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Unlocking the Potential of Alpelisib in Breast Cancer: A Comprehensive Review

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Abstract Alpelisib is a cancer therapy drug that has shown significant promise in the treatment of certain types of cancer. Its pharmacokinetics and pharmacodynamics indicate that it is absorbed better orally and has a prolong half-life, allowing for once-every day dosing. Currently, its mechanism of action is established to be the suppression of phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), which is the pivotal enzyme of PI3K pathway, which is abnomal in most cancers. The chemistry of alpelisib involves its selective inhibition of PI3K, targeting specifically HR-positive, HER2-negative breast cancer with PIK3CA mutations. The common side effects associated with alpelisib include fever, peripheral edema, fatigue, headache, skin rash, alopecia, pruritis, hyperglycemia, increased gamma-glutamyl transferase, decreased serum calcium, weight loss, diarrhea, nausea, increased serum lipase, decreased appetite, stomatitis, vomiting, dysgeusia, lymphocytopenia, prolonged PTT, and increased serum creatinine. The use of alpelisib in cancer therapy is being extensively studied through various clinical trials, aiming to determine the optimal patient populations for treatment and explore alternative tumor indications and drug combine regimens.

Keywords Alpelisib, Cancer therapy, HER2, PIK3CA

In the world of oncology, the search for targeted therapies that can effectively combat cancer while minimizing harm to healthy cells is a continuous journey. One such promising agent that has gathered attention is Alpelisib, a selective inhibitor of the PI3K signaling pathway. This comprehensive review will discuss about the mechanism of action of Alpelisib, its Pharmacokinetics, Pharmacodynamics and clinical applications in treating specific types of cancer(1).

On 2022, April 5, the FDA awarded approved the drug alpelisib at Vijoice, Novartis Pharmaceuticals for paediatric patients two years and older also adults suffering severe PIK3CA-related overgrowth spectrum (PROS) who require systemic medication.(2)

Alpelisib exerts its therapeutic effects by specifically targeting the PI3K, a crucial pathway implicated for the proliferation, cell growth & survival. By inhibiting PI3K, Alpelisib disrupts downstream signalling cascades, leading to the suppression of tumor growth and survival. Notably, Alpelisib demonstrates a high degree of specificity towards tumors harbouring PIK3CA mutations, which are frequently observed in various cancer types. This targeted approach enhances the efficacy of Alpelisib while minimizing off-

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target effects on normal cells, making it a promising therapeutic option for patients with PIK3CA-mutated cancers(3).

In the clinical setting, Alpelisib has shown significant promise in HER2-negative breast cancer treatment & hormone receptor-positive, particularly combined with endocrine therapies such as aromatase inhibitors. The addition of Alpelisib to standard treatment regimens has shown to improve progression-free survival and overall response rates in this patient population. Furthermore, ongoing research is exploring the potential synergies of Alpelisib with other targeted agents, such as CDK4/6 inhibitors, in overcoming resistance mechanisms and enhancing treatment outcomes. Despite its efficacy, the management of side effects, such as hyperglycaemia and rash, remains a challenge in optimizing patient adherence and quality of life during Alpelisib therapy(4).

Looking ahead, the future of Alpelisib research holds promise and challenges alike. Researchers are actively investigating the expansion of Alpelisib's utility beyond breast cancer into other malignancies, such as endometrial and gynaecologic cancers, where dysregulation of the PI3K pathway is prevalent. However, the development of resistance mechanisms to Alpelisib poses a significant hurdle in long-term treatment success. Understanding these mechanisms and devising strategies to overcome or circumvent resistance will be critical in maximizing the clinical benefits of Alpelisib. Ongoing clinical trials and collaborative research efforts are underway to unravel these complexities and pave the way for the next generation of targeted therapies in oncology(5).

1. Chemistry

The stereochemistry of alpelisib refers to the arrangement of atoms in three-dimensional space. Alpelisib contains several chiral centers, leading to different possible stereoisomers. The stereochemistry of alpelisib is specified by the (2S)-configuration in its chemical name, indicating that it is the S enantiomer at the chiral centre on the piperazine ring.

Chiral centers are indicated by asterisks (*) in structural diagrams. However, due to the limitations of text-based representation, I'll describe the stereochemistry of alpelisib without visual aids.

Alpelisib's stereochemistry involves the chirality at the following carbon atoms:

The carbon atom in the piperazine ring: This is indicated by (2S)- in the chemical name, suggesting that the configuration is S at this chiral centre.

In a simplified form:- Alpelisib is the (2S)-enantiomer(6).

