Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part I
DOI: 10.54254/2753-8818/3/20220314

Alpelisib: a novel PI3K inhibitor for the treatment of breast cancer

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Abstract. Breast cancer is a common malignancy that causes people to die easily, especially for women. HR-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancers occur in more than 70% of patients, who have a driver mutant kinase catalytic subunit alpha (PIK3CA) in the phosphatidylinositol 4, 5-diphosphate 3-kinase gene, resulting in impaired phosphatidylinositol 3-kinase (PI3K) and in 40% of cases, loss of cell growth. However, drug resistance remains a problem in the early stages of endocrine therapy in these patients. And a promising new approach to overcome resistance to autologous treatment in breast cancer is the inhibition of PI3K. Alpelisib is a selection PI3K inhibitor for HR-positive, HER2-negative, PIK3CA patients - with mutant breast cancer that has advanced on autologous treatment. FDA approved alpelisib in 2019 which was produced by Novartis Pharmaceuticals Corporation. It is recommended to take this drug with fulvestrant which is also an estrogen receptor antagonist that slows the growth of breast cancer. Although alpelisib is an effective drug for the treatment of breast cancer, some adverse reactions may happen, such as stomatitis, nausea, diarrhe, dermatitis, and so on. Sometimes it also causes skin reactions, such as SIS, TEN, EM. Thus, when these serious adverse reactions happen, dosage should be reduced. As a result, some recommendations are provided for patients, and they must follow the instructions in order to live a more pleasant life. In this article, the working mechanism, structure, characteristics, clinical studies of alpelisib were reviewed and its comparison with other drugs was also provided for reference.

Keywords: Breast cancer, Alpelisib, Clinical

1. Introduction

According to the newest data, the breast was the second leading neoplasm, and breast cancer ranked in top five which were causes of non-communicable deaths [1]. Some kinds of skin cancer are the most common. It is common to see that breast cancer happens among women who are fifty years or over. However, young women will also get this cancer too. Breast cancer is a cancer that can treat difficultly, and young survivors may find it overwhelming. CDC is currently focusing on calling for people to know more about breast cancer. At the same time, they are also trying to improve young women's life quality. The death rate of Black women is higher than White women. Although it is really rare to happen to men, the truth is that they may get breast cancer. In the US, it can be found about 1 out of every 100 breast

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DOI: 10.54254/2753-8818/3/20220314

cancers are diagnosed, and the most common type of breast cancer in men are the same type in women [2].

Alpelisib is a PI3K (phosphatidylinositol 3-kinase) inhibitor that selectively acts on p110-α. PI3K pathway is one of the significant signaling pathways in cells and is also a frequent signaling pathway with the unusual presentation in cancer cells. Regulation of cell growth, differentiation, glucose transport, and apoptosis are involved in the PI3K signaling pathway. PI3K, Akt and mTOR are three important "junctions" of this pathway. PI3K, Akt and mTOR are the three important "connectors" of this pathway, among which PI3K plays a key role in this pathway by converting PIP2 to PIP3 to activate downstream effectors [3-5]. PI3Ks are a family of lipid kinase proteins divided into three classes with different structures and functions of each isoform. PI3Ks can be subdivided into PI3Kα, PI3Kβ, PI3Kδ and PI3Kγ. PI3Kα is distributed in various tissues and organs and is closely related to cancer [6].

Alpelisib is produced by Novartis Pharmaceuticals Corporation. Clinical studies have shown that alpelisib can significantly prolong progression-free survival and increase patients' survival compared with placebo. Although alpelisib is a useful drug to treat the breast cancer, there are still several precautions mentioned that what kind of diseases are not allowed to use the alpelisib, so doctors can adjust the dosage of drug for the patients. Many studies have also identified adverse reactions including blood glucose increased, diarrhea, rash and so on. In addition, some suggestions are provided for patients and they need to follow the instructions in order to have an easier lives.

The article mainly reviewed the advancement of alpelisib about its working mechanism, structure, characteristics, clinical studies and compared it with other similar drugs to provide reference to clinicians and patients.

