Management of toxicity to isoform $\alpha$-specific PI3K inhibitors

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Alterations in the phosphoinositide 3-kinase (PI3K)/AKT pathway are frequently found in cancer and are especially common in breast cancer, where it is estimated that 70% of tumors have some type of genetic alteration that could lead to pathway hyperactivation. A variety of PI3K pathway inhibitors have been developed in an attempt to target this pathway and improve cancer control. One of the challenges in treating patients with PI3K/AKT pathway inhibitors is the associated toxicity from on-target and off-target effects. Such side-effects are common, but reversible, and include hyperglycemia, rash, stomatitis, diarrhea, nausea, and fatigue. As a result, dose reductions, treatment delays, and treatment discontinuation are frequently reported. This impairs not only patients' quality of life but also treatment efficacy. Most side-effects are reversible with drug interruption, since these drugs typically have a short half-life and are manageable with early intervention. An interdisciplinary approach with proactive management of patients receiving PI3K pathway inhibitors should include comprehensive education of patients about the range of toxicities, frequent monitoring, early toxicity recognition, active intervention, as well as prophylactic strategies.

Key words: PI3K inhibitors, toxicities, supportive care

Introduction

The phosphoinositide 3-kinase (PI3K)/AKT pathway plays a central role in cell physiology by transmitting diverse extracellular stimuli through a signaling cascade. These stimuli control many cellular functions such as proliferation, growth, survival, motility, and metabolism [1]. Phosphoinositide 3-kinases (PI3Ks) are a family of three different classes of lipid kinases. Class I PI3K is the most studied and is clearly implicated in oncogenic transformation and tumor growth [1, 2]. Class I PI3Ks are heterodimers consisting of a p85 regulatory subunit and a p110 catalytic subunit (p110\textsubscript{a}, p110\textsubscript{b}, p110\textsubscript{c}, or p110\textsubscript{d}). AKT is a serine/threonine kinase with 3 isoforms (AKT1, AKT2, and AKT3). It is a downstream target of the PI3K pathway and plays an important role in cell survival, proliferation, growth, and glucose metabolism [3]. Mammalian target of rapamycin (mTOR) is a serine/threonine kinase composed by two distinct protein complexes: a rapamycin and nutrient-sensitive multiprotein complex (mTORC1) and a growth factor-sensitive but nutrient insensitive and rapamycin-insensitive complex (mTORC2). mTORC1 responds to amino acids, stress, oxygen, energy, and growth factors and promotes cell growth and cell cycle progression. mTORC2 responds to growth factors and regulates cell survival and metabolism, as well as the cytoskeleton [4]. mTORC1 and mTORC2 are downstream and upstream from AKT, respectively [5]. Alterations in the PI3K/AKT pathway are frequently found in cancers and are especially common in breast cancer, where it is estimated that up to 70% of tumors have some type of genetic alteration that could render the pathway hyperactivated [6].

Classes of PI3K pathway inhibitors

Because of the PI3K/AKT pathway’s role in oncogenesis, a variety of PI3K pathway inhibitors have been developed, attempting to improve cancer control. These inhibitors can be divided into several classes, and despite sharing a common on-target toxicity profile, some have unique toxicities (Table 1):

- The mTORC1 inhibitors, including sirolimus and its analogs (temsirolimus, everolimus, and deforolimus), are allosteric
irreversible inhibitors of mTORC1 kinase [7]; the mTORC1 or 2 inhibitors block both mTORC1-dependent phosphorylation of s6K1 and mTORC2-dependent phosphorylation of Akt [7]. Everolimus is Food and Drug Administration (FDA) and European Medicines Agency approved in combination with endocrine therapy for treatment of Aromatase inhibitor-resistant metastatic breast cancer, based on the increase in progression-free survival (PFS) seen in the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) phase III trial [8].

- **Pan-PI3K inhibitors**: these agents block all class IA PI3Ks. They are represented by several small-molecule drugs including buparlisib (BKM120), pilaralisib (XL147), and pictilisib (GDC-0941) [9]. Due to the poorly tolerated toxicity profile associated with buparlisib, which included liver toxicity and mood disorders, and overall limited efficacy of pan-PI3K inhibitors in breast cancer [10–12], clinical development of these agents was arrested [13].