2. The PI3K/AKT/mTOR Pathway and Breast Cancer

The pathway is involved in cell division, size control, and apoptosis. Currently, there are several treatment procedures being used in the management of breast cancer with the aim of eradicating the disease or at least controlling its progress, with therapeutic methods focusing on three main aspects in the path of the disease. BOLERO-2 was a study of a randomized, double-blind, placebo-controlled phase III trial design. A research compared everolimus, a mTOR inhibitor,

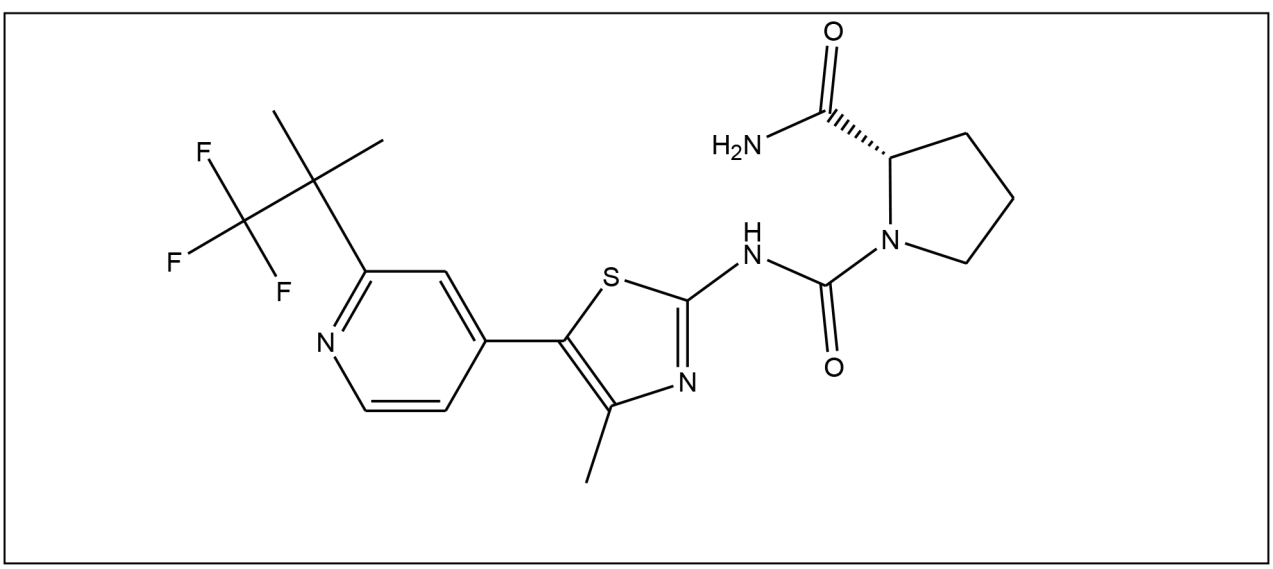

Figure 1: Structure of Alpelisib

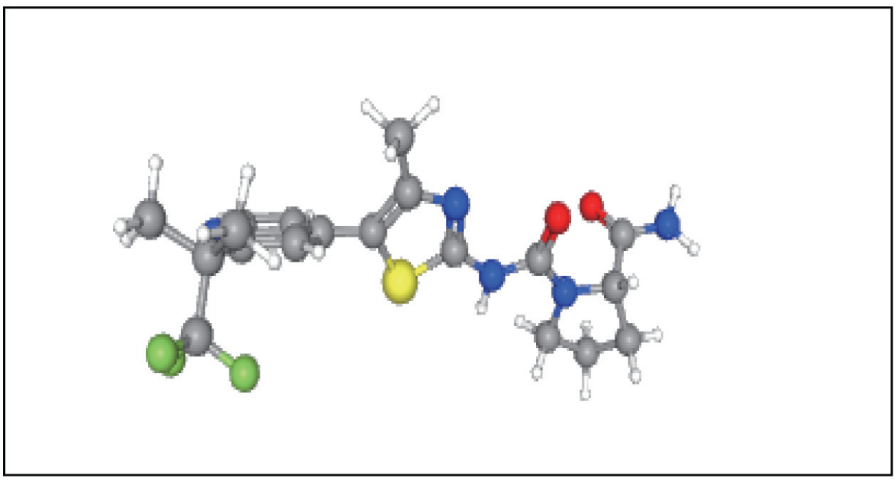

Figure 2: 3D Structure of Alpelisib

to exemestane with placebo in postmenopausal HR+/HER2 negative MBC patients(7).

Central review revealed an increase in the median PFS from 4. 1 to 10. 6 months; HR 0. 36, p<0. 001(7)(8).

The AKT inhibitor capivasertib was assessed in the Phase II FAKTION trial(9). The publications included were trial based: investigating the effects of capivasertib added to fulvestrant versus fulvestrant and placebo in the treatment of HR+/HER2-negative MBC(8). patients who received capivasertib had a PFS of ten point three months while the ones who received placebo had a PFS of 4. 8months with a Hazard ratio of 0. 58p= 0. 0018(9).

PI3Ks belong to the lipid kinase group(10). This pathway is activated by receptor tyrosine kinase;, activation of PI3K(11). Class I PI3K is further broken into two subclasses: IA and IB only with noted marginal differences, indicating that for the most part, the programs share essential features with one another. Thus, Class IA PI3Ks are heterodimers that comprise a p110α catalytic subunit coupled to a p85 regulatory subunit. There are four catalytic isoforms of PI3K(8): Accompanying these, there are α, β, γ and Δ (12).

