

New Approaches to Endocrine Therapy for Breast Cancer

Presented by William J. Gradishar, MD

Abstract

The management of advanced hormone receptor–positive disease has evolved with the emergence of CDK4/6 inhibitors. Improvements in progression-free survival of approximately 10 months were noted in pivotal trials of palbociclib. Strong efficacy was also seen with ribociclib, which was recently approved by the FDA. In the adjuvant treatment setting of hormone receptor–positive disease, an important issue for consideration is the duration of endocrine therapy.

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New Approaches to Endocrine Therapy

Optimizing the treatment of estrogen receptor (ER)–positive breast cancer depends on overcoming resistance to endocrine agents. This tall effort has met with some success with the availability of targeted agents that inhibit cyclin-dependent kinases 4 and 6 (CDK4/6), according to William J. Gradishar, MD, Chair of the NCCN Breast Cancer Panel and Betsy Bramsen Professor of Breast Oncology, Feinberg School of Medicine, Northwestern University, and Director, Maggie Daley Center for Women’s Cancer Care, Robert H. Lurie Comprehensive Cancer Center.

Dr. Gradishar focused on the use of targeted agents as additions to endocrine therapy for metastatic breast cancer and the issue of optimal treatment duration of adjuvant endocrine therapy for early-stage breast cancer. Because these have been key topics of panel discussion for several years, the revisions to this year’s NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer are more “nuanced” than substantial, he said.

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Overcoming Resistance Is Critical

“A current focus of clinical research is determining how to overcome the resistance to endocrine therapy that ultimately occurs in metastatic ER-positive breast cancer,” Dr. Gradishar said. “We are starting to understand that specific signaling pathways may be responsible.”

The NCCN Guidelines have been incorporating “partnering strategies,” which involve the addition of targeted agents to endocrine therapy in an effort to combat resistance. To this end, the mTOR inhibitor everolimus was FDA-approved in 2012, the CDK4/6 inhibitor palbociclib entered the armamentarium in 2015, and in 2017 another CDK4/6 inhibitor, ribociclib, earned approval. Additionally, abemaciclib is in late-stage development.

Enthusiasm Builds for CDK4/6 Inhibitors

“The strategy for overcoming resistance that has gained the most attention in the past few years is the recognition that in breast cancer, as well as in other cancers, there are a variety of mitogens that can drive the cancer cell cycle. In breast cancer, one of these is cyclin D,” he said. Cyclin D interacts with cyclin D kinase, leading to a cascade of events that cause cell proliferation.

Enthusiasm for CDK4/6 inhibitors was triggered by results from the open-label, first-line, phase II PALOMA-1 trial, which demonstrated an absolute 10-month improvement in progression-free survival (PFS) when palbociclib was added to letrozole (hazard ratio [HR], 0.49; $P=0.0004$).¹ These findings were confirmed by

Gradishar

the larger phase III PALOMA-2 trial, in which the combination produced >10-month improvement in median PFS (24.8 vs 14.5 months; HR, 0.58; $P < .000001$).²

“It was remarkable that the results of PALOMA-2 were superimposable on PALOMA-1,” Dr. Gradishar commented. “Clearly, this was not just a signal but pretty definitive evidence of improvement in clinical outcomes across the board with the addition of palbociclib.”

PALOMA-3 tested palbociclib combined with fulvestrant in patients with prior aromatase inhibitor (AI) therapy, “reflecting what we may do in practice when a patient progresses,” he added. The combination doubled the duration of PFS, from 4.6 to 9.6 months.³ Together, the 3 pivotal trials with palbociclib confirmed a consistent absolute improvement in median PFS of approximately 10 months versus endocrine therapy alone (Table 1).

Ribociclib similarly extended PFS when given with letrozole in the first-line phase III MONALEE-SA-2 trial.⁴ At 18 months, PFS was 63.0% in the ribociclib plus letrozole arm versus 42.2% in those treated with letrozole alone (HR, 0.56; $P = 3.29 \times 10^{-6}$). Median PFS was not reached with the combination versus 16.4 months with letrozole.

Use of palbociclib in conjunction with either letrozole or fulvestrant for recurrent or stage IV ER-positive and HER2-negative disease is a category 1 recommendation in the NCCN Guidelines.⁵ Ribociclib was only recently approved, so it had not yet been incorporated at the time, but the panel has since included ribociclib in the 2.2017 version of the NCCN Guidelines.

A third CDK4/6 inhibitor, abemaciclib, is being evaluated in a number of ongoing trials. In the MONARCH 1 trial of single agent abemaciclib, responses were seen in 19.7% of patients who had been heavily pretreated.⁶ The drug is being combined with fulvestrant in MONARCH 2 and with anastrozole or letrozole in MONARCH 3.