2. The working mechanism of alpelisib

PI3K is an active intracellular PI kinase (phosphatidylinositol kinase). PI3K/AKT/mTOR signaling pathway is one of the major signaling pathways in cells. At present, three types of PI3K have been found, among which class IA PI3K is a heterodimer composed of P85 regulatory subunit and P110 catalytic subunit [7], which is obviously associated with human cancer [8]. P110α, p110β and p110δ are three homologous class IA catalytic isomers [9]. Normally, to initiate receptor tyrosine kinase activation, the p85 regulatory subunit interacts with p110 and inhibits its activity, p110 is deregulated [10,11] and PIP2 is phosphorylated at the matrix membrane to generate PIP3. The second messenger PIP3 leads to phosphorylation of PDK-1 [12-14]. Furthermore, Akt phosphorylates downstream factors, including the mTOR complex [15,16]. (Figure 1) On the other hand, tumor suppressor phosphatase and PTEN dephosphorylated PIP3, thereby counteracting the effect of PI3K signaling [17].

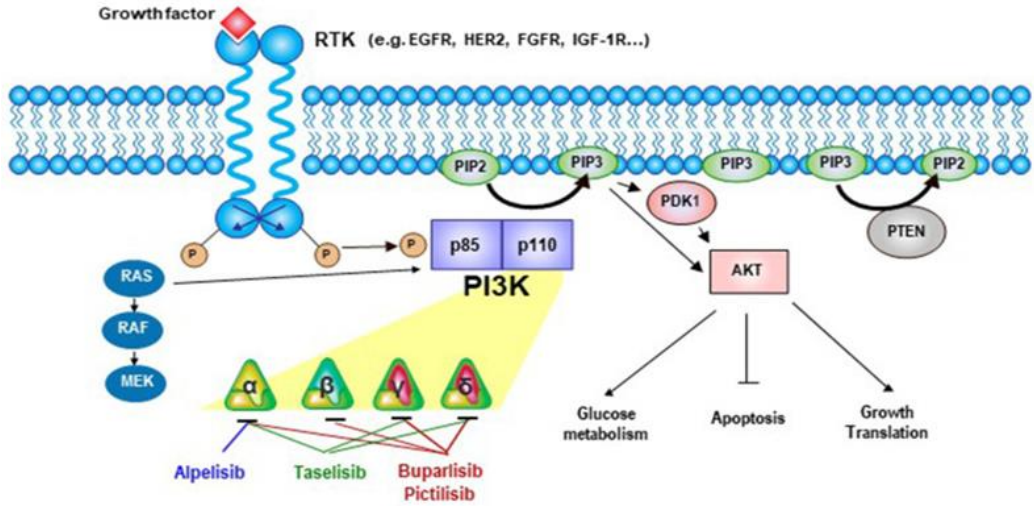

Figure 1. The signaling of mammalian rapamycin (mTOR)/Akt/phosphoinositol-3-kinase (PI3K) pathway [24].

DOI: 10.54254/2753-8818/3/20220314

Nearly 40% of ER+/HER2 - patients have highly activated α-type PI3K (P110α) and PIK3CA gene mutations, which lead to the activation of PI3K signaling pathway and promote tumor proliferation, metastasis and invasion. PIK3CA gene mutations in women may develop breast cancer. Women with mutations in the PIK3CA gene increased risk of suffering from not only breast cancer but also other common female-associated cancers [3,14,18-20] Therefore, mutant PIK3CA is likely to become a biomarker and a new risk factor for breast cancer, especially ER+/HER2 - breast cancer, as a biomarker and a new therapeutic target [21-23].

Alpelisib is the first PI3K inhibitor whose inhibitory activity primarily targets PI3Kα. PI3K catalyzes PIK3CA, leading to PI3Kα and Akt signaling activation, cell transformation and tumorigenesis. In vivo, alpelisib inhibits the PI3K/Akt signaling pathway and reduces tumor growth, which shows that protein inhibition of PI3K kinase induces an increase in ER (estrogen receptor) transcription in breast cancer cells, manifests antitumor activity in the presence of Alpelisib.