- **Pan-Akt inhibitors**: target the three isoforms of Akt (Akt1, 2, and 3). Because of the structural similarities among the three isoforms, isoform-specific inhibitors are proving challenging to develop. Two of these inhibitors, capivasertib (AZD5363) and ipatasertib (GDC0068) are currently in phase III clinical trials (NCT03997123; NCT03337724) for breast cancer in combination with chemotherapy [5].

- **Dual PI3K and mTOR inhibitors** target the p110 subunit of PI3K and mTOR. This dual targeting might increase clinical efficacy because of more complete inhibition of the PI3K/Akt/mTOR signaling pathway at multiple signaling points and loss of negative feedback loops. Some dual PI3K and mTOR inhibitors that have been in clinical development are SF1126, dactolisib (BEZ235), voxalisib (XL765), and GSK1059615 [5]. These agents have a much broader activity profile and could be used to treat a variety of tumors with a wide range of genetic abnormalities. It is also not surprising that their broad activity leads to more unforeseen clinically relevant side-effects and toxicity, making their development more challenging [7].

- **Isoform-specific PI3K inhibitors**: these agents selectively or predominantly inhibit the PI3K p110α [e.g. alpelisib (BYL719) and taselisib (GDC-0032)] or p110β, p110γ, or p110δ (e.g. idelalisib) isoforms [9]. The initial rationale for the development of isozyme-specific antagonists was to allow higher doses of anti-p110α, anti-p110β, and anti-p110δ agents to be delivered at maximal target-inhibitory doses, potentially avoiding some of the side-effects caused by pan-PI3K inhibitors. PI3Kα is the isoform predominantly mutated in cancer, and studies have shown that selective inactivation of this isoform is enough to block PI3K/akt signaling in response to different growth factors stimuli [14–16]. Results from phase IB trials [16, 17] of alpelisib with endocrine therapy and a global neoadjuvant phase II, randomized, double-blind, placebo-controlled trial of the PI3Kα inhibitor alpelisib combined with letrozole for the pre-operative treatment of postmenopausal women with ER+/HER2− breast cancer (NCT03997123; NCT03337724) for breast cancer in combination with chemotherapy [5].

