Section Editor: Beth Eaby-Sandy

# Alpelisib: A Novel Therapy for Patients With *PIK3CA*-Mutated Metastatic Breast Cancer

TORI WILHOIT, PharmD, JEANNIE M. PATRICK, PharmD, BCOP, and MEGAN B. MAY, PharmD, BCOP

From Baptist Health Lexington, Lexington, Kentucky

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Megan B. May, PharmD, BCOP
1700 Nicholasville Road, Lexington, KY 40503
E-mail: megan.may@bhsi.com

https://doi.org/10.6004/jadpro.2020.11.7.9



**Abstract**

In the United States, 1 in 8 women will be diagnosed with invasive breast cancer in her lifetime. Breast cancer death rates are higher for women in the United States than any other cancer, followed by lung cancer (National Cancer Institute, 2019). More than 70% of breast cancers are hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative, and of those patients, 40% have driver mutations in the gene phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) resulting in damaged phosphatidylinositol 3-kinase (PI3K) and uncontrolled cell growth (Mollon et al., 2018; Setiawan et al., 2009). These patients are initially treated with endocrine therapy, but resistance remains an issue. Inhibition of PI3K is a promising new approach to overcome resistance to endocrine therapy in breast cancer. Previous trials of PI3K inhibitors (pictilisib [GDC-0941], buparlisib [BMK120], and taselisib [GDC-0032]) in breast cancer have shown little efficacy secondary to toxicities due to their nonselectivity to PI3K subunits. Alpelisib is a selective inhibitor of PI3K for patients with HR-positive, HER2-negative, *PIK3CA*-mutated breast cancer who have progressed on endocrine therapy. This drug review will discuss the pharmacology of alpelisib, current data supporting its place in therapy, management of adverse events, and the clinical implications for advanced practitioners treating patients with HR-positive, HER2-negative breast cancer.

Breast cancer is the most common cancer diagnosed in women in the United States. 1 in 8 women will develop invasive breast cancer in her lifetime. It is expected that in 2019, over 268,000 women will be diagnosed with invasive breast cancer in the United States alone (National Cancer Institute, 2019). More than 70% of breast cancers are hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative, and of those pa-

J Adv Pract Oncol 2020;11(7):768–775

tients, nearly 40% have driver mutations in the enzyme phosphatidylinositol 3-kinase (PI3K), resulting in uncontrolled cell growth (Mollon et al., 2018; Setiawan et al., 2009).

Patients with locally advanced or metastatic HR-positive breast cancer are initially treated with hormonal therapy to block estrogen in the body. Endocrine therapy, with or without the use of a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, is the standard treatment for patients with HR-positive, HER2-negative advanced or metastatic breast cancer (National Comprehensive Cancer Network [NCCN], 2019). However, acquired resistance to endocrine-based therapy remains a challenge. This is why inhibition of PI3K is a promising approach to overcome resistance to endocrine therapy in breast cancer.

In 2016, pictilisib, a nonselective PI3K inhibitor, along with fulvestrant was tested in a two-part, randomized, double-blind, placebo-controlled, phase II study (FERGIE II). This trial found that there was no difference in progression-free survival (PFS) between the treatment group (6.6 months; 95% confidence interval [CI] = 3.9–9.8) and placebo (5.1 months; 95% CI = 3.6–7.3). The authors concluded that the dosing of pictilisib was limited due to toxicities associated with pan-inhibition of PI3K, thereby rendering the ceiling dose of pictilisib ineffective (Krop et al., 2016). It was hypothesized that this could be overcome with a more selective agent for targeting the catalytic subunit of PI3K pathway (Krop et al., 2016). Other nonselective PI3K inhibitors, including buparlisib and taselisib (NCT01589861, NCT02389842, NCT02340221; National Library of Medicine, 2019) had similar limitations due to toxicities in clinical trials.

