BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

Section Editor: Hope S. Rugo, MD

Phosphoinositide 3-Kinase Inhibition in the Treatment of Hormone Receptor–Positive Breast Cancer

Hope S. Rugo, MD
Professor of Medicine
Director of Breast Oncology and Clinical Trials Education
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California

H&O Which patients are eligible for treatment with alpelisib?

HR One of the major advances this year in treating hormone receptor (HR)-positive breast cancer has been the US Food and Drug Administration (FDA) approval of alpelisib (Piqray, Novartis) in May. Alpelisib is an alfa-specific phosphoinositide 3-kinase (PI3K) inhibitor that was approved for use in combination with fulvestrant (Faslodex, AstraZeneca) in patients with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer that tests positive for the *PIK3CA* mutation. Patients may be men or postmenopausal women whose disease has progressed on endocrine therapy. Testing for mutations in *PIK3CA* can be done using tumor tissue or blood.

Approximately 40% of patients with HR-positive breast cancer harbor the *PIK3CA* mutation, which leads to relative resistance to endocrine therapy. This mutation also leads to estrogen-independent growth of HR-positive breast cancer through hyperactivation of the PI3K pathway.

H&O What have been the historical barriers to development of agents targeting the PIK3CA pathway?

HR We knew from preclinical studies that we could inhibit the growth of *PIK3CA*-mutated cancers with PI3K inhibitors. These agents tend to produce off-target toxicities, however. The first wave of clinical trials evaluated pan-PI3K inhibitors, generally in combination with endocrine therapy. These studies demonstrated minimal or no benefit from the addition of the PI3K inhibitors, and produced significant toxicity that made adherence difficult.

Later studies looked at a more-restricted PI3K inhibitor called taselisib that has alfa and delta activity. Although taselisib produced less toxicity than pan-PI3K inhibitors did, the toxicity was still high enough and the benefit in progression-free survival (PFS) modest enough that the drug was not developed further. Still, these trials showed us that the subset of patients with *PIK3CA* mutations seemed to have the greatest chance of benefit from the PI3K inhibitor. In addition, the earlier trials also showed that finding *PIK3CA* mutations in blood using cell-free DNA technology could potentially predict response.

H&O Could you talk about the study that was the basis for approval of alpelisib?

HR Alpelisib was approved based on the results of the phase 3 SOLAR-1 trial (Study Assessing the Efficacy and Safety of Alpelisib Plus Fulvestrant in Men and Postmenopausal Women With Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor Treatment), which was published in the *New England Journal of Medicine* in 2019. In that trial, 572 patients whose cancers had progressed on prior treatment with aromatase inhibitors were randomly assigned to receive fulvestrant plus either placebo or alpelisib. Patients were stratified before randomization by *PIK3CA* mutation status.

The primary endpoint was investigator-assessed PFS in the *PIK3CA*-mutant group. We found that the

addition of alpelisib to fulvestrant resulted in a significant improvement in PFS in this subgroup, increasing from 5.7 months in the placebo arm to 11.0 months in the alpelisib arm (hazard ratio, 0.65; *P*=.00065) by local assessment, and from 3.7 to 11.1 months (hazard ratio, 0.48) in a central blinded review that was conducted in 50% of patients. In patients with measurable disease and *PIK3CA*-mutated cancer, the overall response was markedly better in the alpelisib group than in the placebo group, at 35.7% vs 16.2%, respectively.

> It is encouraging that so far, prior exposure to a CDK4/6 inhibitor does not appear to increase toxicity.

In subset analysis, the benefit of alpelisib appeared to be independent of line of therapy. The trial enrolled patients who developed progressive disease that occurred during or after first-line treatment with an aromatase inhibitor or within a year after treatment with an adjuvant aromatase inhibitor. (Before an amendment, the trial also enrolled patients with progressive disease that occurred more than a year after treatment with an adjuvant aromatase inhibitor.) Patients who received fulvestrant as second-line therapy had a hazard ratio of 0.61 with alpelisib, and PFS increased from 3.7 to 10.9 months. Those who were treated in the first-line metastatic setting had a hazard ratio of 0.71, with PFS increasing from 6.8 to 11 months. Alpelisib provided a similar degree of benefit in PFS regardless of the subtype of *PIK3CA* mutation.

The secondary endpoint for this trial is overall survival. Although we do not yet have enough data on overall survival, the first interim analysis (which Dr Dejan Juric presented at the San Antonio Breast Cancer Symposium in 2018) demonstrated a median overall survival of 26.9 months in the placebo group and not reached in the alpelisib group. We had only reached 52% of the planned events, however, so the hazard ratio was 0.73 and the *P* value was .06. We need more events to know whether this trial will show a survival benefit with alpelisib.

