Mechanisms and pathogenicity of the PI3K pathway: from basic research to clinical application

Siyi Chen[1,†], Yingying Ling[2,†], Chenyang Li[3,*,†]

[1] Yew Wah International Education School, Guangzhou, 510000, China

[2] School Basic Medical Sciences, Fujian Medical University, 350122, Fuzhou, Fujian, China

[3] School of Basic Medical Sciences, Fujian Medical University, 350122, Fuzhou, Fujian, China

* Corresponding Author Email: lcy000809@fjmu.edu.cn

[†]These authors contributed equally

Abstract. PI3K signaling pathway is one of the most important signaling pathways in tumorigenesis. Dysfunction of PI3K signalling pathway has been widely found in lymphatic hematologic tumors and solid tumors. Different PI3K inhibitors have shown anti-tumor activity against a variety of tumors. Furthermore, the FDA has approved various PI3K inhibitors for marketing or clinical studies, and have achieved considerable efficacy, especially in lymphoma and breast cancer. However, drug resistance and treatment-related adverse reactions remain unsolved. The PI3K signaling pathway also involves several other physiological functions related signaling pathway networks, and the combination therapy of selective inhibition of these signaling pathways needs to be further explored. New strategies include the combination of allosteric inhibitors and orthosteric inhibitors of PI3Kα and the development of inhibitors of salvage mutation sites. This review summarizes the clinical research progress and common drug resistance mechanisms of various common malignancies involved in PI3K inhibitors. In addition to targeting cancer cells, PI3K inhibitors also have great potential in cancer immunotherapy in the future.

Keywords: Enter key words or phrases in alphabetical order, separated by commas.

1. INTRODUCTION

Phosphatidylinositol-3-kinase (PI3K) was firstly discovered in 1985 in a study of Polyoma middle-T antigen [1]. There are three classes in PI3K family: class1, class2 and class3. Class1 PI3Ks are able to phosphorylate Phosphatidylinositol-4,5-P_2 and produce PI-3,4,5-P_3, an essential second messenger in cell signalling transmitting. PI-3,4,5-P_3 can bind SH2 domain to recruit downstream proteins, through which PI3Ks regulate cell growth, cell cycle and cell survival [2]. Since its function is overactive in various cancer, small molecule inhibitors of PI3Ks have been a hotspot in anti-cancer drug development, especially in leukaemia [3]. Several PI3K inhibitors have been approved in clinical treatment, for example, Duvelisib [4]. However, adverse side effects remain a problem, which may be caused by essential roles of PI3Ks in normal cell activities. Yet PI3Ks inhibitors still have promising potential in cancer treatment and requires more attention. In this review, how PI3Ks work and what drug development has been carried out on this target is to be discussed.

2. structure and function of PI3Ks

2.1. Structure of PI3Ks

Among multiple kinds of phospholipid which forms basic skeleton of cell membrane, Phosphatidylinositol (PI) (PubChem CID 53480050) counts for the least part, but has an indispensable job in cell signalling [5]. There are five free hydroxyls on PI that can be phosphorylated, and phosphorylated derivates of PI such as PI-3-P, PI-4-P, PI-5-P (PubChem CID:53480192), PI-4,5-P_2 (PubChem CID:53480224) and PI-3,4,5-P_3 (PubChem CID:53480339), have been identified as important second messengers in numerous cell signalling (Figure 1).