Studies began on alpelisib (Piqray), a PI3K inhibitor that selectively targets protein p110-alpha isoform. Alpelisib selectively binds 50 times more efficiently to the alpha isoform than other isoforms found in this pathway. In May 2019, the U.S. Food & Drug Administration (FDA) approved alpelisib in combination with fulvestrant for the treatment of HR-positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer that has progressed on hormonal therapy (Novartis Pharmaceuticals Corporation, 2019).

## PHARMACOLOGY AND MECHANISM OF ACTION

Alpelisib is a novel therapy approved for HR-positive, HER2-negative breast cancer in patients who have progressed on first-line hormonal therapies. Alpelisib's novel mechanism selectively inhibits the PI3K pathway, a driver mutation found in HR-positive, HER2-negative breast cancers. Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors in many tumor types (Katso et al., 2011). In this pathway, the *PIK3CA* gene provides instructions for making the p110-alpha protein, which is one subunit of the enzyme PI3K. The p110-alpha protein is the catalytic subunit performing the action of PI3K. PI3K phosphorylates certain signaling molecules, which triggers a series of additional reactions that transmit signals within cells. PI3K signaling is important for many cell activities, including cell growth and proliferation, movement of cells, production of new proteins, transport of materials within cells, and cell survival. Mutations in this gene have been found in many types of cancers, including breast, ovarian, lung, brain, and stomach. Previously, it has been shown that the p110-alpha isoform is the subunit that is essential for angiogenesis (Graupera et al., 2008). When the *PIK3CA* mutation is involved with cancer, it manifests as a somatic mutation, meaning the mutation is acquired during a person's lifetime and is only present in the cells that give rise to cancer. Cancer-associated PI3K genetic changes result in a driver mutation causing uncontrolled proliferation of cells leading to the development of cancer. Resistance to a variety of therapeutic interventions, including chemotherapy, hormonal therapy, and anti-HER2 therapies can also be linked to constitutive activation of the PI3K pathway (McCubrey et al., 2006).

The PI3K pathway is frequently altered in HR-positive breast cancer. Gain-of-function mutations in PI3K have been observed in approximately 40% of HR-positive breast cancer patients (Mollon et al., 2018). Inactivation of the tumor suppressor gene phosphatase and tensin homolog (PTEN) via loss-of-function mutations, gene deletion, or transcriptional downregulation also leads to PI3K pathway activation and has been reported in approximately 13% of HR-positive breast cancer

patients (Cancer Genome Atlas Network, 2012). Patients with locally advanced or metastatic HR-positive breast cancer are initially treated with hormonal therapy to block estrogen in the body. Endocrine therapy, with or without the use of a CDK4/6 inhibitor, is the standard treatment for patients with HR-positive, HER2-negative advanced breast cancer (NCCN, 2019). However, acquired resistance to endocrine-based therapy remains a challenge. This is why inhibition of the PI3K pathway has sparked interest in the oncology field. In patients with PI3K mutations that have previously been treated on endocrine therapy, this estrogen deprivation leads to hyperactivation of the PI3K/mTOR pathway, which in turn induces an increase in cell proliferation and survival. Treatment with PI3K inhibitors in the absence of estrogen can inhibit proliferation of these estrogen-deprived cell lines and lends support to the concept of using a combination of a PI3K inhibitor with endocrine therapy in breast cancer. Currently, fulvestrant is the agent of choice with PI3K pathway inhibitors, in part because this has been the main agent studied with alpelisib, and because it is the only agent to downregulate estrogen receptors leading to decreased estrogen response in cancer cells.

