Hormone Receptor–Positive, HER2-Negative Breast Cancer: Recent Advances and Best Practices

PRESENTED BY LEE SCHWARTZBERG, MD, FACP, and HEATHER GREENE, MSN, FNP, AOCNP®

Abstract

Lee Schwartzberg, MD, FACP, and Heather Greene, MSN, FNP, AOCNP®, reviewed optimal therapy for patients with hormone receptor–positive, HER2-negative breast cancer, as well as the management of adverse events associated with treatment.

Approximately 70% of patients with metastatic breast cancer have hormone receptor–positive, HER2-negative disease, and nearly 30,000 patients die from this disease each year, but there has been a marked change in treatment over the past 5 years. CDK4/6 inhibitors have transformed the approach to therapy along with the identification of relevant biomarkers such as those related to BRCA and PIK3CA gene mutations. At JADPRO Live 2019, Lee Schwartzberg, MD, FACP, and Heather Greene, MSN, FNP, AOCNP®, of West Cancer Center and Research Institute in Memphis, Tennessee, discussed the selection of optimal therapy for patients with hormone-positive, HER2-negative breast cancer in accordance with evidence-based treatment recommendations, as well as the selection of therapy based on the presence of relevant biomarkers. The clinicians also discussed the management of adverse events associated with treatment and the clinical significance of emerging data in the field.

“Molecular profiling is coming of age in breast cancer, and next-generation sequencing is now being recommended in other tumor types at the time of diagnosis,” said Dr. Schwartzberg, Medical Director of the West Cancer Center in Memphis, Chief Medical Officer for One Oncology, and Professor of Medicine at the University of Tennessee Health Science Center. “Next-generation sequencing, at some point in the journey of a hormone receptor–positive metastatic breast cancer patient, makes sense and will help drive decisions for you.”

CDK4/6 INHIBITORS

As Dr. Schwartzberg explained, CDK4/6 inhibitors, a class of drugs
that target particular enzymes called CDK4 and CDK6 have been a tremendous breakthrough in the past 5 years. Three agents have been approved by the U.S. Food & Drug Administration: palbociclib, ribociclib, and abemaciclib. All three drugs are indicated for initial endocrine-based therapy in postmenopausal women with an aromatase inhibitor (ribociclib is recommended with fulvestrant or an aromatase inhibitor) and also for disease progression following endocrine therapy with fulvestrant (Table 1).

Data from the first-line trials of CDK4/6 inhibitors with a nonsteroidal aromatase inhibitor in hormone receptor–positive, HER2-negative metastatic breast cancer demonstrated similar Kaplan-Meier curves across three separate trials, each with slightly different criteria of inclusion and exclusion (Finn et al., 2016; Goetz et al., 2017; Hortobagyi et al., 2018).

“Some differences make cross-trial comparisons difficult, but all three trials show an approximately 10-month improvement in median progression-free survival with the addition of the CDK4/6 inhibitor vs. standard therapy of nonsteroidal aromatase inhibitor in patients who are receiving their first endocrine therapy for metastatic breast cancer,” said Dr. Schwartzberg.

Moreover, said Dr. Schwartzberg, despite multiple lines of endocrine therapy and chemotherapy for these patients, updated overall survival data also showed a 30% improvement for ribociclib compared to placebo and endocrine therapy (Im et al., 2019).

“If you’re going to see this kind of impact down the line for these patients, first-line therapy with a CDK4/6 inhibitor might make sense,” said Dr. Schwartzberg, who noted that these agents offer improvement from a quality-of-life perspective, as well. “Patients with metastatic breast cancer don’t just want to live longer; they want to live a good quality of life.”

### TOXICITIES AND MANAGEMENT FOR CDK4/6 INHIBITORS

As Ms. Greene explained, CDK4/6 inhibitors are generally well tolerated, with most toxicities being hematologic and gastrointestinal. Nevertheless, there are some differences among the three approved agents. Palbociclib and ribociclib are associated with higher rates of grade 3 and 4 neutropenias, said Ms. Greene, and abemaciclib is associated with higher rates of grade 3 and 4 diarrhea. Ribociclib is also the only CDK4/6 inhibitor that has an increased risk of QTc prolongation. Finally, all three agents can cause some mild elevation in liver enzymes (Table 2).

“With abemaciclib, diarrhea typically occurs quickly,” said Ms. Greene, who noted that manufacturers initially provided samples of loperamide with starter packs of abemaciclib. “That being

### Table 1. CDK4/6 Inhibitors

| HR+/HER2– advanced or metastatic breast cancer | Palbociclib | Ribociclib | Abemaciclib |
|-----------------------------------------------|------------|------------|-------------|
| Initial endocrine-based therapy in postmenopausal women | With AI | With fulvestrant or AI | With AI |
| Initial endocrine-based therapy in pre-/perimenopausal women | – | With AI | – |
| With disease progression following endocrine therapy | With fulvestrant | With fulvestrant | With fulvestrant |
| Dose/schedule | 21 days on, 7 days off (28-day cycle) | 21 days on, 7 days off (28-day cycle) | Continuously until disease progression or unacceptable toxicity |
| Dose frequency | Once daily | Once daily | Twice daily |
| With/without food | With | With or without | With or without |

**Note.** HR = hormone receptor; HER2 = human estrogen receptor 2; AI = aromatase inhibitor. Information from Eli Lilly and Company (2019); Novartis (2020); Pfizer (2019).
said, as oncology advanced practitioners, we know how to manage diarrhea: loperamide, atropine and diphenoxylate, and the ‘BRAT’ diet. There are also dose reductions that we can consider.”