PIK3CA is a Promoting Oncogene that encodes the p110α catalytic subunit. The three frequent mutations that are found on PIK3CA include the Exon 9 mutations, E545K and E542K, and Exon 20 mutation, H1047R. The mutated gene in this cancer is PIK3CA that triggers the function of p110α catalytic subunit leading to uncontrolled cell growth, proliferation and survival(12).

Among three somatic mutations that are most frequently targeted in breast cancer, there is PIK3CA. According to the previous research, it was established that PIK3CA mutation exists in 20-50% of the breast tumors(13). Most commonly this change is identified in 11 HR positive/HER2 positive breast cancer subgrouping where its frequency ranges from 35% to 23% respectively. It has, therefore, been possible to come up with medications that directly target PIK3CA mutation and affect the survival and proliferation of cancer cells(14).

3. Isoform-Specific PI3K Inhibitors

Pan-PI3K inhibitors have slightly increased doses, lower effectiveness, and the appearance of toxic effects compared to isoform-specific PI3K inhibitors(12). Beta-sparing PI3K inhibitor Taselisib was tested in the phase III SANDPIPER clinical trial(8). Postmenopausal women are already enrolled in this trial based on the randomization of 516 women into fulvestrant with placebo arm and the experimental arm of fulvestrant with taselisib. The combined therapy of group amplified the investigator estimative PFS from 5.4 to 7.4 months. The confirmed expectancy was 6 months, then the investigator estimative had the better expectancy at 11 months. The therapy of group increased the investigatork estimative overall survival from 4. 4 to 7. 4 months (HR 0. 70, CI 0. 52–0. 95, p = 0. 0037). The more frequently reported grade 3/4 AEs included diarrhoea, hyperglycaemia, colitis, and stomatitis(8).

Selective PI3Kα inhibitor is named Alpelisib (NVP-BYL719) and it is as an oral and bioavailable agent. This medication's efficacy and safety was first experimentally assessed in PIK3CA-mutated solid tumours in animals. This led to more studies about the efficacy of alpelisib as a new targeted therapy in patients with PIK3CA-mutated breast cancer(11).

4. Alpelisib in the Treatment of PIK3CA Mutated Breast Cancer

After the positive preclinical findings regarding the safety and effectiveness of alpelisib, the first-human phase Ia study was performed to prove its efficacy and safety in advanced solid tumor's based on PIK3CA alteration(8)(15). In this study, total 134 patients with unresectable, advanced solid tumors were included and the socio demographic and baseline clinical characteristics are shown in Table 1. The commonest type of solid tumours were colorectal with 26. 1% followed by breast with 26. 9% and head and neck cancer with 14. 2%.

The findings exposed a relatively unilateral safety disposition with the doses of up to 150mg twice every day and 400mg every day. An objective tumor response was indicated at 270mg or more once a day. An overall response rate of six (6) percent was achieved in the study. 0 percent was observed in eight patients; the seven of the patients exhibited a partial recovery, and one exhibited complete recovery.

The results obtained for the patients with HR+/ HER2 negative breast cancer identified the median PFS of 5. 5 months. The common adverse effects in the majority of the subjects were, nausea (51%) matured hyperglycaemia (52%), reduced food intake (42%), vomiting (31%) and diarrhoea (40%). Nine patients were reported with DLTs during the dose escalation phase. DLTs were observed in 2 patients in the 450mg once every day dose group as hyperglycemia with values ranging from 20. 2 to 21. 6mmol/L and four patients in the 200mg twice every day as hyperglycemia with values ranging from 20. 3 to 21. 3mmol/L, nausea in two patients in the 450mg once every day dose group and one patient each had combine hyper (15).

According to the previous study findings, PIK3CA mutation is noted in approximately 35% of patients with HR+ breast cancer.

According to the preceding literatures alpelisib has been proven to reduce the activity o f PI3K, thus enhancing the expression of estrogen receptor in breast cancer cells. (6).

This article has established that incorporation of PI3K inhibitors along with endocrine therapy in HR+ breast tumors with PIK3CA mutation offers a longer therapeutic window than endocrine therapy on its own. The median PFS in the changed PIK3CA group receiving alpelisib was 9. This means that among the PWDs, the mean health facility utilization was 34. 3 visits per one-year reference period or 1 months (95% CI, 6. 6-14. 6), compared to 4. 7 months (95% CI, 1. 9-5. 6) in the wild type group(8). The group for those who met the criteria for the PIK3CA alteration had an overall response rate of 29 percent, however, the wild type group did not even have an objective tumor response.

The main grade 3-4 AE reported in patients receiving alpelisib 400mg once every day dose were hyperglycemia 22 % and maculopapular rash 13 % AEs. (15). Based on the previous studies providing the proof of alpelisib's effectiveness and safety as MTD and with endocrine therapy, a phase 3 trial was designed. SOLAR-1 trial assessed the effectiveness and tolerability of alpelisib in combine with fulvestrant in those with HER2-negative, HR-positive, advanced breast cancer that owes PIK3CA mutation for metastasis and who have undergone aromatase inhibitor treatment but have not taken chemotherapy before. Hence the study trial involved 572 participants, among whom 341 had been diagnosed with a PIK3CA mutation. In PIK3CA-mutant patients, at 20 months of follow-up, PFS was 11. 0 months in the alpelisib + fulvestrant combine arm as compared to 5. 7 months in the fulvestrant arm (HR 0.65, $p<0.001$)(8).