## CLINICAL TRIALS

The phase III clinical trial SOLAR-1 was the landmark trial that led to FDA approval for alpelisib in 2019. This was a randomized, phase III trial to evaluate the efficacy and safety of alpelisib plus fulvestrant in patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer who had received endocrine therapy. This study found that treatment with alpelisib and fulvestrant prolonged PFS among this patient population (André et al., 2019). Trial participants were separated into two cohorts based on *PIK3CA* mutation status. Within each cohort, patients were randomly assigned in a 1:1 ratio. Treatment groups received oral alpelisib at a dose of 300 mg regardless of body weight with continuous daily dosing plus fulvestrant administered as a 500-mg intramuscular injection on days 1 and 15 of cycle 1 and on day 1 of subsequent 28-day cycles. The comparator arm received placebo plus fulvestrant. Patients received treatment until disease progression, unacceptable level of toxic effects, withdrawal of consent, loss to follow-up, or death. The primary endpoint of this trial was PFS, as assessed by trial investigators in the cohort with *PIK3CA* mutations. Key secondary endpoints were overall survival in the *PIK3CA*-mutated cancer cohort, PFS and overall survival in the cohort without *PIK3CA*-mutated cancer, PFS according to the level of circulating tumor DNA, overall response, clinical benefit (defined as a complete or partial response or as stable disease for more than 6 months), and safety.

Between July 26, 2015, and July 21, 2017, a total of 1,244 patients were tested for PI3K mutation status, and interpretable results were available for 94.3% of patients (André et al., 2019). A total of 572 patients underwent randomization. Of these, 341 patients had *PIK3CA*-mutated disease. 169 patients were randomized to treatment with alpelisib plus fulvestrant and 172 were assigned to receive placebo plus fulvestrant. The remaining 231 patients did not carry a *PIK3CA* mutation, and of these, 115 received alpelisib plus fulvestrant and 116 received placebo plus fulvestrant. Treatment groups were well balanced, with a median age of 63 years. In the cohort with *PIK3CA* mutations, the median duration of exposure to alpelisib was 5.5 months (interquartile range [IQR], 1.6–13.0 months) compared with the placebo at 4.6 months (IQR, 1.9–4.6 months). The most common reason for discontinuation of therapy within this cohort was progression of disease (55% in the alpelisib and fulvestrant group and 68% in the placebo and fulvestrant group).

The efficacy of alpelisib plus fulvestrant in this cohort showed a median PFS of 11.0 months compared with 5.7 months in the placebo arm. At 12 months, the percentage of patients with PFS was 46.3% in the alpelisib and fulvestrant group and 32.9% in the placebo and fulvestrant group. Overall response among all the patients in this trial was greater in the alpelisib and fulvestrant group than in the placebo and fulvestrant group, as was clinical benefit and tumor response. When comparing these results to the cohort without *PIK3CA* mutations, a clear improvement of PFS for *PIK-3CA*-mutated patients can be seen. Median PFS was 7.4 months (95% CI = 5.4–9.3) in the alpelisib and fulvestrant group and 5.6 months (95% CI = 3.9–9.1) in the placebo and fulvestrant group. At 12

months, PFS was 28.4% in the alpelisib and fulvestrant group and 22.2% in the placebo and fulvestrant group.

These results showed nearly double the improvement in patient outcomes with the addition of alpelisib in *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer. These findings validate the use of PI3K as an important treatment target in this population of patients who have progressed on endocrine therapy.

## DOSING AND ADMINISTRATION

Dosing for alpelisib plus fulvestrant was based on an open-label, single-arm, phase Ib study of alpelisib plus fulvestrant that was conducted at 10 centers in five countries (Juric et al., 2019). The trial enrolled 87 postmenopausal women with *PIK3CA*-mutated or *PIK3CA* wild-type estrogen receptor (ER)-positive advanced breast cancer whose cancer progressed during or after antiestrogen therapy. During this study, the maximum tolerated dose, safety, and activity of alpelisib were assessed. Doses of alpelisib were initiated at 300 mg plus a fixed dose of fulvestrant at 500 mg in the dose escalation phase of the trial. During the trial, 87 women received escalating once-daily doses of alpelisib (300 mg, n = 9; 350 mg, n = 8; 400 mg, n = 70).