Same Class, Different Drugs

The various CDK4/6 inhibitors “should not be assumed to be exactly the same—clinically, pharmacodynamically, or kinetically,” Dr. Gradishar said. “We believe these drugs are not identical, either in terms of efficacy or side effects. We should learn more about

Table 1. Consistent Clinical Benefit Across PALOMA Studies

	1003 (PALOMA-1)	1008 (PALOMA-2)	1023 (PALOMA-3)
Design	Phase II; open label	Phase III; placebo control	Phase III; placebo control
Endocrine partner	Letrozole	Letrozole	Fulvestrant
Patients in study, n	165	666	521
Efficacy (palbociclib vs control arm)			
Primary end point: PFS			
HR	0.49	0.58	0.46
Median PFS, mo	20.2 vs 10.2 (↑10 mo)	24.8 vs 14.5 (↑10.3 mo)	9.6 vs 4.6
Secondary end points, %			
ORR (ITT, measurable disease)	43 vs 33 55 vs 39	42 vs 35 55 vs 44	19 vs 9 25 vs 11
CBR (ITT)	81 vs 58	85 vs 70	67 vs 40

Abbreviations: CBR, clinical benefit response; HR, hazard ratio; ITT, intent-to-treat; ORR, overall response rate; PFS, progression-free survival. Data from Finn RS, et al. *Lancet Oncol* 2015;16:25–35; and Cristofanilli M, et al. Data from *Lancet Oncol* 2016;17:425–439.

their distinguishing features as we see more data from the pivotal trials.”

The main toxicity with palbociclib and ribociclib appears to be hematologic, whereas with abemaciclib, gastrointestinal toxicity predominates. It is necessary to monitor WBC counts in patients receiving palbociclib and ribociclib, but those who develop neutropenia “generally don’t feel the effects” and febrile neutropenia is uncommon, he indicated.

“As we move forward,” he added, clinicians can expect “the coming of the CDK4/6 wars,” and efforts by the manufacturers to make distinctions among these drugs.

Everolimus-Containing Regimen Now Follows the CDK4/6 Inhibitor

The robust activity of the CDK4/6 inhibitors has essentially relegated the mTOR inhibitor, everolimus, to a later line of therapy. “Everolimus in combination with exemestane is in the guidelines, but considered mostly after the patient has had a CDK4/6 inhibitor,” Dr. Gradishar explained.

The FDA approved everolimus in combination with exemestane based on the BOLERO-2 trial, in which median PFS was 7.8 months with everolimus plus exemestane versus 3.2 months with exemestane alone (HR, 0.45; $P < .0001$).⁷

Unanswered Questions With These Additional Agents

With both the CDK4/6 inhibitors and everolimus, there is a need to determine which patients are most likely to benefit from combination therapy and who will have an exceptional response to endocrine therapy alone. “Despite our efforts, we just don’t have this information yet,” Dr. Gradishar said. “Biomarker development is critical.”

Another challenge is to determine how best to sequence the CDK4/6 inhibitors and how to target other signaling pathways implicated in resistance. Of particular interest is the PI3K/Akt/mTOR pathway, because PI3 kinase is mutated in many patients with luminal A breast cancer. Dozens of drugs targeting this pathway are in development.

Is There a Place for Extended Endocrine Therapy in the Adjuvant Setting?

The NCCN Guidelines for Breast Cancer were updated to indicate that women who are postmenopausal at diagnosis and received an AI for 5 years “can consider an AI for an additional 5 years.”⁵ This includes women who received tamoxifen for 5 years and wish to extend endocrine therapy to 10 years’ total duration.

According to Dr. Gradishar, one can “make the case” for extended treatment based on the observation

of very late recurrences of ER-positive disease. “Even out to 20 years, you see a progressive increase in recurrence rates,” he noted. Pan et al⁸ reported that, at year 20, the risk for recurrence ranged from 14% in the lowest-risk group to 47% in the highest-risk group. “This begs the question of whether continued therapy beyond that 5 years is prudent for some patients,” Dr. Gradishar said.

Results from the ATLAS and ATOM trials suggest that extended endocrine therapy exerts a protective effect on mortality only after 10 years,⁹ and a number of trials have consistently shown a modest (3%–5%) benefit for disease-free survival but no effect on overall survival. In the recently reported NSABP B-42,¹⁰ DATA,¹¹ and IDEAL¹² studies, no statistically significant difference in disease-free survival was seen with 5 additional years of an AI after initial tamoxifen or AI therapy.

The benefits versus risks of extended adjuvant endocrine therapy must be carefully evaluated and discussed with patients in the decision-making process. Extended duration of endocrine therapy reduces risk of recurrence; however, it does not significantly prolong overall survival. “Also, with longer duration of treatment, the side effects known to us accumulate. So using longer duration of therapy for every patient is incorrect,” Dr. Gradishar concluded. “Someday, with gene profiling, we may be able to define which patients will benefit from longer durations.”

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