Thus, the combine group showed better overall response rate compared to the fulvestrant only group in patients with PIK3CA mutation where overall response rate was 26. 6% for the combine group and 12. 8% for fulvestrant alone group. With the alpelisib plus fulvestrant, hyperglycemia and rash rates were 36. 6% and 9. 9% of grade 3-4 AE, accordingly. 6. Regarding the toxicity, only a single patient in the combo group reported Grade 3 diarrhea. The number of patients experiencing grade 4 diarrhea was also not found. The discontinuation rates in the combine group were 1. 25 times higher than in the fulvestrant alone arm (4. 2%). Alpelisib in combine with fulvestrant for postmenopausal women and man with HR+/HER2 negative, PIK3CA mutated advanced or metastatic breast cancer who have progressed after endocrine-based regimen was approved by FDA on May 24, 2019.(16)(8).

a. A Novel Targeted Therapy in Cancer Treatment

Cancer remains one of the most formidable challenges in the modern medicine, with its diverse and complex array of manifestations demanding equally varied therapeutic strategies. Among the myriad approaches to cancer treatment, targeted medicines have come to prominence as an exciting field, presenting the possibility of more specific & effective intervention

while minimizing harm to healthy tissues. In this context, Alpelisib, a selective inhibitor of phosphatidylinositol 3-kinase alpha (PI3Kα), has garnered considerable attention for its role in the management of certain advanced malignancies(17).

b. Understanding the Role of PI3Kα in Cancer Biology

To appreciate the significance of Alpelisib, it is essential to grasp the pivotal role of PI3Kα in cancer biology. The phosphatidylinositol 3kinase (PI3K) pathway is an important signalling cascades that regulates cellular development, proliferation, their survival, & metabolism. Lysates from cells harboring the PIK3CA H1047R mutation exhibited increased levels of both basal and insulin-stimulated Akt phosphorylation in general compared to the other cell lines, as well as to normal cells, cause dysregulation of this pathway, a common feature of cancer.(15).

PI3Kα, as a key isoform of PI3K, is particularly implicated in oncogenesis, exerting its effects through downstream signaling molecules such as AKT and mTOR. Hyperactivation of PI3Kα signaling promotes tumor cell proliferation, survival, and resistance to apoptosis, driving tumor growth and progression. Consequently, targeting PI3Kα presents an attractive therapeutic strategy to disrupt these aberrant cellular processes and impede cancer progression(16).

c. The Development of Alpelisib as a Selective PI3Kα Inhibitor

In this context, Alpelisib emerges as a promising therapeutic agent. Developed by Novartis Pharmaceuticals, Alpelisib is a potent and selective inhibitor of PI3Kα, designed to specifically target the dysregulated signaling pathway implicated in various cancers. Its selectivity for PI3Kα offers the potential for enhanced efficacy and reduced off-target effects compared to earlier generation pan-PI3K inhibitors(18).

The development of Alpelisib represents a culmination of extensive preclinical research elucidating the role of PI3Kα in cancer pathogenesis, coupled with rigorous clinical investigation aimed at validating its therapeutic utility. Preclinical studies demonstrated Alpelisib's ability to inhibit PI3Kα signaling, induce apoptosis, and suppress tumor growth across a range of cancer models, providing compelling rationale for clinical translation(11).

5. In silico molecular docking studies

Molecular docking experiments found that most ligands have a higher G score for PIK3Cα, with binding energies measured in kcal/mol versus 18 proteins. Amongst 14 coumarin-carbonodithioate compound's, 2a, 2d, 2e, & 2f showed higher G scores than alpelisib; a recognized inhibitor of the PIK3Cα protein. Prime MM-GBSA research over molecular docking energies enhances binding energy-calculations.

The 'MM-GBSA' research demonstrates that the ligands have a greater affinity for the receptor. The study indicated that alpelisib &2f compound have greater affinity for PIK3Cα than other ligands. Lead compounds used to create PIK3Cα inhibitors include 2a, 2d, 2e, & 2f(19).