The maximum tolerated dose of alpelisib when combined with fulvestrant was 400 mg once daily, and researchers of this trial recommended the phase II dose to be 300 mg once daily (Juric et al., 2019). The dosing for alpelisib in the package insert is 300 mg once daily with food (Novartis Pharmaceuticals Corporation, 2019). When given with alpelisib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15, and 29, and once monthly thereafter. Albelisib comes in three tablet strengths: 200 mg, 150 mg, and 50 mg. These tablets are currently supplied to patients in color-coded blister packs to create the combined daily doses of 300 mg, 250 mg, and 200 mg. Patients taking 300 mg and 250 mg should be counseled that they will be taking two tablets once daily to achieve their prescribed dose instead of one tablet.

## ADVERSE EVENTS

In the SOLAR-1 trial, the safety profile showed the most common adverse events observed were hyperglycemia, gastrointestinal toxic effects, fatigue, and rash, most of which were reversible (André et al., 2019). The trial reported that 4.6% of patients permanently discontinued both alpelisib and fulvestrant, and 21% permanently discontinued alpelisib alone due to adverse events. The most frequent adverse events leading to treatment discontinuation of alpelisib in > 2% patients receiving alpelisib plus fulvestrant were hyperglycemia (6%), rash (4.2%), diarrhea (2.8%), and fatigue (2.5%). Other reported serious adverse events included acute kidney injury (2.5%), abdominal pain (2.1%), and anemia (2.1%; Novartis Pharmaceuticals Corporation, 2019).

Hyperglycemia, including ketogenesis, has been reported (any-grade hyperglycemia, 63.7%; grade 3, 32.7%; grade 4, 3.9%; ketoacidosis, 0.4%). Patients with type 1 or uncontrolled type 2 diabetes (hemoglobin A1c > 6.5%) were excluded from the clinical trial. Before initiating treatment with alpelisib, providers should test fasting plasma glucose (FBG), hemoglobin A1c, and optimize blood glucose. In grade ≥ 2 (FPG 160–250 mg/dL) hyperglycemia, the median time to first occurrence of hyperglycemia was 15 days (range, 5 to 517 days; Novartis Pharmaceuticals Corporation, 2019). After initiating treatment, blood glucose should be monitored periodically. Antihyperglycemic medications can be initiated as clinically indicated to improve blood glucose levels. When monitoring blood glucose, alpelisib dosage is not reduced until grade 2 (FPG > 160 to 250 mg/dL) is reached (Table 1). First-line recommendations for antidiabetic therapy are metformin or insulin sensitizers; short-acting insulin may also be used in the short term until hyperglycemia resolves.

Other reported adverse events were dermatologic reactions, including grade 2 and 3 skin rashes with a median time to onset of 12 days (Novartis Pharmaceuticals Corporation, 2019). During treatment, rash occurred in 54% (n = 284) of patients receiving alpelisib, with 4.2% being a rash that caused discontinuation of alpelisib. A rash caused by alpelisib may manifest in many forms, including maculopapular, macular, generalized rash, and a pruritic rash. It is not recommended to start alpelisib in patients with a history of Stevens-Johnson Syndrome, erythema multiforme, or toxic epidermal necrolysis. Antihistamine treatment