H&O What is the relationship between PI3K inhibitors and CDK4/6 inhibitors?

HR Because SOLAR-1 began enrolling patients before cyclin-dependent kinase 4/6 (CDK4/6) inhibitors were in common use, very few patients—only 5.3% to 6.9%—received a CDK4/6 inhibitor before alpelisib. As a result, this trial did not provide information on how prior CDK4/6 inhibition would impact subsequent therapy with alpelisib.

In response, the BYLieve trial (Study Assessing the Efficacy and Safety of Alpelisib Plus Fulvestrant or Letrozole, Based on Prior Endocrine Therapy, in Patients With *PIK3CA* Mutation With Advanced Breast Cancer Who Have Progressed on or After Prior Treatments) is designed to evaluate the effectiveness of alpelisib in patients who have previously received CDK4/6 inhibitors. Patients receive either fulvestrant or letrozole as their endocrine therapy, depending on their immediate prior therapy, and could have progressed on that hormone therapy as long as it is not the last treatment they received. BYLieve is a nonrandomized phase 2 trial. At the 2019 annual meeting of the American Society of Clinical Oncology, we presented early data from the first cohort of patients with at least 16 weeks of follow-up. One hundred patients had enrolled, and 55 patients had at least 6 months of follow-up: 33 in the fulvestrant arm and 22 in the letrozole arm. The clinical benefit rate was 33.3% for those on fulvestrant and 36.4% for those on letrozole. Toxicity was similar to that seen in SOLAR-1, with no new adverse event signals. It is encouraging that so far, prior exposure to a CDK4/6 inhibitor does not appear to increase toxicity, and that efficacy has been maintained in a population of patients with known *PIK3CA* mutations. The study is ongoing, and more data will be available in 2020.

H&O What are the side effects of alpelisib?

HR PI3K inhibitors have class-specific toxicities that vary depending on the isoform inhibited. Alpelisib is an alfa-specific PI3K inhibitor, and the primary toxicities in clinical trials have included hyperglycemia, diarrhea, and rash. In the *PIK3CA*-mutated cohort in SOLAR-1, hyperglycemia was seen in 65% of patients treated with alpelisib vs 8.8% of patients receiving placebo, with grade 3/4 hyperglycemia seen in 36.7% of patients on alpelisib. Diarrhea was seen in 54.4% of patients taking alpelisib and 11.1% of patients taking placebo, with grade 3 diarrhea seen in 7.7% of patients taking alpelisib. All-grade rash was seen in 39.6% of patients taking alpelisib compared with 6.4% of patients taking placebo, and grade 3 rash was seen in 13% of patients taking alpelisib. Other low-grade toxicities included weight loss, anorexia, and stomatitis. In SOLAR-1, 6.3% of patients discontinued alpelisib for hyperglycemia and 3.2% discontinued for rash.

We have learned that we need to screen patients for hyperglycemia with fasting glucose and hemoglobin A_{1C} levels before starting alpelisib. Patients with borderline

glucose control at baseline appear to be at higher risk for clinically relevant elevations in glucose during alpelisib therapy. Hyperglycemia should be treated aggressively, initially with metformin. If hyperglycemia persists, we recommend comanagement with an endocrinologist specializing in diabetes. A low-carbohydrate diet also may be helpful, and this approach is currently under evaluation. Because we used a proactive approach to detecting and treating hyperglycemia in BYLieve, the rate of discontinuation owing to hyperglycemia was lower than it had been in SOLAR-1.

Given that *PIK3CA* mutations can be acquired with disease progression, we generally recommend that testing of tumor tissue be done on the most recently obtained tumor sample.

Diarrhea should be managed with antidiarrheal therapy, and then dose reduction and delay for persistent symptoms. Rash is an area of interest, given that SOLAR-1 found that patients who were taking antihistamines had a reduced rate of rash. My approach is to use nonsedating antihistamines prophylactically. I start antihistamines the day before starting alpelisib and continue for at least the first month of treatment. We also double the dose if the patient develops a rash—usually to twice a day compared with once a day. This approach has had a nice effect, virtually eliminating rash as a problematic toxicity with alpelisib.

Better management and education will make use of alpelisib much easier for patients, and fewer issues with toxicity will occur. Clearly we need more direction in management as use of alpelisib becomes more widespread.

H&O What is the best way to determine which patients are candidates for alpelisib?

HR When we learned that alpelisib was effective only in patients with a *PIK3CA* mutation, it raised the question of the best way to assess for that mutation. Was tissue biopsy required, or could we simply do a blood test and use cell-free tumor DNA? The FDA approved the use of alpelisib based on the results of SOLAR-1, which used a companion diagnostic called the Therascreen PIK3CA RGQ PCR Kit (Qiagen) that is able to detect the *PIK3CA* mutation in either tissue or blood. The Therascreen test was approved in conjunction with alpelisib.