3. Comparison drug and alpelisib

Alpelisib, Ribociclib and Everolimus are three breast cancer drugs with different drug targets, all developed by Novartis. CDK4/6 is overactive in many malignant tumors, especially HR-positive breast cancers, and shows significant activity, contributing to the proliferation and spread of cancer cells, while CDK4/6 inhibitors inhibit tumor cell proliferation by blocking the cell cycle during the growth phase. Inhibitors of CDK4/6 may inhibit tumor cell proliferation by blocking the cell cycle during the growth phase. PI3K/Akt/mTOR pathway causes Akt gene to go out of control and activates mTOR to trigger abnormal cell growth. Cross-linking with a variety of intracellular signaling pathways can inhibit the spread of breast cancer cells by inhibiting their own pathways.

Ribociclib is a cell cycle protein-dependent kinase 4 and 6 (D-CDK4/6) inhibitor. These kinases are excited by binding to cell cycle proteins and function as key players in signaling pathways that lead to cell cycling progression and cell multiplication. Regulating cell cycle progression is phosphorylated by this cell cycle protein-D-CDK4/6 complex through the retinoblastoma protein (pRb). ribociclib decreases pRb phosphorylation, resulting in G1 phase cessation of the cell cycle and inhibition of breast cancer cell line multiplication. It was shown that in a human rat xenograft model, treatment of tumor cells with a single drug, Rbociclib, resulted in a reduction in tumor volume associated with inhibition of pRb phosphorylation.

Everolimus, an anticancer drug, is a small-molecule inhibitor of mTOR that interferes with the growth of cancer cells and slows their spread in the body. Its mammalian target is a protein kinase, which can block the activity of the target. Regulation stimulates cell growth and angiogenesis.

4. Structure and characteristics of alpelisib

In May, 2019, FDA approved a new drug called alpelisib and it was being treated for breast cancer. The form of alpelisib is a white powder, and it is sold in tablets. There are several specifications of this drug, such as 50 mg, 150 mg, and 200 mg. The recommended dosage is 300 mg and when patients are taking this drug, it is better to take it with food. Patients should try their best to take the drug regularly, which means that if a patient take it at three o' clock in the afternoon, it is better to follow this schedule for every single day. It is still possible that patients forget to take it, but it is better to remember to take it in nine hours [25]. However, if it is over than nine hours, patients do not need to take it, and the drug still needs to take as usual on the next day. To remind, alpelisib should be taken as a whole, which means that it is not allowed to eat by pieces, or chew it, or crush it [25].

Secondly, if some adverse reactions happened to patients, the dosage can be decreased to 250 mg, or the reaction is more serious, it can be reduced to 200 mg. If it is possible that the dosage must be decreased to under 200 mg, the patients should not use alpelisib because this drug is not suitable for them [25]. The common adverse reactions include hyperglycemia, stomatitis, nausea, diarrhea, cravings, rash, fatigue, so the dosage needed to reduce, or suspend or discontinue taking the alpelisib when these adverse reactions happened on patients [25]. Throughout looking for some previous cases, they showed that for patients who got severe adverse reactions which were some severe allergic reactions include

DOI: 10.54254/2753-8818/3/20220314

dyspnea, flushing, rash, fever, or tachycardia [25]. Although the reactions above did not happen frequently, once they happened, patients did not allow to use alpelisib anymore which was permanent discontinuation [25]. SJS, TEN and EM were three serious skin reactions that may occur after taking alpelisib. Thus, if these situations happened, patients also have to stop taking this drug until they knew which disease they got. At the same time, if patients got the three skin reactions above, they have to discontinue taking the medicine. In a contrast, if the patients did not get three skin reactions, doctors could adjust the dosage or maybe doctors could suggest they to take the drug in another way.