**Table 1. Alpelisib Dose Adjustments for Hyperglycemia**

| Grade | Fasting blood glucose | Dosage adjustments |
|---|---|---|
| 1 | FPG > ULN to 160 mg/dL | • No alpelisib dosage adjustment required; initiate or intensify antidiabetic therapy |
| 2 | FPG > 160 to 250 mg/dL | • No alpelisib dosage adjustment required; initiate or intensify antidiabetic therapy as described below<br>• If FPG does not decrease to ≤ 160 mg/dL within 21 days with appropriate antidiabetic therapy, reduce alpelisib dose by one dose level and continue to follow FPG-specific recommendations |
| 3 | FPG > 250 to 500 mg/dL | • Interrupt alpelisib therapy<br>• Initiate or intensify antidiabetic therapy; may consider additional antidiabetic medications for 1 to 2 days until hyperglycemia improves<br>• Administer IV hydration and consider appropriate intervention for electrolyte, ketoacidosis, hyperosmolar disturbances<br>• If FPG decreases to ≤ 160 mg/dL within 3 to 5 days with appropriate antidiabetic therapy, resume alpelisib with the dose reduced by one dose level<br>• If FPG does not decrease to ≤ 160 mg/dL within 3 to 5 days with appropriate antidiabetic therapy, consultation with a clinician with expertise in hyperglycemia management is recommended. Permanently discontinue alpelisib if FPG does not decrease to ≤ 160 mg/dL within 21 days following appropriate antidiabetic therapy |
| 4 | FPG > 500 mg/dL | • Interrupt alpelisib therapy<br>• Initiate or intensify antidiabetic therapy<br>• Administer IV hydration and consider appropriate intervention for electrolyte, ketoacidosis, hyperosmolar disturbances<br>• Recheck FPG within 24 hours (and as clinically indicated). If FPG decreases to ≤ 500 mg/dL, follow FPG value-specific recommendations for grade 3 hyperglycemia<br>• Permanently discontinue alpelisib if FPG is confirmed at > 500 mg/dL |

*Note*. Metformin recommendations: Initiate metformin at 500 mg once daily; based on tolerance, may increase to 500 mg twice daily (with meals), and further increase to 500 mg with breakfast and 1,000 mg with dinner, followed by a further increase to 1,000 mg twice daily (with meals). FBG = fasting blood glucose; ULN = upper limit of normal. Information from Novartis Pharmaceuticals Corporation (2019).

prior to rash onset may decrease the severity of rash based on SOLAR-1. A subgroup analysis of 86 patients received prophylactic antihistamine prior to rash onset. Of the patients treated prophylactically, 27% experienced a rash and 3.5% experienced a rash leading to discontinuation of alpelisib (Novartis Pharmaceuticals Corporation, 2019). For rashes grade 2 and lower, it is recommended to initiate a topical corticosteroid and consider adding an oral antihistamine or low-dose systemic corticosteroid. Dose adjustments for rash do not occur until grade 3, at which point therapy would be interrupted, and topical or systemic corticosteroids would be initiated or intensified. Once rash is improved, the patient may resume the previous alpelisib dosing regimen if this was the first occurrence of rash. If this was the second occurrence, then they should be moved to the next lower dose level (Table 2). For grade 4 rashes, alpelisib should be discontinued.

The SOLAR-1 trial also showed that 58% of patients receiving alpelisib experienced diarrhea during treatment. Grade 3 diarrhea occurred in 7% (n = 19) of patients. Among patients with grade 2 or 3 diarrhea, the median time to onset was 46 days. If a patient experiences grade 2 or lower diarrhea, practitioners may initiate appropriate medical therapy and interrupt alpelisib dosing until recovery and then resume at the same dose. Dose modifications will need to be made with the occurrence of grade 3 or greater diarrhea. Dosing should first be interrupted until the patient's recovery to grade 1 or less, then alpelisib can be resumed at the next lower dose level (Table 2).

Other adverse reactions can manifest as abnormalities in laboratory values, including elevations in creatinine, gamma-glutamyl transferase, alanine aminotransferase, lipase, and prolonged activated partial thromboplastin time and decreases in lymphocyte count, calcium, hemoglobin, and weight. These abnormal laboratory values were reported in > 10% of SOLAR-1 trial patients. A standard dose reduction guide can be found in Table 2.