Updated data regarding use of cell-free tumor DNA to evaluate *PIK3CA* mutations in patients enrolled in SOLAR-1 were presented at the San Antonio Breast Cancer Symposium in December 2018. The benefit of alpelisib was similar in patients whose mutation was detected in blood compared with those whose mutation was detected by tissue biopsy. In patients whose mutation was detected in blood, the median PFS increased from 3.7 to 10.9 months (for a hazard ratio of 0.55) with the addition of alpelisib to fulvestrant. These encouraging results were similar to those seen in the overall trial population. This analysis also showed that mutations in cell-free tumor DNA were found slightly more often in plasma than in blood, which is why the FDA approval specifies that the mutation can be detected by blood testing. This is the first drug associated with a companion diagnostic that can detect the gene mutation in the blood, which is really exciting.

In cases where blood testing is negative for *PIK3CA* mutations, the FDA specifies that tissue testing should be done because this will occasionally reveal an undetected mutation. One decision that arises is which tumor sample to choose for testing. Given that *PIK3CA* mutations can be acquired with disease progression, we generally recommend that testing of tumor tissue be done on the most recently obtained tumor sample, and if at all possible, a sample that was obtained in the metastatic setting. Of course, testing blood eliminates this issue.

H&O What other PI3K inhibitors are in clinical trials for breast cancer?

HR Alpelisib is being studied in HER2-positive and triple-negative breast cancer in several trials. In addition, 2 other PIK3CA-targeted agents are in clinical trials. GDC-0077 is a potent, alfa-specific oral PIK3CA inhibitor that is under evaluation in a multiarm trial in patients with *PIK3CA*-mutated, HR-positive metastatic breast cancer (NCT03006172). GDC-0077 will be tested alone, in combination with palbociclib (Ibrance, Pfizer)/letrozole or letrozole alone, in combination with palbociclib/fulvestrant or fulvestrant alone, and with palbociclib, fulvestrant, and metformin. Copanlisib (Aliqopa, Bayer) is an intravenous alfa- and delta-specific PI3K inhibitor approved for the treatment of lymphoma that is being tested in metastatic HR-positive breast cancer in combination with fulvestrant or letrozole and palbociclib (NCT03128619), as well as in HER2-positive advanced breast cancer (NCT02705859).

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

HR It is very exciting to have another marker in breast cancer that can help direct the use of effective therapy. Our challenges moving forward are understanding the optimal setting and combinations for alpelisib, and improving toxicity management.

Disclosure

Dr Rugo has received research support for clinical trials at the University of California from Pfizer, Merck, Novartis, Lilly, Genentech, OBI, Odonate, Daiichi Sankyo, Eisai, Seattle Genetics, MacroGenics, and Immunomedics. She has received travel support for educational meetings from Daiichi Sankyo, Mylan, Pfizer, Amgen, Merck, AstraZeneca, Macrogenics, and Puma.

Suggested Readings

André F, Ciruelos E, Rubovszky G; SOLAR-1 Study Group. Alpelisib for *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940.

Juric D, Ciruelos E, Rubovszky G, et al. Alpelisib + fulvestrant for advanced breast cancer: subgroup analyses from the phase III SOLAR-1 trial [SABCS abstract GS3-08]. *Cancer Res*. 2018;78(4)(suppl).

Juric D, Loibl S, Andre F, et al. Alpelisib (ALP) with fulvestrant (FUL) in patients (pts) with *PIK3CA*-mutated hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (ABC): primary or secondary resistance to prior endocrine therapy (ET) in the SOLAR-1 trial [ASCO abstract 1038]. *J Clin Oncol*. 2019;37(suppl).

Rugo HR, Bianchi GV, Chia SK, et al. BYLieve: a phase II study of alpelisib (ALP) with fulvestrant (FUL) or letrozole (LET) for treatment of *PIK3CA* mutant, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (aBC) progressing on/after cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy [ASCO abstract TPS1107]. *J Clin Oncol*. 2018;36(suppl).

Rugo HS, Borrego MR, Chia SK, et al. Alpelisib (ALP) + endocrine therapy (ET) in patients (pts) with *PIK3CA*-mutated hormone receptor-positive (HR+), human epidermal growth factor-2-negative (HER2-) advanced breast cancer (ABC): first interim BYLieve study results [ASCO abstract 1040]. *J Clin Oncol*. 2019;37(suppl).

This is part 1 of a 3-part series on the treatment of HR-positive breast cancer. Next month: CDK4/6 inhibitors in HR-positive breast cancer.