As mentioned above, it was better to take with foods, and there was a suggestion which was also to take alpelisib with fulvestrant [25]. This is because fulvestrant is an estrogen receptor antagonist that binds to estrogen receptors in breast cancer cells, and it works by binding and blocking the estrogen receptor, which slows the growth of cancer [26]. Then, for the pahrmacokinetics of Alpelisib, the exposure of this drug was proportional to the increase in dose in the range of 30 to 450 mg. The time to reach Cmax was about 2 - 4 hours. Daily diet had no essential impact on the exposure of Alp. But, when patients were eating high- fat and high- calorie diets, the AUC increased 73%, and Cmax rose by 84%; when patients were eating low- fat and low-calorie diet, the AUC increased 77%, and Cmax rose by 145% [25]. In vitro, chemical breakdown and enzymatic hydrolysis made up the majority of Alp's metabolism. Alpelisib was mostly metabolized by cytochrome P, CYP in the liver. BZG791 was a primary metabolite, and CYP3A4 was a only small part of metabolism. On the contrary, without eating anything, the most amount of metabolism was through excreting which could excrete about 81% (36% for the original drug, 32% for BZG791). The other small amount of metabolite was passed through urine which was about 14% (2% for original drug, 7.1% for BZG791) [25].

5. Clinical studies

Alpelisib's PI3K selectivity and pharmacokinetics led to successful breast cancer trials and the drug's FDA approval in 2019 [27]. Novartis has 23 clinical trials planned for the treatment of PIK3CA gene mutated breast cancer, of which one lacks complete data. The remaining 22 trials have a cumulative total of 2,853 breast cancer patients, including 15 Phase I trials with 1,390 patients, 2 Phase I/II trials with 91 patients, 4 Phase II trials with 800 patients, and 1 Phase III trial with 572 patients. At the time of FDA approval, the majority of clinical trials had been completed, with a few clinical trials still in data processing. Numerous phase II and III clinical studies on alpelisib are now being conducted to identify the best suitable patient category for the medicine as well as other tumor indications and drug combination regimens. According to preliminary findings, alpelisib may be effective for solid tumors, gastroesophageal junction adenocarcinoma, advanced lung cancer, and advanced gastric cancer. Two representative clinical trials were reviewed in this article.

5.1. SOLAR-1 (NCT02437318)

SOLAR-1 is a randomized, double-blind, placebo-controlled phase 3 study aimed at evaluating the efficacy and safety of α-specific PI3K inhibitor + fulvestrant in patients with advanced PIK3CA mutation, HR+ and HER2- breast cancer [28].

In this trial, alpelisib and fulvestrant were compared with placebo and fulvestrant. Patients were divided into two groups based on the presence of PIK3CA mutations in tumor tissue. Progression-free survival in the PIK3CA mutant group was the primary goal of the study. Integrated responsiveness and security were added as secondary objectives [28]. The SOLAR-1 study showed that the addition of alpelisib to fulvestrant therapy was statistically and clinically significant. After more than three years of follow-up, three times as many patients in the alpelisib plus fulvestrant group as in the placebo plus fulvestrant group continued treatment [29].

Clinical trials have shown alpelisib’s activity in patients with advanced breast cancer with a PIK3CA, HR-positive and HER2-negative mutation occurring during or after treatment with aromatase inhibitors [28]. As a result, integrating genetic testing for PIK3CA mutations into regular clinical practice may help in therapy selection. Moreover, this drug's diagnostic kit is used to assess individuals who are candidates for alpelisib treatment so that doctors can test the mutation of the PIK3CA gene which is a

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biomarker and establish treatment plans based on the molecular type of breast cancer. As a result, alpelisib may change how people with advanced breast cancer are treated. It is anticipated that alpelisib will provide tumor patients with more treatment options as research into the drug progresses.

5.2. BYLieve (NCT03056755)

The SOLAR-1 trial, on which alpelisib's first approval was based, began before CDK4/6i therapy became a first-line treatment standard. In SOLAR-1, prior therapy with early CDK4/6i in combination with an aromatase inhibitor improved progression-free survival in the alpelisib+fulvestrant group in comparison with the placebo+fulvestrant group [30].