## PLACE IN THERAPY

The approval of alpelisib marks the first time a treatment plan can be developed for a patient's genomic profile specifically with the PIK3CA biomarker. Patients who are determined to have locally advanced or metastatic HR-positive and HER2-negative breast cancer should be assessed for *PIK3CA* mutation with a tumor or liquid biopsy (NCCN, 2019). If the patient does have *PIK3CA*-mutated disease, alpelisib should be considered as part of the treatment plan once patients progress on initial endocrine based therapy with or without a CDK4/6 inhibitor. Alpelisib is a first-in-class treatment option for *PIK3CA*-mutated breast cancers according to the NCCN Guidelines for breast cancer (version 3.2019). The use of alpelisib in combination with fulvestrant is an NCCN Category 1 recommendation for recurrent or stage IV breast cancer in HR-positive, HER2-negative, and postmenopausal patients with *PIK3CA*-mutated tumors (NCCN, 2019). The FDA approval of alpelisib supports its use in combination with fulvestrant in postmenopausal women, as well as men, with HR-positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer (Novartis Pharmaceuticals Corporation, 2019). Eligible patients should have already progressed on or after an endocrine-based regimen. The *PIK3CA* mutation must be detected by an FDA-approved test.

Future considerations include incorporating alpelisib upfront in combination with endocrine therapy and a CDK4/6 inhibitor (NCCN, 2019). The pivotal trial, SOLAR-1, included patients who were pretreated with CDK4/6 inhibitors, which is the current standard of care in patients with locally advanced or metastatic HR-positive, HER2-negative breast cancer (André et al., 2019). There are clinical trials evaluating the use of alpelisib in combination with other hormonal agents in addition to fulvestrant (NCT03386162, NCT03056755).

## IMPLICATIONS FOR THE ADVANCED PRACTITIONER

*PIK3CA* is the most commonly mutated gene in HR-positive, HER2-negative breast cancer, occurring in approximately 40% of patients (Cancer Genome Atlas Network 2012; Sabine et al., 2014). Alpelisib is a first-in-class treatment option targeting the PIK3CA pathway, approved for the treatment of HR-positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer following progression on or after endocrine therapy. This new indication is based on the results of the SOLAR-1 trial, in which patients with identified genetic mutations in the *PIK3CA* gene experienced improved PFS following the use of alpelisib in combination fulvestrant compared with fulvestrant monotherapy (André et al., 2019). Advanced practitioners will be required to implement genomic testing and assess *PIK3CA* mutation status as a standard of care for patients with HR-positive, HER2-negative breast cancer, as the presence of a *PIK3CA* mutation may assist in clinicians' treatment selection. According to a study by Arthur and colleagues (2014), *PIK3CA* mutation status does not change in the majority of patients with breast cancer. Thus, testing for *PIK3CA* mutation status may occur at any time point following the diagnosis of advanced or metastatic HR-positive, HER2-negative breast cancer.

Concurrently with the approval of alpelisib, the therascreen PIK3CA companion diagnostic test (CDT) from Qiagen was also approved by the FDA. The therascreen PIK3CA CDT is a real-time qualitative polymerase chain reaction test for the detection of 11 mutations of the *PIK3CA* gene in both tumor tissue or plasma specimens. The ability to obtain results from plasma specimens with this CDT offers a noninvasive approach in the initial assessment of *PIK3CA* mutational status. In the SOLAR-1 trial, of the 317 patients with *PIK3CA*

**Table 2. Dose Reduction Guidelines for Adverse Reactions**

| Alpelisib dose level | Dose and schedule | Number and strength of tablets |
|---|---|---|
| Starting dose | 300 mg once daily | Two 150-mg tablets |
| First dose reduction | 250 mg once daily | One 200-mg tablet and one 50-mg tablet |
| Second dose reduction | 200 mg once daily | One 200-mg tablet |
| If further dose reduction below 200 mg once daily is required, discontinue alpelisib. | | |

*Note.* Information from Novartis Pharmaceuticals Corporation (2019).

mutations confirmed in tumor tissue who had viable plasma samples available for testing, 177 patients (56%) had *PIK3CA* mutations identified in plasma specimen, and 140 patients (44%) did not have *PIK3CA* mutations identified in plasma specimen (Novartis Pharmaceuticals Corporation, 2019). Thus, if no mutation is detected in a plasma specimen, the advanced practitioner should recommend tumor tissue to be tested given the potential for false negatives with plasma samples.

