Based on the top-line result of this interim analysis—showing no benefit from the addition of palbociclib—we cannot recommend using palbociclib in the adjuvant setting,” said Erica L. Mayer, MD, MPH, a medical oncologist at the Dana-Farber Cancer Institute in Boston. She was referring to findings from the Phase III, multicenter, open-label, randomized PALLAS study and reported in *The Lancet Oncology* (2021; https://doi.org/10.1016/S1470-2045(20)30642-2).

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second pre-planned interim analysis of PALLAS, and told Oncology Times the investigators would continue following the patients and intend to present a final analysis when the data are mature.

While the hoped-for improvement in outcomes had not materialized, this international study (with 5,760 patients having stage II-III, histologically confirmed, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer in 21 countries) was expected to yield a vast trove of data with the potential for improving cancer treatment.

“When we designed the study, we required the collection of both tissue and blood-based samples for our biobank. And we have a very large, very comprehensive collection of correlative science samples that we’re now beginning to look at,” said Mayer.

The researchers were anticipating an “incredible amount” of information to emerge from this dataset that could provide understanding about the use of CDK4/6 inhibitors in the adjuvant setting and how to improve a range of treatments for hormone receptor-positive early breast cancer.

**Benefit in Metastatic Setting**

The PALLAS study was prompted by promising clinical benefits observed with the addition of CDK4/6 inhibitors to treatments for metastatic breast cancer.

“For the past 6 years, CDK4/6 inhibitors have played a very important role in the management of metastatic hormone receptor-positive, HER2-negative breast cancer,” noted Mayer.

Additionally, because of the strength of the three available agents (palbociclib, ribociclib, and abemaciclib) in the metastatic setting (when used in combination with endocrine therapy), efforts had been made to test these agents as a way of preventing recurrence in the adjuvant setting among patients who did not have metastatic breast cancer.

“PALLAS is a global collaborative study, co-led by the Austrian Breast & Colorectal Cancer Study Group, designed to randomize patients to receive ongoing standard adjuvant endocrine therapy with the addition of 2 years of palbociclib versus ongoing adjuvant therapy alone,” Mayer explained.

**Research Findings**

At the planned second interim analysis (after a median follow-up of 23.7 months), 170 of 2,883 patients assigned to palbociclib plus endocrine therapy and 181 of 2,877 assigned to endocrine therapy alone had invasive disease-free survival events. Three-year invasive disease-free survival was 88.2 percent for palbociclib plus endocrine therapy and 88.5 percent for endocrine therapy alone (HR: 0.93).

The independent data monitoring committee had recommended discontinuation of palbociclib because the data comparing invasive disease-free survival between groups had crossed the prespecified “futility boundary.”

The most common grade 3-4 adverse events were neutropenia—1,742 patients (61.3%) of 2,840 patients on palbociclib and endocrine therapy, compared with 11 (0.3%) of 2,903 treated with endocrine therapy alone.

There were also differences in toxicity. A total of 857 patients (30.2%) on palbociclib had leukopenia compared with three (0.1%) of controls. And 60 patients taking the study drug had fatigue (2.1%) compared with 10 (0.3%) among patients on endocrine therapy alone. Serious adverse events occurred in 351 (12.4%) of 2,840 patients on palbociclib plus endocrine therapy and 220 (7.6%) of 2,903 patients on endocrine therapy alone. There were no treatment-related deaths.

When asked about the typical risk profile of the patients enrolled, Mayer said they had capped the number of low-risk patients to 1,000.

“We were aware that this would be a diverse mix of patients, although we wanted this to reflect real-world practice as well. Looking at the data subsequently we were able to enroll a very large percentage of high-risk patients,” Mayer told Oncology Times. This was important since the sought-for benefits were more likely to be found in patients with high risk of recurrence.

The two interim analyses had been event-driven. “The second interim analysis was triggered in early 2020—it had boundaries for efficacy as well as futility. When that data was reviewed, it was determined that the arms had crossed the futility boundary,” she said.

The addition of palbociclib had not improved the primary endpoint of invasive disease-free survival compared to taking adjuvant endocrine therapy alone at the moment of the interim analysis. At that time, the patients who were still taking palbociclib were told to stop taking it.

“We do know that CDK4/6 inhibitors have a well-established toxicity profile and, in the PALLAS trial, the toxicity profile was very similar to what we see in the metastatic setting. There were no new or unexpected toxicities,” she said.

When Mayer was asked if the disappointing lack of a benefit from palbociclib was likely to be a class effect or confined to that specific agent, she said the data available from using these therapies in the metastatic setting had not demonstrated much difference between the three available agents. “There’s a remarkably similar hazard ratio across the eight presented randomized trials in the metastatic setting for the three available agents,” she noted.

When she was asked whether there might be justification in some patients for using palbociclib off-label in the adjuvant setting—perhaps because of its evident antineoplastic qualities—she was adamant about her answer—No!

“We all want the best for our patients and we want to use the best available tools. Based on the data we have from PALLAS, we cannot recommend that palbociclib is one of those tools.”

—Erica L. Mayer, MD, MPH, medical oncologist at the Dana-Farber Cancer Institute

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