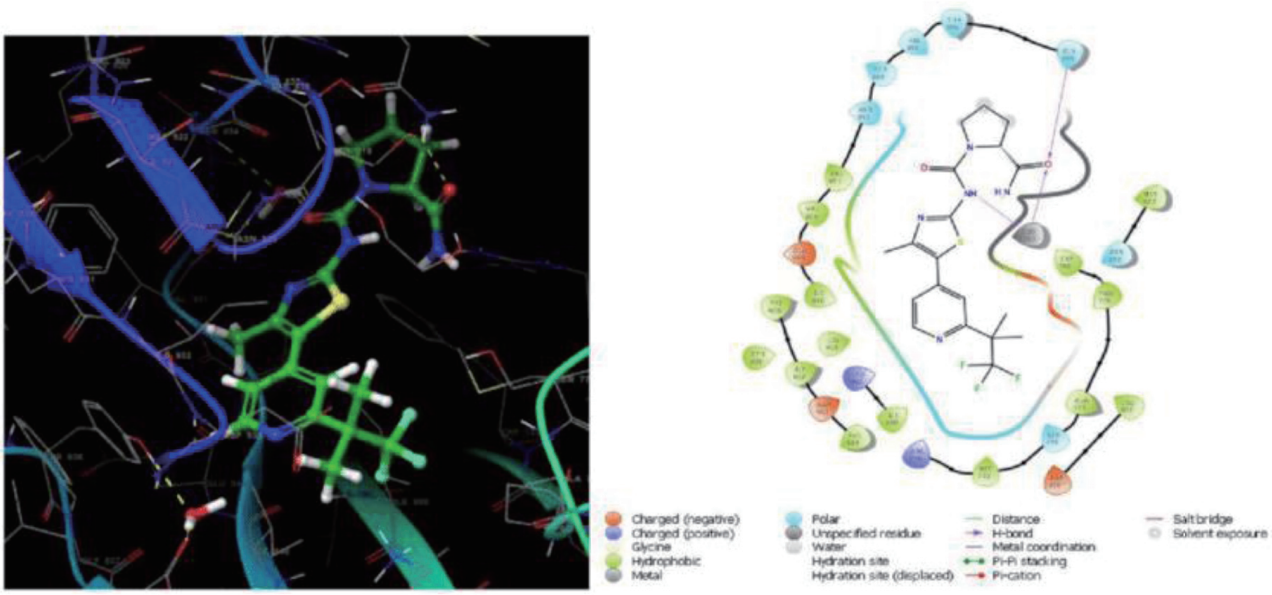

Figure 3: Alpelisib interaction with PIK3Cα, and both 3D, 2D diagrams.

6. Clinical Pharmacology

Alpelisib is also another approved drug for first-line treatment of HR-positive, HER2-negative invasive breast cancer that has quickly progressed through first-line endocrine therapies. Alpelisib specifically inhibits the PI3K pathway and that is a genetic alteration in the HR positive, HER2-negative breast tumors. Typically, PI3K signalling activity is required for change of oncogenes/tumor suppressors and many types of cancers.(18).

The PIK3CA gene encodes the p110-alpha protein, a subunit of the enzyme PI3K. The p110-alpha protein is the catalytic component responsible for PI3K activity. PI3K phosphorylates signaling molecules, initiating a cascade of events that transmit signals within cells. PI3K signaling plays a crucial role in cell growth, proliferation, motility, protein synthesis, intracellular transport, and survival. Mutations in this gene have been linked to multiple malignancies, including breast, ovarian, lung, brain, and stomach. Previous research indicates that the p110-alpha isoform is crucial for angiogenesis(20).

The PIK3CA mutation associated with cancer is a somatic mutation, meaning it is acquired during a person's lifespan and only found in cancer-causing cells. Cancer-associated PI3K genetic alterations lead to unregulated cell proliferation, resulting in cancer. Resistance to many medicines, such as chemotherapy, hormone therapy, and anti-HER2 therapies, may be due to constitutive activation of the PI3K pathway(21). HR-positive breast cancer typically involves alterations to the PI3K pathway. Around 40% of HR-positive breast cancer patients show gain-of-function mutations in PI3K(22).

Amplification at the 3q26 locus increases the expression of phosphatidylinositol 3-kinase (PI3K) resulting in the activation of PI3K pathway due to loss of function mutation, deletion, or down regulation of phosphatase and tensin homolog (PTEN) gene which occur in 13% of HR-positive breast cancer. Locally advanced or metastatic HR positive breast cancer patients are first treated with hormones to ensure minimization of estrogen levels. (21). The initial systemic therapy for patients with advanced breast cancer with hormone receptor–positive, HER2-negative tumors is endocrine therapy, which may be combined with a CDK4/6 inhibitor. However, resistance to endocrine-based therapy but still remains a major problem(23).

This is why its inhibition has been a focal point in cancer research and development work has been carried out. Endocrine treatment causes estrogen deprivation in PI3K mutated woman and it leads to hyper activation of PI3K/mTOR pathway to promote cell survival and proliferation. PI3K inhibitors themselves impact the growth of these estrogen-deprived cell lines when ER is absent and hence, there is thought that combining a PI3K inhibitor with endocrine therapy can be useful in breast cancer. It is found that fulvestrant is used more commonly than alpelisib due to research and down regulation of the estrogen receptors to lessen the estrogen response in cancer cells.(22).

6.1 Mechanism of action

Alpelisib is a PI3K inhibitor that primarily targets PI3Kα. Mutations in the PIK3CA gene activate PI3Kα and Akt signaling, leading to cellular transformation and tumor growth in both In vivo & In vitro model' s. Alpelisib suppressed the phosphorylation of PI3K downstream targets, included Akt, and shows efficacy in PIK3CA mutant cell lines in breast cancer cell lines. Alpelisib suppresses the PI3K/Akt signaling pathway, reducing tumor development for In vivo and for xenograft models of breast cancer.