### Table 1. Classes of PI3K pathway inhibitors

| Class                        | Drug target(s)                  | Drugs                   | Selected toxicities by class                      |
|------------------------------|---------------------------------|-------------------------|--------------------------------------------------|
| Pan-PI3K inhibitors          | All class IA PI3Ks              | Buparlisib (BKM120)     | Hyperglycemia                                    |
|                              |                                 | Pilaralisib (XL147)     | Rash                                             |
|                              |                                 | Pictilisib (GDC-0941)   | Neutropenia                                      |
|                              |                                 |                         | Neuropsychiatric effects                         |
|                              |                                 |                         | (confusion, depression, anxiety)                  |
|                              |                                 |                         | Hepatotoxicity                                    |
|                              |                                 |                         | Diarrhea                                         |
| Isoform-specific PI3K inhibitors | PI3K p110α isoform            | Alpelisib (BYL719)     | Hyperglycemia                                    |
|                              |                                 | Taselisib (GDC-0032)   | Rash                                             |
|                              |                                 |                         | Neutropenia                                      |
|                              |                                 |                         | Neuropsychiatric effects                         |
|                              |                                 |                         | (confusion, depression, anxiety)                  |
|                              |                                 |                         | Hepatotoxicity                                    |
|                              |                                 |                         | Diarrhea                                         |
|                              |                                 |                         | Pneumonitis                                      |
|                              |                                 |                         | Myelosuppression                                  |
|                              |                                 |                         | Hyperglycemia                                    |
|                              |                                 |                         | Rash                                             |
|                              |                                 |                         | Diarrhea                                         |
|                              |                                 |                         | Pneumonitis                                      |
|                              |                                 |                         | Hyperglycemia                                    |
|                              |                                 |                         | Hypertension                                      |
|                              |                                 |                         | Immunosuppression                                 |
| Pan-Akt inhibitors           | Three isoforms of Akt (Akt1, 2, and 3) | Capivasertib (AZD5363) | Rash                                             |
|                              |                                 | Ipatasertib (GDC0068)  | Hyperglycemia                                    |
|                              |                                 | MK2006                  |                                                  |
| mTORC1 (mamalian target of rapamycin complex 1) inhibitors | mTORC1 kinase | Everolimus | Stomatitis                                       |
|                              |                                 | Temsirolimus            |                                                  |
|                              |                                 | Deforolimus             |                                                  |
| Dual PI3K and mTOR inhibitors | p110 subunit of PI3K and mTOR   | Dactolisib (BEZ235)     | Stomatitis                                       |
|                              |                                 | Voxalisib (XL765)       |                                                  |
|                              |                                 | SF1126                  |                                                  |
|                              |                                 | GSK1059615              |                                                  |
by PI3K/AKT [24]. Activation of AKT stimulates glucose import glycolytic enzymes are under dominant transcriptional control sensitivity and glucose metabolism. The genes encoding most are multiple different ways by which these agents affect insulin pathway inhibitors and is considered an on-target effect. There Hyperglycemia is one of the most common side-effects with PI3K inhibitors is the associated toxicity from on-target and off-target effects. Some of the most common side-effects seen with PI3K pathway inhibitors are hyperglycemia, dermatitis and rash, stomatitis, diarrhea, nausea, and fatigue [20–22]. Other much less common side-effects may include elevation of pancreatic enzymes, elevation of liver enzymes, immune dysfunction/lymphocytopenia, and pneumonitis [19, 20, 23]. Pancreatic enzyme or liver enzyme elevation rarely lead to the development of pancreatitis or liver failure. Other uncommon toxicities associated with PI3K/AKT inhibitors include elevation of transaminases (autoimmune hepatitis, seen more frequently with pan-PI3K inhibitors or combination therapies), opportunistic infections (seen more frequently with mTOR inhibitors), hypertension, and central nervous system symptoms (seen with buparlisib, a pan-PI3K inhibitor) [10, 11, 20, 23]. Since these drugs have a short half-life, most side-effects are reversible with drug interruption and are manageable with early intervention (Table 2). In this review, we will review the most common side-effects seen with PI3K isoform-specific inhibitor, alpelisib, and discuss strategies for managing these toxicities.

**Hyperglycemia**

Hyperglycemia is one of the most common side-effects with PI3K pathway inhibitors and is considered an on-target effect. There are multiple different ways by which these agents affect insulin sensitivity and glucose metabolism. The genes encoding most glycolytic enzymes are under dominant transcriptional control by PI3K/AKT [24]. Activation of AKT stimulates glucose import and metabolism. Thus, drug-induced inhibition of PI3K/AKT reduces glucose uptake resulting in increased secretion of insulin levels [25], which, in turn, can activate insulin/insulin-like growth factor 1-receptor in tumor cells and provide a survival mechanism to tumor cells [26]. Glucose transport capacity, glycogen synthesis, and glycolysis have been reported to be reduced by approximately 40% [6]. Hyperglycemia is also in part a result of the induction of a fasted metabolic state characterized by reduced utilization of glucose and preference for fatty acids as a metabolic fuel.

Hyperglycemia, which typically appears within the first two cycles of treatment, has been reported in the range of 51%–65% of patients taking alpelisib with endocrine therapy in clinical trials and was the most common grade 3 or 4 adverse event leading to dose reduction or discontinuation of the drug [17–19, 27]. However, the majority of patients present with grade 1 or 2 hyperglycemia, which is usually asymptomatic and manageable with diabetes medications. Hyperosmolar and ketoacidotic states are extremely rare but may occur in patients with pre-existing diabetes. To avoid these issues, phase III clinical trials with PI3K inhibitors only include patients with a fasting plasma glucose (FPG) ≤ 140 mg/dl and HbA1c < 6.5%.