Appropriate patients may receive one free *PIK3CA* mutation test through the *PIK3CA* Mutation Companion Diagnostic (CDx) Testing Program, which can be accessed at https://neogenomics.com/sites/default/files/Form/PIK3CA-Test-Request-Form.pdf

The most common grade 3/4 adverse events associated with alpelisib in clinical trials include hyperglycemia and rash (André et al., 2019). Hyperglycemia is an on-target effect of PI3K inhibition linked to the role of PI3K/mTOR pathway signaling in glucose homeostasis (Engelman, Luo, & Cantley, 2006). Patients should receive counseling on the possibility of developing hyperglycemia and the need to monitor blood glucose periodically during therapy. Patients should be advised to contact their health-care provider immediately if they experience signs or symptoms of hyperglycemia, such as polydipsia, polyuria, and polyphagia. Baseline FPG and hemoglobin A1c should be obtained prior to the start of treatment. Patients with type 1 diabetes and uncontrolled type 2 diabetes were excluded from clinical trials. Blood glucose should be optimized and controlled in all patients prior to the initiation of treatment. For patients who develop hyperglycemia while on alpelisib, antidiabetic medications may be used for management.

It is recommended to monitor blood glucose while on alpelisib at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated. Hemoglobin A1c should be monitored every 3 months and as clinically indicated. If a patient experiences hyperglycemia after initiating treatment with alpelisib, blood glucose and/or FPG should be monitored as clinically indicated, and at least twice weekly until blood glucose or FPG decreases to normal levels. During treatment with antidiabetic medication, monitoring of blood glucose or FPG should be continued at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. It is recommended to consider consulting a health-care practitioner with expertise in treating hyperglycemia and counseling patients on lifestyle changes.

The median time to first onset of grade 2 or 3 rash is 12 days. A subgroup of 86 patients in the SOLAR-1 trial received prophylaxis including antihistamines prior to the onset of rash. In these patients, rash was reported less frequently than in the overall population for all grades of rash (Novartis Pharmaceuticals Corporation, 2019). Given the results of the subgroup analysis, advanced practitioners should consider the recommendation of prophylactic antihistamines for patients initiating treatment with alpelisib.

## SUMMARY

Alpelisib is a novel approach to overcome resistance to endocrine therapy in HR-positive, HER2-positive breast cancer by inhibiting the enzyme PI3K. Patients with identified genetic mutations in the *PIK3CA* gene experienced improved PFS following the use of alpelisib in combination with fulvestrant. These patients can be identified by the therascreen PIK3CA CDT in real time to expedite treatment initiation. When prescribing alpelisib, practitioners must be mindful of unique adverse drug events such as hyperglycemia and be prepared to treat appropriately. Clinical trials are ongoing for alpelisib in combination with other endocrine therapies, for use as maintenance therapy in HR-positive, HER2-negative, *PIK3CA*-mutated breast cancers, and for use in other cancer types.

### Disclosure

The authors have no conflicts of interest to disclose.

### References

André, F., Ciruelos, E., Rubovszky, G., Campone, M., Loibl, S., Rugo, H. S.,...Juric, D. (2019). Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *New England Journal of Medicine, 380*(20), 1929–1940. https://doi.org/10.1056/NEJMoa1813904

Arthur, L. M., Turnbull, A. K., Renshaw, L., Keys, J., Thomas, J. S.,...Dixon, J. M. (2014). Changes in PIK3CA mutation status are not associated with recurrence, metastatic disease or progression in endocrine-treated breast cancer. *Breast Cancer Research and Treatment, 147*(1), 211–219.

https://doi.org/10.1007/s10549-014-3080-x

Cancer Genome Atlas Network. (2012). Comprehensive molecular portraits of human breast tumors. *Nature, 490*(7418), 61–70. https://doi.org/10.1038/nature11412

