-up of 17 months, the median PFS was 20.1 months in patients receiving endocrine therapy plus palbociclib and 14.4 months in patients receiving capecitabine (hazard ratio, 0.659; 95% CI, 0.437-0.994; *P*=.0469). The 2 groups

were similar in extent of metastatic disease and prior treatment, although more patients in the capecitabine arm had 2 or more metastatic sites. It was interesting to see that approximately 21% to 24% of patients had received prior chemotherapy for metastatic breast cancer, which reflects the bias toward giving chemotherapy first to these young women. In a subgroup analysis, the PFS benefit from palbociclib was even greater among patients who did not have visceral metastases, in those who had fewer prior lines of treatment for metastatic disease, and in those who did not receive prior chemotherapy.

This study provides further data to support the use of endocrine therapy with CDK4/6 inhibitors and ovarian suppression as first-line treatment for metastatic HR-positive breast cancer in premenopausal women. We have seen that we can improve OS with palbociclib, and that chemotherapy does not appear to improve outcomes. Data from the postmenopausal PEARL study will be presented in the near future.

H&O Is there anything you would like to add?

HR The OS data from MONALEESA-7, as well as the data from other studies described above, really solidify the role of CDK4/6 inhibitors in the first-line setting for patients with HR-positive, HER2-negative metastatic breast cancer—this is clearly a standard of care. OS has been such a difficult endpoint to achieve in HR-positive disease, but these data show us that we can see a survival benefit if we study the right population using very active agents that are well tolerated.

Disclosure

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Suggested Readings

Hurvitz SA, Im SA, Lu YS, et al. Phase III MONALEESA-7 trial of premenopausal patients with HR+/HER2– advanced breast cancer (ABC) treated with endocrine therapy ± ribociclib: overall survival (OS) results [ASCO abstract LBA10008]. *J Clin Oncol.* 2019;37(18)(suppl).

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This is part 2 of a 3-part series on the treatment of HR-positive breast cancer. Next month: early-stage HR-positive breast cancer.