Upon treatment initiation, it may be helpful to instruct patients to follow dietary guidelines according to local and/or institutional standards for management of diabetes, such as those provided by the American Diabetes Association (e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day, three small meals and two small snacks rather than one large meal) [28], as this strategy may help minimize the severity of hyperglycemia.

Once hyperglycemia is detected, mild increases in fasting plasma glucose (≤ 160 mg/dl) do not require dose modifications, but initiation of metformin 500 mg once daily is recommended. If no GI intolerance, the dose can be titrated every 7 days by increasing to 500 mg twice daily and increasing each dose by additional 500 mg as needed up to a maximum dose of 2000 mg daily. For fasting plasma glucose between 160 and 250 mg/dl, the PI3K pathway inhibitor can be maintained at the same dose, but one should consider consultation with an endocrinologist and an increase in the metformin dose if not already maximized. If maximized and FPG does not improve, consider the addition of an insulin-sensitizer agent such as pioglitazone. If hyperglycemia does not improve within 21 days to FPG < 160 mg/dl, the patient should restart alpelisib at a lower dose [22]. In patients who develop FPG > 250 mg/dl, treatment with alpelisib should be interrupted for 1–2 days until blood glucose improves. Aggressive hydration and electrolyte management might also be indicated, especially if blood glucose reaches >500 mg/dl. Treatment with insulin may be used until hyperglycemia improves as recommended in the SOLAR-1 trial [19]. Blood glucose will normalize in the majority of patients with drug interruption given the short half-life of alpelisib, so ongoing treatment with insulin might not be required. However, some patients might require insulin therapy to control their blood glucose throughout treatment [22]. If FPG decreases to ≤ 160 mg/dl within 3 to 5 days with appropriate treatment, patients can resume alpelisib at a lower dose. Consultation with an endocrinologist is also strongly advocated. However if FPG does not improve to ≤ 160 mg/dl within 21 days despite aggressive treatment with anti-diabetic medications, alpelisib should be permanently discontinued [22]. For patients who develop FPG > 500 mg/dl and do not improve to <500 mg/dl within 24 h of aggressive treatment with insulin and i.v. hydration, treatment with alpelisib should be discontinued [22].

**Rash**

The PI3K/AKT pathway has been demonstrated to have an important role in keratinocyte differentiation, and inhibition of the pathway blocks the expression of certain growth and differentiation markers thus leading to epidermal cell death [29]. Skin disorders, namely rash and maculopapular rash, were another of the
reported to occur in anywhere from 45% to 64% of patients and most commonly seen toxicities with alpelisib in trials. Rash was reported to occur in anywhere from 45% to 64% of patients and was also the second most common grade 3 or 4 toxicity [17–19]. The most common form of rash that develops is a maculopapular rash, with or without pruritus and dry skin. Only a minority of patients present with acneiform rash. The onset is typically within the first 2 months of starting treatment and is reversible with adequate medication and treatment interruption if necessary. Skin reactions may fade slowly over 10 days or more and may not require ongoing concomitant therapy. If there are no new lesions or new areas of involvement developing, and if the appearance is changing color from red to pale or light brown, it is likely that the eruption is beginning to resolve and not considered active any longer. Only one case of Stevens–Johnson syndrome has been reported.

Early intervention with topical corticosteroids, systemic antihistamines for pruritus, and, in more severe cases, systemic corticosteroids are effective in controlling this side-effect. Consideration of avoidance of heat and sun exposure (which could increase skin hyperemia and in turn higher drug exposure in the dermis) should be given for patients taking alpelisib. Interestingly, some investigators have attempted rash prophylaxis, with some anecdotal success, with twice a day non-drowsy antihistamines that were started upon initiation of alpelisib use. However, structured evidence supporting these measures is still lacking.

