

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer in Focus

Inhibition of Cyclin-Dependent Kinases 4 and 6 in Breast Cancer



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H&O What is the mechanism of action for inhibitors of cyclin-dependent kinase (CDK) 4 and 6?

EM Control of the cell cycle is an essential part of cellular growth and duplication. A well-known hallmark of cancer is loss of control of the cell cycle, which results in uncontrolled growth and metastatic spread.

A network of supportive proteins establishes control of the cell cycle and passage through the different checkpoints. The ability to pass through the G1-S checkpoint is controlled by the Rb protein, which is encoded by the retinoblastoma gene. When the Rb protein is hypophosphorylated, it acts as a brake on the G1-S cell cycle transition. Release of that brake requires phosphorylation of Rb, which is accomplished by the complex of cyclin D and CDK4. CDK6 performs approximately the same role as CDK4. Once this complex phosphorylates Rb, the brake is released, leading to progression through the cell cycle. In cancer cells, loss of control of the G1-S transition may result from a variety of different mechanisms. These can include loss or mutation of the Rb protein, amplification of cyclin D or CDK4, or loss of one of the endogenous CDK4 inhibitors, such as p16. It is hoped that inhibitors of CDK4/6 will diminish phosphorylation of Rb and subsequently reestablish control of the cell cycle.

Breast cancer often exhibits dysregulation of the G1-S cell-cycle checkpoint, given that many breast tumors, especially those that are estrogen receptor (ER)-positive, exhibit overexpression or amplification of cyclin D1 or have alterations in p16. These findings make breast cancer a particularly attractive target for CDK4/6 inhibitors.

H&O What makes these agents especially useful in ER-positive breast cancer?

EM In early preclinical work evaluating CDK4/6 inhibitors, Dr Richard Finn and colleagues exposed a broad spectrum of breast cancer cell subtypes to the CDK4/6 inhibitor palbociclib (Ibrance, Pfizer). Notably, the luminal type breast cancer cell lines, which are typically ER-positive, appeared to demonstrate the most sensitivity to CDK4/6 inhibition with palbociclib. Additionally, the combination of antiestrogen therapy with palbociclib proved synergistic. These observations provided much of the background and rationale for subsequent development of CDK4/6 inhibitors for ER-positive breast cancer.

H&O Could you please describe the palbociclib studies that have been presented or are in the recruiting stages?

EM Dr Finn first presented the results of the PALOMA-1 phase 2 trial on palbociclib at the 2012 San Antonio Breast Cancer Symposium, and subsequently published final results in *Lancet Oncology* in January 2015.

The study was an open-label trial of 165 postmenopausal women with advanced ER-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer who were randomly assigned to receive letrozole (Femara, Novartis) alone or letrozole plus palbociclib. After a median follow-up of 28 to 30 months, the median progression-free survival was 10.2 months in the letrozole group and 20.2 months in the palbociclib plus letrozole group. There was no evidence of improvement in overall survival.

Neutropenia was the most commonly observed toxicity. Grade 3 or 4 neutropenia was more common in the patients who received palbociclib (54%) than in those who did not (1%), but very few people had to stop therapy for this reason—only 13% of patients taking palbociclib discontinued because of adverse events. Other nonhematologic toxicities seen with palbociclib included gastrointestinal toxicity, which was usually fairly mild; fatigue; and alopecia in rare cases.

Based on the presented data, the US Food and Drug Administration (FDA) granted accelerated approval to palbociclib in February 2015. The agent is indicated for use in postmenopausal patients with advanced ER-positive, HER2-negative breast cancer, to be used in combination with letrozole as part of first-line endocrine therapy.

Multiple ongoing trials are evaluating palbociclib in advanced breast cancer. The PALOMA-2 study is a phase 3 trial with a similar design as PALOMA-1, but is accruing a larger number of patients (NCT01740427). It is hoped that PALOMA-2 will confirm the results that were seen in PALOMA-1.

PALOMA-3 is a phase 3 study for patients with pretreated metastatic ER-positive, HER2-negative breast cancer (NCT01942135). Patients are randomly assigned to the endocrine agent fulvestrant (Faslodex, AstraZeneca) alone or in combination with palbociclib.

H&O How can the lack of improvement in overall survival with palbociclib be explained?

EM Demonstrating an overall survival benefit in metastatic ER-positive breast cancer trials is challenging, and has been a complex topic in the development of agents for this category of breast cancer. As for PALOMA-1, this was a small randomized phase 2 trial that was not statistically designed to be able to determine whether an overall survival benefit is present with this drug. The ability to define whether an overall survival benefit is present typically requires a large trial with extended follow-up. Therefore, it would be appropriate to wait for results from PALOMA-2, which is the larger randomized phase 3 study, for a more definitive readout on both progression-free survival and overall survival endpoints.

H&O What other palbociclib studies are ongoing?

EM There is also another randomized phase 3 study called PEARL that is randomly assigning patients with metastatic ER-positive breast cancer and prior exposure to endocrine therapies to either the aromatase inhibitor exemestane in combination with palbociclib, or the chemotherapy agent capecitabine alone (NCT02028507).

In the adjuvant setting, the phase 3 PENELOPE-B study (NCT01864746) is for patients who have residual

disease in the breast or lymph nodes after neoadjuvant chemotherapy and surgery. Approximately 800 patients with ER-positive, HER2-negative disease will be randomly assigned to receive either standard adjuvant endocrine therapy or endocrine therapy with palbociclib.

In the preoperative setting, there are a variety of trials being conducted in patients who have been diagnosed with ER-positive breast cancer. These trials are looking at combinations of palbociclib and a variety of endocrine therapies before surgery.