According to Ms. Greene, neutropenia associated with CDK4/6 inhibitors can also be quite profound and differs significantly from neutropenia associated with cytotoxic chemotherapy. For grade 1 and 2 neutropenia, Ms. Greene advised monitoring the patient very closely. For grade 3 and 4 neutropenia, on the other hand, there will be dose reductions, interruptions, or delays. Nevertheless, said Ms. Greene, these patients almost never need a growth factor.

Finally, palbociclib and abemaciclib recently updated their package insert to include a risk for interstitial lung disease and pneumonitis. “If you have patients coming in with worsening pulmonary symptoms, you need to pay attention to make sure that it is not pneumonitis,” Ms. Greene cautioned. “If it is, that’s a permanent discontinuation on both of these drugs” (Table 3).

**NEXT TREATMENT: ALPELISIB PLUS FULVESTRANT**

For patients with hormone receptor–positive, HER2-negative advanced breast cancer who progress on or after an aromatase inhibitor, the next option is alpelisib plus fulvestrant. As Dr. Schwartzberg reported, results of the SOLAR-1 trial showed progression-free survival in the PIK3CA-mutated cohort that was twice what it was than in the patients who received fulvestrant only (from 5.7 months to 11 months), and the number of patients with a measurable response doubled from 16% to 35%, as well (André et al., 2019).

Alpelisib was approved in combination with fulvestrant in patients with PIK3CA-mutated, hormone receptor–positive breast cancer in men or postmenopausal women following progression on endocrine therapy. According to Dr. Schwartzberg, however, clinicians still have the option for up to three rounds of endocrine therapy for these patients.

Regarding toxicities, Ms. Greene reported that the most common adverse reactions on alpelisib were diarrhea, nausea, stomatitis, fatigue, weight decrease, decreased appetite, and rash. In addition, 79% of patients on trial had hyperglycemia, which is not a toxicity clinicians are used to managing in the solid-tumor world, said Ms. Greene, who noted that clinicians must monitor fasting plasma glucose prior to starting therapy.

Diarrhea is another ongoing side effect, with 58% of patients developing some grade of diarrhea on the SOLAR-1 trial. Finally, said Ms. Green, alpelisib also carries a small risk for pneumonitis, which was reported in 1.8% of patients on trial.

**PARP INHIBITORS**

Because de novo BRCA mutations occur in metastatic breast cancer in approximately 3% to 5% of patients, a PARP inhibitor is another option for patients who are positive for the germline mutation. As Dr. Schwartzberg reported, there are two PARP inhibitors approved for germline-mutated
BRCA. Studies showed an improvement in progression-free survival of approximately 45% for both PARP inhibitors and an 18% improvement in overall survival for these heavily treated patients (Litton et al., 2018; Robson et al., 2017). According to Dr. Schwartzberg, these response rates are much higher with either talazoparib or olaparib compared to chemotherapy.

“There is a bias sometimes that chemotherapy gives us the best response rate, but that’s not true against CDK4/6 inhibitors, and it’s not true against BRCA inhibitors,” said Dr. Schwartzberg. “The biologic drugs give you better outcomes when compared head-to-head with chemotherapy, and these drugs are less toxic than chemotherapy.”

Dr. Schwartzberg underscored the NCCN Guidelines that recommend testing for germline-mutated BRCA in patients with HER2-negative metastatic breast cancer. Insurance will cover this, said Dr. Schwartzberg, and this can be done before starting chemotherapy or even endocrine therapy. If patients don’t have wild-type PIK3CA mutation or germline-mutated BRCA, they should get chemotherapy after two lines of therapy, he added. While germline BRCA mutations occur in 3% to 5% of hormone receptor–positive, HER2-negative metastatic breast cancer, somatic PIK3CA mutations occur in 30% to 40% patients with this disease.

“I would recommend giving a PARP inhibitor for germline BRCA mutation before chemothera-

**Table 3. Summary of Management of Nonhematologic Toxicities for CDK4/6 Inhibitors**

| CDK4/6 inhibitor | CTCAE grade | Dosage modifications |
|------------------|-------------|----------------------|
| Abemaciclib      | 1 or 2      | None required        |
|                  | 3 or 4      | If grade 2 persists > 7 days, withhold until resolution to baseline or grade ≤1, then resume at next lower dosage |
| Palbociclib      | 1 or 2      | None required        |
|                  | ≥ 3         | Withhold until resolution to grade ≤1 or grade ≤2 if not a safety risk for patient, then resume at next lower dosage |
| Ribociclib       | 1 or 2      | None required        |
|                  | 3           | Withhold until resolution to grade ≤1, then resume at same dosage; if grade 3 recurs, resume at next lower dosage |
|                  | 4           | Discontinue ribociclib |

*Note. CTCAE = Common Terminology Criteria for Adverse Events. Information from Eli Lilly and Company (2019); Novartis (2020); Pfizer (2019).*
Finally, said Ms. Greene, given the risk of hematologic toxicity, a complete blood count should be tested at baseline and then monthly. With worsening cytopenias, however, Ms. Greene noted that this test could be performed more frequently.

Disclosure
Ms. Greene is on the speakers bureau for Pfizer, and Dr. Schwartzberg is a consultant for Amgen, AstraZeneca, Genentech/Roche, and Pfizer.

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