Management varies based on extent of body surface area (BSA) involved and the presence of pruritus. Rash in <10% BSA does not require dose modifications and can be easily managed with high-potency topical steroids (triamcinolone, betamethasone) 3–4 times daily for at least a month. If the rash is pruritic, a non-drowsy antihistamine orally twice a day can be used, whereas hydroxyzine or diphenhydramine can be used for pruritus at bedtime. If the rash does not resolve or covers 10%–30% BSA, low-dose systemic steroids (prednisone 20–40 mg day for up to 10 days) should be considered discontinuation of the PI3K pathway inhibitor [22]. Other measures to be considered for symptomatic rash that does not improve with the above treatments include:

- Topical antibiotics if evidence of superinfection or acneiform rash: clindamycin 1%–2%; erythromycin 1%–2% (gel or solution formulation can be used; ointments cannot be used); metronidazole 1%; silver sulfadiazine
- Oral antibiotics if evidence of superinfection but can also provide some anti-inflammatory effect: doxycycline 100 mg

| Side-effect | Reported incidence of any grade* | Supportive treatment(s) |
|-------------|---------------------------------|-------------------------|
| Hyperglycemia | 65% | Metformin 500 mg once daily. Dose can be titrated every 7 days by increasing to 500 mg twice daily then increasing each dose by additional 500 mg as needed up to maximum dose of 2000 mg daily. If not controlled on max metformin dose, consultation with endocrinologist recommended for addition of an insulin-sensitizer agent such as pioglitazone and/or insulin therapy. For glucose >250, i.v. hydration, correction of electrolyte abnormalities, drug interruption until glucose improves. For glucose >500, the above measures with insulin therapy; if glucose does not improve within 24 h, discontinue alpelisib. |
| Rash | 54% | For mild rash, topical steroids (triamcinolone, betamethasone) 3–4 times daily. For rash that does not resolve or covers 10%–30% BSA, low-dose systemic steroids (prednisone 20–40 mg day for up to 10 days). Drug interruption necessary if rash not responding to above measures. For pruritus, non-drowsy antihistamines orally twice a day can be used; hydroxyzine or diphenhydramine at bedtime. |
| Diarrhea | 58% | First line: Loperamide, initial administration of 4 mg, then 2 mg every 4 h (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. Second line: octreotide acetate subcutaneous 100–150 μg every 8 h; opium tincture 10–15 drops (10 mg/ml) in water every 3–4 h. |
| Stomatitis | 25% | Dexamethasone 0.5 mg/5 ml oral solution (swish for 2 min and spit, four times daily) for a minimum of 8 weeks as prophylaxis. |
| Pneumonitis | 2% | High-dose systemic corticosteroids. Drug discontinuation. |

*Based on data from SOLAR-1 phase III clinical trial and report from the Food and Drug Administration [13].
twice daily; minocycline 100 mg twice daily; oxytetracycline 500 mg twice daily
• Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily
• GABA agonists for severe and refractory pruritus, such as gabapentin 300 mg every 8 h or pregabalin 50–75 mg every 8 h

Diarrhea

Diarrhea is seen in over 50% of patients taking alpelisib with reported ranges of 52%–60% in clinical trial data [17–19]. It is usually mild, but grade 3 or 4 toxicity has been seen in up to 6.7% of patients [19]. Once other causes of diarrhea are excluded (e.g., infection), some general guidelines should be implemented, such as stopping all lactose-containing products, alcohol, laxatives, bulk fiber and stool softeners, as well as high-osmolar food supplements such as Ensure Plus® (Abbott Laboratories, Abbott Park, IL) and Jevis Plus® (Abbott Laboratories, Abbott Park, IL) (with fiber). Patients should be encouraged to stay hydrated by drinking at least 8–10 large glasses of clear liquids per day. Additionally, eating frequent small meals (e.g. bananas, rice, apple sauce, toast) is strongly recommended.