Additional studies are being planned to investigate palbociclib in patients with advanced HER2-positive disease, and as adjuvant therapy in patients with ER-positive disease.

H&O Could you describe your own research in this area?

EM At Dana-Farber, we are leading a phase 2, single-arm pilot study that is looking at the feasibility and tolerability of 2 years of palbociclib in combination with adjuvant endocrine therapy (NCT02040857). This is a single-arm trial in which all of the patients receive adjuvant endocrine therapy as prescribed by their provider, and palbociclib is added to the standard medication. Given that this trial is focused on feasibility, the primary endpoint is the treatment discontinuation rate at 2 years. We are also carefully monitoring toxicity and side effects as well as adherence to oral therapy as we follow these patients for the planned 2 years. We hope that both this study and PENELOPE-B will generate information that will inform the design of a larger adjuvant study looking at palbociclib with endocrine therapy.

H&O Could you discuss the trials being conducted with the investigational CDK4/6 inhibitors abemaciclib and ribociclib?

EM Lilly's abemaciclib (LY2835219) and Novartis' ribociclib (LEE011) both are actively in development. Phase 1 trials have been completed with abemaciclib, and the agent is now in phase 2 and 3 studies of patients with ER-positive, HER2-negative breast cancer.

Abemaciclib has some distinct features that set it apart from other CDK4/6 inhibitors. First of all, preclinical work in animal models suggested that the drug could cross into the brain. This characteristic may be relevant in the treatment of patients with brain metastases, and suggests a rationale to study the activity of abemaciclib in this patient population. The drug also has activity as monotherapy, and a phase 1 study of abemaciclib monotherapy has highlighted a somewhat higher rate of gastrointestinal toxicity—including nausea, vomiting, and diarrhea—than that observed with palbociclib.

A second-line study called MONARCH 1 is evaluating abemaciclib monotherapy for patients whose disease has progressed despite previous chemotherapy (NCT02102490). MONARCH 2 is looking at patients who are receiving fulvestrant with or without abemaciclib (NCT02107703), and MONARCH 3 is looking at abemaciclib as first-line treatment for women taking an aromatase inhibitor (NCT02246621). Overall, the development program for abemaciclib is similar to that of palbociclib, although there do appear to be some differences between the agents.

A similar development program is in place for ribociclib, with the MONALEESA trials. MONALEESA-2 is a phase 3 trial in the first-line metastatic setting that randomizes postmenopausal breast cancer patients to letrozole alone or letrozole with ribociclib (NCT01958021). Ribociclib appears to have somewhat less hematologic and gastrointestinal toxicity than palbociclib or abemaciclib, although those are the primary toxicities for this drug class.

Provocative preclinical work has been performed using ribociclib in novel combinations with other drugs. Work from my colleague Dr Sadhna Vora at Massachusetts General Hospital has suggested that inhibitors of both CDK4/6 and phosphoinositide 3-kinase (PI3K) may have a synergistic relationship in the treatment of tumors with *PIK3CA* mutations. This observation, in addition to the known synergy between CDK4/6 inhibitors and endocrine therapy, supports the exploration of “triplet” therapy for metastatic ER-positive breast cancer. Clinical trials evaluating the combination of ribociclib, the PI3K inhibitor BYL-719, and endocrine therapy are ongoing (NCT01872260).

H&O Could you talk more about the toxicity and side effect profiles of CDK4/6 inhibitors?

EM These are agents that cause a fair amount of neutropenia. Although we have not seen any strong signals of infectious complications, this observation is from trials that include patients who are carefully selected and monitored. In a real-world setting, it is possible that the risk of infectious complications or other issues related to the hematologic side effects of these medications might increase. We need to be attentive about monitoring our patients and evaluating them for toxicities.

As we continue to use and study these agents, we are going to learn more about the side effect profiles and the subtle or not-so-subtle differences among these 3 agents. I also think that the experience of receiving these drugs in the adjuvant setting may be different than receiving these drugs in the metastatic setting. As these drugs make

their way into the adjuvant setting, it will be important to carefully describe and evaluate the toxicity profiles in patients who are being treated in a curative fashion, and who may have received adjuvant chemotherapy recently.

H&O How many women stand to benefit from the use of CDK4/6 inhibitors?

EM Approximately two-thirds of breast cancers, including metastatic breast cancer, fall into the ER-positive, HER2-negative subset. As a result, a fairly substantial number of patients with metastatic breast cancer may benefit from the addition of palbociclib to their treatment in the first-line setting. Women with pretreated metastatic breast cancer may be eligible for a clinical trial using a CDK4/6 agent.

H&O What else would you like to say about these new agents?

EM We have seen great developments in the management of HER2-positive breast cancer over the past several years, with the introduction of at least 2 new agents. There also has been a tremendous amount of research trying to unlock the secrets of triple-negative breast cancer. Recent advances in the treatment of ER-positive, HER2-negative breast cancer have been more limited, particularly after the FDA revoked approval of bevacizumab (Avastin, Genentech) in 2011. So it is very exciting to see a new drug enter the treatment arena, particularly one that has performed well in trials so far and appears to have a fairly manageable side effect profile.

A caution is that the approval from the FDA was based on a relatively small randomized phase 2 study. As palbociclib enters the clinic, we cannot forget that we need more data to confirm that these drugs are safe and provide a benefit for our patients. We also need to know more about the strengths and weaknesses of each of these 3 agents. With this further knowledge, we hope to develop a better sense of the role of CDK4/6 inhibitors in the management of breast cancer

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