The therapy based on Alpelisib is been demonstrated in decrease of PI3K also to Increase estrogen receptor (ER) transcription for breast cancer cells. Fulvestrant & Alpelisib were combined in xenograft models formed by ER-positive, PIK3CA mutant breast cancer cell lines were displayed more anti-tumor effectiveness than either treatment alone(6).

6.2 Pharmacodynamic

Cardiac Electrophysiology

To evaluate alpelisib's impact on the QTcF interval, serial ECGs were conducted after a single dose and at steady state in patients with advanced cancer. Clinical ECG data analysis indicates that the prescribed 300 mg dose of alpelisib, whether taken alone or with fulvestrant, does not significantly prolong the QTcF interval (i.e., no increase greater than 20 ms).(6).

6.3 Pharmacokinetic

Alpelisibs pharmacokinetics has researched for both adult patients and healthy individuals having solid malignancies. Under fed conditions, alpelisib steady-state show Area under curve (AUC) and maximum plasma concentration (Cmax) increases equally between 30-450 mg (0.1-1.5 times the approved therapeutic dose). Alpelisib reaches steady-state plasma concentrations within 3 days of every day administration, with an average accumulation ranging

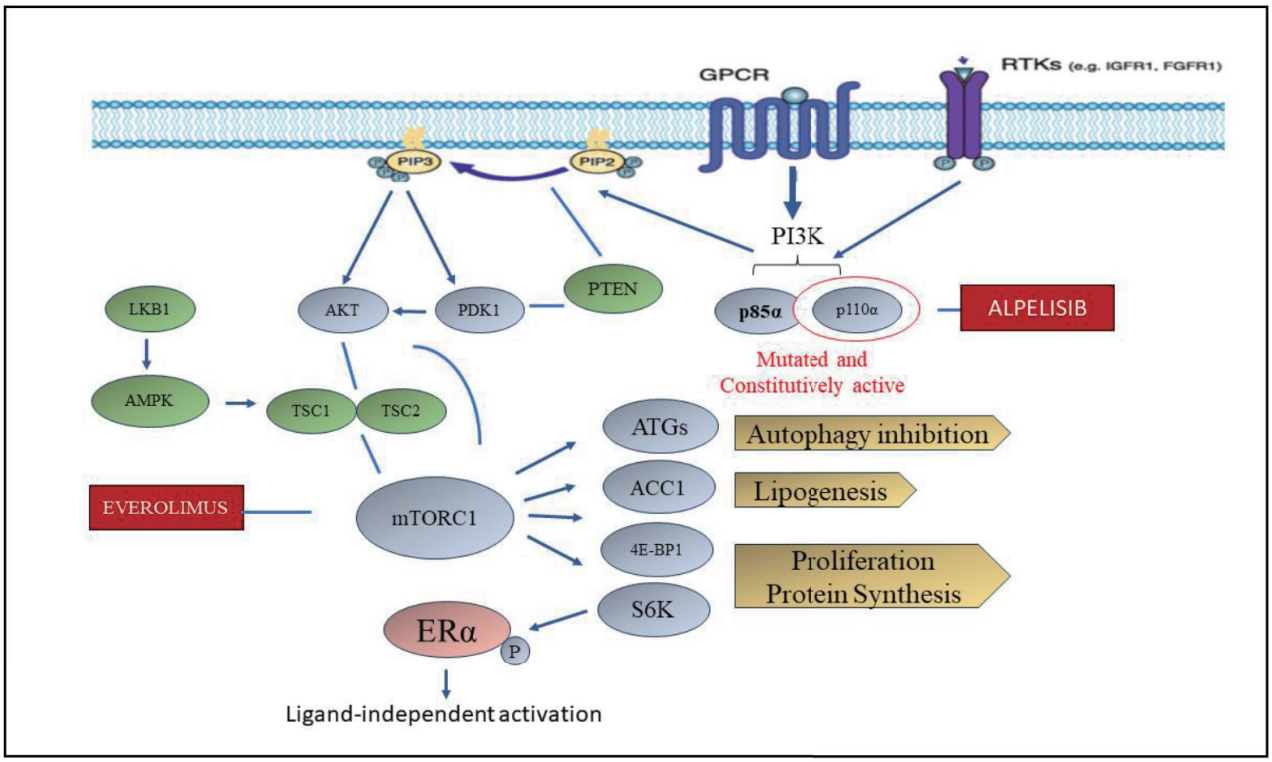

Figure 4: MOA of Alpelisib

from 1.3 to 1.5 times the initial concentration. In adult patients, the population determined alpelisib mean steady-state [coefficient of variation (CV%)] for AUC0-24hr was 33224 (21%) ng*h/mL and Cmax was 2480 (23%) ng/mL who receives the PIQRAY 300 mg once every day in the SOLAR-1 trial (6).

7. Clinical Applications and Efficacy of Alpelisib in Cancer Treatment

In the clinical setting, Alpelisib has shown promise as the Mono-therapy and in combine with others in the treatment of numerous advanced solid-tumors, especially HER2-negative breast cancer with PIK3CA mutations and hormone receptor-positive.(2). Clinical trials evaluating Alpelisib in conjunction with endocrine therapy showed enhanced progression-free survival & overall response rates compared to endocrine therapy alone, underscoring the therapeutic potential of PI3Kα inhibition in this setting(17).