If diarrhea persists with above measures, patients should be instructed to start oral loperamide [initial administration of 4 mg, then 2 mg every 4 h (maximum of 16 mg/day)] at the first sign of loose stool or symptoms of abdominal pain [22]. Persistent symptoms may require the administration of high-dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate based on severity and duration of diarrhea and related signs/symptoms. Octreotide acetate can be administered subcutaneously 100–150 μg every 8 h, and dosing of opium tincture with 10–15 drops (10 mg/ml) in water every 3–4 h has been shown to be effective in managing cancer treatment-associated diarrhea [30]. Another first-line treatment of diarrhea is diphenoxylate hydrochloride/atropine sulfate. This medication may be used in place of loperamide; however, it is important to note that loperamide and diphenoxylate hydrochloride/atropine sulfate must not be used in conjunction with one another antidirrheal agent due to the risk of developing paralytic ileus. For severe cases of diarrhea, treatment with alpelisib should be interrupted. However, once the diarrhea improves, it can be restarted at a lower dose [22].

Stomatitis

Stomatitis is a relatively common side-effect of PI3K pathway inhibitors and is usually grade 1. Any grade of stomatitis was reported in 25% of patients taking alpelisib plus endocrine therapy in the SOLAR-1 phase III trial [19]. Stomatitis is most strongly associated with mTOR inhibition but is also commonly seen with alpelisib [27]. Topical steroids have been shown to reduce the morbidity of stomatitis associated with these drugs [31]. Other causes of stomatitis, such as HSV-associated eruption, should be considered before initiating treatment with steroids. A single-arm trial of prophylactic dexamethasone 0.5 mg/5 ml oral solution (swish for 2 min and spit, four times daily) for a minimum of 8 weeks reduced the incidence of grade 2 or higher stomatitis from 33% (as seen in the BOLERO-2 trial [8]) to 2%, and also reduced the severity [31]. As a result, prophylactic steroid mouthwashses should be recommended to patients taking PI3K pathway inhibitors.

Pneumonitis

Pneumonitis, including interstitial lung disease and acute interstitial pneumonitis, is rare with alpelisib but has been reported [19]. Patients should be monitored throughout treatment of any new computed tomography scan abnormalities (such as appearance of ground glass infiltrates) or new pulmonary symptoms. Any patient reporting new respiratory symptoms should be evaluated for possible pneumonitis. Treatment with alpelisib should be interrupted if there is high suspicion of pneumonitis, all while evaluating for other possible infectious and non-infectious causes of worsening respiratory symptoms. Consultation with a pulmonologist should be highly considered for bronchoalveolar lavage or biopsy, if necessary, to rule out other causes and confirm the diagnosis. If pneumonitis is confirmed, treatment includes high-dose systemic corticosteroids and discontinuation of the PI3K pathway inhibitor [22].

Discussion

PI3K/AKT pathway inhibitors are associated with on-target and off-target side-effects. The most commonly seen toxicities with the PI3K isoform-specific inhibitor, alpelisib, are hyperglycemia, rash, and diarrhea. These side-effects can significantly impair patients’ quality of life as well as treatment efficacy. Toxicities can often lead to dose reductions, treatment delays, and treatment discontinuation if they are not successfully managed. Fortunately, most toxicities are reversible with drug interruption, due to the short half-life of the drug, and manageable with early intervention and supportive medications. Patients can be successfully treated with PI3K pathway inhibitors with a proactive and inter-disciplinary approach that includes comprehensive education about the range of toxicities, frequent monitoring and early toxicity recognition, prophylactic measures when available, and active intervention with supportive care.

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References

1. Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat Rev Genet 2006; 7(8): 606–619
2. Zhao L, Vogt PK. Class I PI3K in oncogenic cellular transformation. Oncogene 2008; 27(41): 5486–5496
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3. Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer 2009; 9(8): 550–562.

4. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell 2012; 149(2): 274–293.

5. Mayer IA, Arteaga CL. The PI3K/AKT pathway as a target for cancer treatment. Annu Rev Med 2016; 67(1): 11–28.

6. Hernandez-Aya LF, Gonzalez-Angulo AM. Targeting the phosphatidylinositol 3-kinase signaling pathway in breast cancer. Oncologist 2011; 16(4): 404–414.