Engelman, J. A., Luo, J., & Cantley, L. C. (2006). The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nature Reviews Genetics, 7*(8), 606–619. https://doi.org/10.1038/nrg1879

Graupera, M., Guillermet-Guibert, J., Foukas, L. C., Phng, L.-K., Cain, R. J., Salpekar, A.,...Vanhaesebroeck, B. (2008). Angiogenesis selectively requires the p110alpha isoform of PI3K to control endothelial cell migration. *Nature, 453*(7195), 662–666. https://doi.org/10.1038/nature06892

Juric, D., Janku, F., Rodón, J., Burris, H. A., Mayer, I. A., Schuler, M.,...Rugo, H. S. (2019). Alpelisib plus fulvestrant in *PIK3CA*-altered and *PIK3CA*-wild-type estrogen receptor-positive advanced breast cancer: A phase 1b clinical trial. *JAMA Oncology, 5*(2), e184475. https://doi.org/10.1001/jamaoncol.2018.4475

Katso, R., Okkenhaug, K., Ahmadi, K., White, S., Timms, J., & Waterfield, M. D. (2011). Cellular function of phosphoinositide 3- kinases: Implications for development, homeostasis, and cancer. *Annual Review of Cell and Developmental Biology, 17*(2011), 615–675. https://doi.org/10.1146/annurev.cellbio.17.1.615

Krop, I. E., Mayer, I. A., Ganju, V., Dickler, M., Johnston, S., Morales, S.,...Schimd, P. (2016). Pictilisib for oestrogen receptor-positive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): A randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncology, 17*(6), 811–821. https://doi.org/10.1016/S1470-2045(16)00106-6

Lexicomp. (2019). Alpelisib. Retrieved from http://online.lexi.com

McCubrey, J. A., Steelman, L. S., Abrams, S. L., Lee, J. T., Chang, F., Bertrand, F. E.,...Libra, M. (2006). Roles of the RAF/MEK/ERK and PI3K/PTEN/AKT pathways in malignant transformation and drug resistance. *Advances in Enzyme Regulation, 46*(1), 249–279. https://doi.org/10.1016/j.advenzreg.2006.01.004

Mollon, L., Aguilar, A., Anderson, E., Dean, J., Davis, L., Warholak, T.,...Tang, D. (2018). A systematic literature review of the prevalence of *PIK3CA* mutations and mutation hotspots in HR+/HER2-metastatic breast cancer. *Cancer Research, 78*(13 suppl). https://doi.org/10.1158/1538-7445.AM2018-1207

National Cancer Institute. (2019). SEER Cancer Stat Facts: U.S. Breast Cancer Statistics. Retrieved from https://seer.cancer.gov/statfacts/html/breast.html

National Comprehensive Cancer Network. (2019). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (Version 3.2019). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Library of Medicine. (2019). ClinicalTrials.gov. Retrieved from https://clinicaltrials.gov/ct2/results?cond=breast+cancer&term=alpelisib&cntry=&state=&city=&dist=

Novartis Pharmaceuticals Corporation. (2019). Piqray (alpelisib) package insert. Retrieved from https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/piqray.pdf

Sabine, V., Crozier, C., Brookes, C., Drake, C., Piper, T., van de Velde, C. J. H.,...Bartlett, J. M. S. (2014). Mutational analysis of PI3K/AKT signaling pathway in tamoxifen exemestane adjuvant multinational pathology study. *Journal of Clinical Oncology, 32*(27), 2951–2958. https://doi.org/10.1200/JCO.2013.53.8272

Setiawan, V. W., Monroe, K. R., Wilkens, L. R., Kolonel, L. N., Pike, M. C., & Henderson, B. E. (2009). Breast cancer risk factors defined by estrogen and progesterone receptor status: The multiethnic cohort study. *American Journal of Epidemiology, 169*(10), 1251–1259. https://doi.org/10.1093/aje/kwp036