BYLieve is a phase 2 multicenter, open-label, uncontrolled trial currently evaluating the safety and efficacy of alpelisib combined with fulvestrant in hormone receptor-positive (HR+), HER2-negative (HER2-) and PIK3CA-mutated advanced breast cancer (ABC) patients [31].

Consistent with the results of the solar-1 study, BYLieve demonstrated that alpelisib + fulvestrant is an active treatment option with controlled toxicity for patients with confirmed pik3ca-mutated disease who immediately received cdk4/6i with AI [31,32]. Although BYLieve had three parallel groups, each was evaluated individually, and the study was not intrinsically comparable in nature. In an absence of a comparator, analysis was performed to match the real-world cohort to offer further perspective into the results. Regardless of the treatment regimen, the combination of alpelisib with fulvestrant was consistently improvement in patients of BYLieve cohort A when compared to standard therapies for patients with HR+, HER2-, PIK3CA-mutated ABC, and previous CDK4/6i-based therapy [33].

6. Conclusion

Breast cancer is one of the common malignant tumors that affect women. There are some drugs used in treatment, however, the tolerability of these drugs will continue to be an issue due to their different virulence properties. In 2019, the GDA approved its use in conjunction with fulvestrant for the treatment of advanced or metastatic breast cancer that includes PIK3CA mutations and is HR+/HER2-. Alpelisib is now the focus of multiple clinical trials to discover the optimal patient groups for the drug, as well as alternative tumor indications and drug combination regimens. As research develops, it is expected that tumor patients will have access to more effective therapies in the future. Numerous studies revealed that patients who take alpelisib could nevertheless experience a wide range of negative side effects. Nevertheless, it is still a good choice for people who suffer from breast cancer if they follow precautions and be careful with the usage and dosage. Breast cancer has existed for a long time, and it is one of the most serious cancers for women, with a high fatality rate.If drugs can act on all three common signalling pathways, mammalian rapamycin (mTOR)/Akt/phosphoinositol-3-kinase (PI3K), then there may be further therapeutic benefits for breast cancer Despite the fact that scientists have conducted extensive research on breast cancer and that there are numerous drugs and technologies available around the world, there is still room for improvement in these drugs and technologies, which means that they cannot completely cure breast cancer. Thus, in the future, scientists and doctors still need to work in this field and study further on it.

References

[1] Ayele, W., Führer, A., Braun, G., Formazin, F., Wienke, A., & Taylor, L. et al. (2022). Breast cancer morbidity and mortality in rural Ethiopia: data from 788 verbal autopsies. BMC Women's Health, 22(1).

[2] CDC. (2019). CDC - Breast Cancer Statistics. Centers for Disease Control and Prevention. https://www.cdc.gov/cancer/breast/statistics/index.htm

[3] Mollon, L., Aguilar, A., et.al. (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). 10.1158/1538-7445.

[4] Ma CX, Ellis MJ. The Cancer Genome Atlas: clinical applications for breast cancer. Oncology (Williston Park). 2013 Dec;27(12):1263-9, 1274-9.