Moreover, ongoing research continues to explore the utility of Alpelisib across a spectrum of malignancies, including gynecologic, gastrointestinal, and hematologic cancers, with emerging evidence suggesting broader applicability beyond breast cancer(1).

8. Side Effects

As with any medication, alpelisib can have side effects, which may include diarrhoea, hyperglycaemia (high blood sugar), rash, nausea, fatigue, and others. Patients ought to speak about potential adverse effects & risks with their physician before beginning treatment. Additionally, regular monitoring is typically required during treatment with alpelisib to manage any side effects and assess its effectiveness.

The uncommon side effects associated with alpelisib include increased alanine aminotransferase, renal impairment, and electrolyte abnormalities such as increased serum potassium, decreased serum magnesium(4).

9. Dosing and Administration

The combine dosage of alpelisib and fulvestrant were determined in an open-label, single-arm phase Ib study conducted at 10 locations in five countries. (15). This trial involved 87 postmenopausal women with either PIK3CA-mutated or wild-type estrogen receptor (ER)-positive metastatic breast cancer, all of whom had seen their disease progress during or after anti-estrogen therapy. The study aimed to identify the maximum tolerated dose, as well as assess the safety and

Table1: Dose Reduction Guidelines for Adverse Reactions

Adverse Reaction Severity	Dose Adjustment	New Dose	Tablet Strength	Number of tablets
Grade 1 or 2	No dose reduced	300 mg	200 mg + 100 mg	1*200 mg + 1*100 mg
Grade 3 [1st Occurrence]	Dose reduced	250 mg	200 mg + 50 mg	1*200 mg + 1*50 mg
Grade 3[2nd Occurrence]	Dose reduced	200 mg	200 mg or 2 *100 mg	1*200 mg or 2*100 mg
Grade 4	Discontinue treatment	N/A	N/A	N/A

If dose reduction is done furtherly, than it should be below 200 mg, one dose is required every day to discontinue the administration of alpelisib.[* means x]

effectiveness of alpelisib. During the dose escalation phase, alpelisib was administered at a dose of 300 mg along with a fixed dose of 500 mg of fulvestrant. The trial included 87 participants who received increasing every day doses of alpelisib: 9 women at 300 mg, 8 women at 350 mg, and 70 women at 400 mg.

The highest tolerable alpelisib dose is when it is mixed with fulvestrant and was found to be 400 mg once every day. However, researchers suggest a phase II dose of 300 mg once every day.(15). According to package information, the suggested alpelisib dose is 300 mg once every day with food .(6). When used with alpelisib, the suggested dose of fulvestrant is 500 mg administered via intramuscular injection on days 1, 15 & 29, followed by once in a month. Alpelisib strengths comes in such as [50 mg, 150 mg, and 200 mg] tablets. Patients receive these tablets in color-coded blister packs, resulting in every day doses of 300 mg, 250 mg & 200 mg. Patients prescribed 250mg /300 mg should take two pills once every day to achieve their required dose, rather than just one tablet.(22).

10. Conclusion

In summary, Alpelisib represents a paradigm shift in the landscape of targeted cancer therapy, leveraging the specificity of PI3Kα inhibition to disrupt oncogenic signaling pathways and impede tumor progression. Its development underscores the importance of precision medicine in oncology, offering tailored therapeutic strategies informed by the molecular underpinnings of individual tumors. As research into Alpelisib and its clinical applications continues to evolve, its role in the oncologist's armamentarium is poised to expand, offering renewed hope for patients grappling with advanced malignancies.

In conclusion, the evolution of Alpelisib as a targeted therapy represents a significant advancement in the field of precision medicine for cancer treatment. Its unique mechanism of action, clinical efficacy in specific cancer subtypes, and ongoing research endeavors underscore its potential to reshape the landscape of cancer therapy. As we navigate the complexities of resistance mechanisms and strive for improved patient outcomes, the journey towards unlocking the full potential of Alpelisib continues to drive innovation and hope in the fight against cancer.

Conflict of interest

The authors declare that they have no competing interests.

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Not Applicable.

List of Abbrivations

1. PIK3CA - Phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha
2. FDA – Food and Drug Administration
3. PROS - PIK3CA-related overgrowth spectrum
4. DLT – Dose Limiting Toxicity
5. PFS – Progression-free Survival
6. MTD – Maximum Tolerated Dose
7. MM-GBSA – Molecular Mechanics with Generalized Born and Surface Area
8. ECG - Electrocardiogram