7. Wander SA, Hennessy BT, Slingerland JM. Next-generation mTOR inhibitors in clinical oncology: how pathway complexity informs therapeutic strategy. J Clin Invest 2011; 121(4): 1231–1241.

8. Baselga J, Campone M, Piccart M et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012; 366(6): 520–529.

9. Akinleye A, Avvaru P, Furqan M et al. Phosphatidylinositol 3-kinase (PI3K) inhibitors as cancer therapeutics. J Hematol Oncol 2013; 6(1): 88.

10. Campone M, Im S-A, Iwata H et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant for postmenopausal, hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: overall survival results from BELLE-2. Eur J Cancer 2018; 103: 147–154.

11. Baselga J, Im S-A, Iwata H et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18(7): 904–916.

12. Krop IE, Mayer IA, Ganju V et al. Pictilisib for oestrogen receptor-positive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2016; 17(6): 811–821.

13. Janku F, Yap TA, Meric-Bernstam F. Targeting the PI3K pathway in cancer: are we making headway? Nat Rev Clin Oncol 2018; 15(5): 273–291.

14. Utermark T, Rao T, Cheng H et al. The p110α isoform of PI3K is essential for proper growth factor signaling and oncogenic transformation. Proc Natl Acad Sci U S A 2006; 103(44): 16296–16300.

15. Mayer IA, Abramson VG, Formisano L et al. A phase Ib study of alpelisib (BYL719), a PI3Kα-specific inhibitor, with letrozole in ER+/HER2- metastatic breast cancer. Clin Cancer Res 2017; 23(1): 26–34.

16. Mayer IA, Prat A, Egle D et al. A phase II randomized study of neoadjuvant letrozole plus alpelisib for hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (NEO-ORB). Clin Cancer Res 2019; 25(10): 2975–2987.

17. Andre F, Ciruelos E, Rubovszyk G et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019; 380(20): 1929–1940.

18. Chia S, Gandhi S, Joy AA et al. Novel agents and associated toxicities of inhibitors of the pi3k/Akt/mtor pathway for the treatment of breast cancer. Curr Oncol 2015; 22(1): 33–48.

19. Esposito A, Viale G, Curigliano G. Safety, tolerability, and management of toxic effects of phosphatidylinositol 3-kinase inhibitor treatment in patients with cancer: a review. JAMA Oncol 2019; 5(9): 1347.

20. Piqray (Alpelisib). East Hanover, NJ: Novartis Pharmaceuticals Corporation 2019.

21. Greenwell IB. PI3K inhibitors: understanding toxicity mechanisms and management. Cancer Network. https://www.cancernetwork.com/article/pi3k-inhibitors-understanding-toxicity-mechanisms-and-management. 2017. (10 November 2019, date last accessed).

22. Majumder PK, Febbo PG, Bikoff R et al. mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways. Nat Med 2004; 10(6): 594–601.

23. Bendell JC, Rodon J, Burris HA et al. Phase I, dose-escalation study of BKM120, an oral pan-class I PI3K inhibitor, in patients with advanced solid tumors. J Clin Oncol 2012; 30(3): 282–290.

24. Fox EM, Kuba MG, Miller TW et al. Autocrine IGF-I/insulin receptor axis compensates for inhibition of AKT in ER-positive breast cancer cells with resistance to estrogen deprivation. Breast Cancer Res 2013; 15(4): R55.

25. Common Terminology Criteria for Adverse Events (CTCAE). U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute 2017; 155.

26. Franz MJ, Bantle JP, Beebe CA et al; American Diabetes Association. Nutrition principles and recommendations in diabetes. Diabetes Care 2004; 27(Suppl 1): s36.

27. Calautti E, Li J, Saoncella S et al. Phosphoinositide 3-kinase signaling to Akt promotes keratinocyte differentiation versus death. J Clin Invest 2005; 208(38): 32856–32865.

28. Benson AB, Ajani JA, Catalano RB et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 2004; 22(14): 2918–2926.

29. Rugo HS, Seneviratne L, Beck JT et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. Lancet Oncol 2017; 18(5): 654–662.