DOI: 10.54254/2753-8818/3/20220314

[5] Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer. 2009 Aug;9(8):550-62.
[6] Paplomata E, O'Regan R. The PI3K/AKT/mTOR pathway in breast cancer: targets, trials and biomarkers. Ther Adv Med Oncol. 2014 Jul;6(4):154-66.
[7] Foster JG, Blunt MD, et al. Inhibition of PI3K signaling spurs new therapeutic opportunities in inflammatory/autoimmune diseases and hematological malignancies. Pharmacol Rev. 2012 Oct;64(4):1027-54.
[8] 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.
[9] Yuan TL, Cantley LC. PI3K pathway alterations in cancer: variations on a theme. Oncogene. 2008;27(41):5497–5510.
[10] Fruman DA, Meyers RE, Cantley LC. Phosphoinositide kinases. Annu Rev Biochem. 1998; 67: 481–507.
[11] Yu J, Wjasow C, Backer JM. Regulation of the p85/p110 alpha phosphatidylinositol 3′-kinase. Distinct roles for the N-terminal and C-terminal SH2 domains. J Biol Chem. 1998;273(46):30199–30203.
[12] Franke TF, Kaplan DR et.al. Direct regulation of the Akt proto-oncogene product by phosphatidylinositol-3,4-bisphosphate. Science. 1997;275(5300):665–668.
[13] Klippel A, Kavanaugh WM, et.al. A specific product of phosphatidylinositol 3-kinase directly activates the protein kinase Akt through its pleckstrin homology domain. Mol Cell Biol. 1997;17(1):338–344.
[14] Mora A, Komander D, van Aalten DMF, Alessi DR. PDK1, the master regulator of AGC kinase signal transduction. Semin Cell Dev Biol. 2004;15(2):161–170.
[15] Sarbassov DD, Guertin DA, et.al. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. 2005;307(5712):1098–1101.
[16] Wang L, Lawrence JC Jr, et.al. Mammalian target of rapamycin complex 1 (mTORC1) activity is associated with phosphorylation of raptor by mTOR. J Biol Chem. 2009;284(22):14693–14697.
[17] Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. 2012;149(2):274–293.
[18] Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J Biol Chem. 1998;273(22):13375–13378.
[19] Mui E，Ambrini G，et al．The phosphoinositide 3-kinase α selective inhibitor BYL719 enhances the effect of the protein kinase C in- hibitor AEB071 in
[20] GNAQ/GNA11-mutant uveal melanoma cells．Mol Cancer Ther，2014，13(5): 1044-1053
[21] PI3K/Akt/mTOR pathway as a therapeutic target for colorectal cancer: a review of preclinical and clinical evidence［J］. Curr Drug Target, 2019, 20（12）:1217-1226.
[22] Samels Y，Ericon K. Oncogenic PI3K and its role in cancer．Curr Opin Oncol，2006，18(1): 77-82．
[23] Sarbsov DD, Gutin DA, et.al. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. 2005;307(5712):1098–1101.
[24] Chang DY, Ma WL, Lu YS. Role of Alpelisib in the PIK3CA-Mutated Breast Cancer: Patient Selection and Clinical Perspectives. Ther Clin Risk Manag. 2021 Mar 5; 17: 193-207.
[25] Highlights of Prescribing Information Pneumonitis: Severe Cases of ... https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212526s000lbl.pdf.
[26] "Fulvestrant: Uses, Dosage, Side Effects, Warnings." Drugs.com, https://www.drugs.com/fulvestrant.html.

DOI: 10.54254/2753-8818/3/20220314

[27] Narayan, P. et al. FDA Approval Summary: Alpelisib plus fulvestrant for patients with HRpositive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer. Clin Cancer Res (2020).
[28] André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019;380(20):1929-1940.
[29] André F, Ciruelos EM, Juric D, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol. 2021;32(2):208-217.
[30] Juric D, Ciruelos EM, Rubovszky G et al. Alpelisib (ALP) + fulvestrant (FUL) for advanced breast cancer (ABC): Phase 3 SOLAR-1 trial results. Presented at: San Antonio Breast Cancer Symposium; December 4–8, 2018; San Antonio, TX.
[31] Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. The Lancet Oncology. 2021;22(4):489-498.
[32] Rugo HS, Lerebours F, Ciruelos E et al. Alpelisib + fulvestrant in patients with PIK3CAmutated hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (ABC) previously treated with cyclin-dependent kinase 4/6 inhibitor (CDKi) + aromatase inhibitor (AI): BYLieve study results. Presented at: 56th Annual Meeting of the American Society of Clinical Oncology; May 29–31, 2020; Virtual.
[33] Turner S, Chia S, Kanakamedala H, Hsu WC, Park J, Chandiwana D, Ridolfi A, Yu CL, Zarate JP, Rugo HS. Effectiveness of Alpelisib + Fulvestrant Compared with Real-World Standard Treatment Among Patients with HR+, HER2-, PIK3CA-Mutated Breast Cancer. Oncologist. 2021 Jul;26(7):e1133-e1142.