References

1. Narayan P, Prowell TM, Gao JJ, Fernandes LL, Li E, Jiang X, et al. FDA approval summary: Alpelisib plus fulvestrant for patients with hr-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer. Clin Cancer Res. 2021;27(7):1842–9.
2. Singh S, Bradford D, Li X, Mishra-Kalyani PS, Shen YL, Wang L, et al. FDA Approval Summary: Alpelisib for PIK3CA-Related Overgrowth Spectrum. Clin Cancer Res. 2024;30(1):23–8.
3. Savas P, Lo LL, Luen SJ, Blackley EF, Callahan J, Moodie K, et al. Alpelisib Monotherapy for PI3K-Altered, Pretreated Advanced Breast Cancer: A Phase II Study. Cancer Discov. 2022;12(9):2058–73.
4. Alpelisib - Wikipedia [Internet]. Available from: https://en.wikipedia.org/wiki/Alpelisib
5. Konstantinopoulos PA, Barry WT, Birrer M, Westin SN, Cadoo KA, Shapiro GI, et al. Olaparib and α-specific PI3K inhibitor alpelisib for patients with

epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial. Lancet Oncol [Internet]. 2019;20(4):570–80. Available from: http://dx.doi.org/10.1016/S1470-2045(18)30905-7
6. Novartis Pharmaceuticals Corporation. Piqray (alpelisib) USPI. 2022; Available from: www.fda.gov/medwatch.
7. Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, et al. Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer. 2011;1–10.
8. Armaghani AJ, Han HS. Alpelisib in the Treatment of Breast Cancer: A Short Review on the Emerging Clinical Data. Breast Cancer Targets Ther [Internet]. 2020 Nov;Volume 12:251–8. Available from: https://www.dovepress.com/alpelisib-in-the-treatment-of-breast-cancer-a-short-review-on-the-emer-peer-reviewed-article-BCTT
9. Jones RH, Casbard A, Carucci M, Cox C, Butler R, Alchami F, et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol [Internet]. 2020;21(3):345–57. Available from: http://dx.doi.org/10.1016/S1470-2045(19)30817-4
10. Verret B, Cortes J, Bachelot T, Andre F, Arnedos M. Efficacy of PI3K inhibitors in advanced breast cancer. Ann Oncol Off J Eur Soc Med Oncol [Internet]. 2019;30(10):x12–20. Available from: https://doi.org/10.1093/annonc/mdz381
11. Fritsch C, Huang A, Chatenay-Rivauday C, Schnell C, Reddy A, Liu M, et al. Characterization of the novel and specific PI3Ka inhibitor NVP-BYL719 and development of the patient stratification strategy for clinical trials. Mol Cancer Ther. 2014;13(5):1117–29.
12. LoRusso PM. Inhibition of the PI3K/AKT/mTOR pathway in solid tumors. J Clin Oncol. 2016;34(31):3803–15.
13. Koboldt DC, Fulton RS, McLellan MD, Schmidt H, Kalicki-Veizer J, McMichael JF, et al. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61–70.
14. Stemke-Hale K, Gonzalez-Angulo AM, Lluch A, Neve RM, Kuo WL, Davies M, et al. An integrative genomic and proteomic analysis of PIK3CA, PTEN, and AKT mutations in breast cancer. Cancer Res. 2008;68(15):6084–91.
15. Juric D, Janku F, Rodón J, Burris HA, Mayer IA, Schuler M, et al. Alpelisib Plus Fulvestrant in PIK3CA -Altered and PIK3CA -Wild-Type Estrogen Receptor-Positive Advanced Breast Cancer: A Phase 1b Clinical Trial. JAMA Oncol. 2019;5(2):1–9.
16. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA -Mutated, Hormone Receptor–Positive Advanced Breast Cancer . N Engl J Med. 2019;380(20):1929–40.
17. Armaghani AJ, Han HS. Alpelisib in the treatment of breast cancer: A short review on the emerging clinical data. Breast Cancer Targets Ther. 2020;12:251–8.
18. Katso R, Okkenhaug K, Ahmadi K, Timms J, Waterfield MD. 3-K INASES : Implications for Development , Class I PI3Ks. Annu Rev Cell Dev Biol. 2001;17:615–75.
19. Pattar SV, Adhoni SA, Kamanavalli CM, Kumbar SS. In silico molecular docking studies and MM/GBSA analysis of coumarin-carbonodithioate hybrid derivatives divulge the anticancer potential against breast cancer. Beni-Suef Univ J Basic Appl Sci. 2020;9(1).
20. Graupera M, Guillermet-Guibert J, Foukas LC, Phng LK, Cain RJ, Salpekar A, et al. Angiogenesis selectively requires the p110α isoform of PI3K to control endothelial cell migration. Nature. 2008;453(7195):662–6.
21. McCubrey JA, Steelman LS, Abrams SL, Lee JT, Chang F, Bertrand FE, et al. Roles of the RAF/MEK/ERK and PI3K/PTEN/AKT pathways in malignant transformation and drug resistance. Adv Enzyme Regul. 2006;46(1):249–79.
22. Wilhoit T, Patrick JM, May MB. Alpelisib : A Novel Therapy for. J Adv Pract Oncol. 2020;11(7):768–75.
23. Tankova T, Senkus E, Beloyartseva M, Borštnar S, Catrinoiu D, Frolova M, et al. Management Strategies for Hyperglycemia Associated with the α-Selective PI3K Inhibitor Alpelisib for the Treatment of Breast Cancer. Cancers (Basel). 2022;14(7).