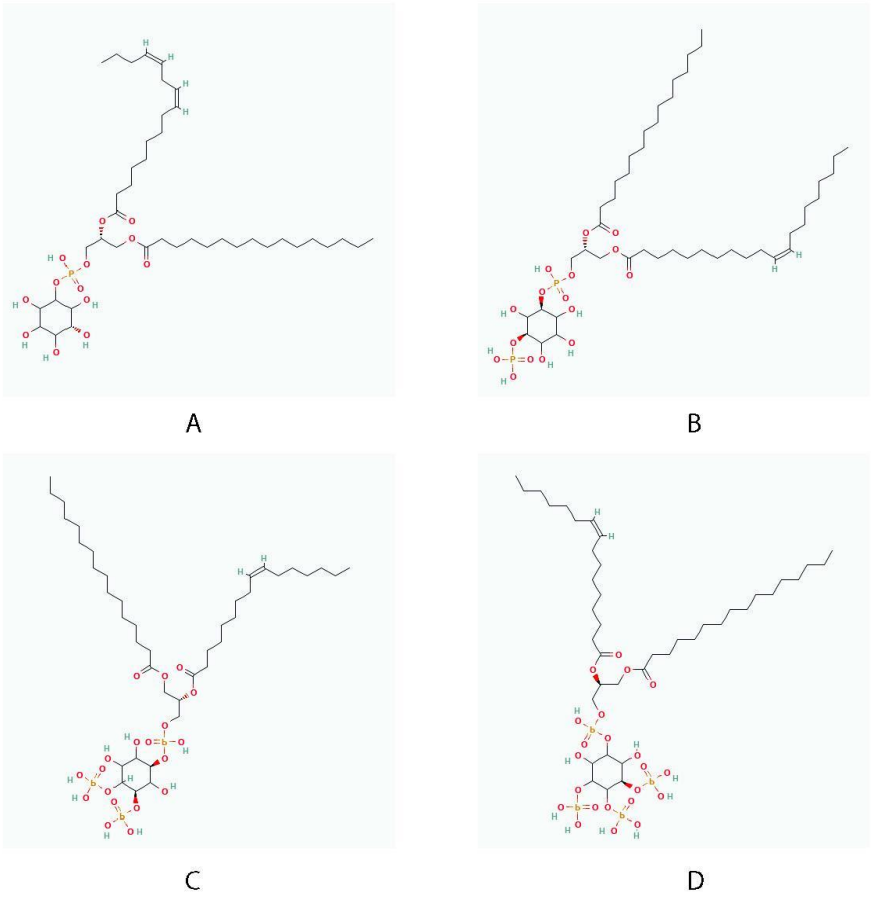


Figure 1. Phosphatidylinositol (PI) and Phosphorylated Derivates of PI.

PI3Ks are phosphorylases that could phosphorylate PI, PI-4-P, PI-4,5-P_2. PI-4,5-P_2 is its major substrate and PI-3,4,5-P_3 is the most important product. There are three classifications of PI3K: Class 1, Class 2 and Class 3 [6]. Since it is the most thoroughly studied classification and its product has been attached to great importance, Class 1 PI3Ks will be mainly discussed in the following parts.

2.1.1. Class 1 PI3Ks

Class 1 PI3Ks are heterodimeric proteins consisting of two subunits: p85, a regulatory subunit, as well as p110, a catalytic subunit, which are named by their molecular weight [7]. Class 1 PI3K have two subgroups: Class 1A and Class 1B. Among Class 1A PI3Ks, p110 has three isoforms: p110α, p110β and p110δ. In Class 1B PI3Ks, p110 has only one isoform: p110γ.

p85 protein has two isoforms which are p85α and p85β [8]. Both of them have domains homologous to other signalling proteins, which contain N-terminal src-homology3 (SH3) domain, src-homology 2 (SH2) domains, etc. Various homologous domains equip p85 with the ability to conjugate with other signalling protein, leading to the recruiting of PI3Ks. Between the two SH2 domains is the region where it interacts with p110 [8]. p85 can also remove the trans-inhibition of p110 to promote the following kinase activity.

p110 has three main domains: a N-terminal domain interacting with p85, a domain can conjugate with small G protein Ras which allows Ras directly activate the catalytic subunit, a kinase domain homologous to other PI kinase [9]. It is noted that p110γ lack the N-terminal domain, which means it not able to bind p85 subunit. It is also demonstrated that PI3K has serine/threonine kinases activities, Which are mainly occurred on the serine residues of regulatory subunit or catalytic subunit [7], suggesting PI3K may have a self-regulation function.

2.1.2. Class 2 and Class3 PI3Ks

Class 2 PI3Ks are 170-210kd monomeric proteins, containing a PIK domain and a domain homologous to C2 domain in C-terminal. It has demonstrated that Class 2 PI3Ks can catalyze phosphorylation of PI and PI-4-P. However, the substrates and functions of class 2 PI3Ks remain unclear. Class 3 PI3Ks have been confirmed only being able to phosphorylate PI and are responsible for increasement of PI-3-P, which is related to vesicle trafficking [10].

2.2. PI3K in cell signalling

2.2.1. PI3K-AKT pathway

Thus, various homologous domains contained in p85 make it possible to interact with other protein and transmit the signal. For instance, tyrosine phosphorylation is very common in activation of numerous cell signalling. Phosphorylated tyrosine can be specifically bind by SH2 domains on the p85 in a certain sequence, such as pTyr-Met-X-Met (pYMXM) [10]. Since a protein conjugate with certain domain on p85, PI3Ks will be recruited to cell membrane and kinase activities will be conducted by p110 catalytic subunit. Additionally, small G protein Ras can directly bind to p110 and activate p110 [6].

With the catalytic subunit of PI3Ks phosphorylating PI-3,4,5-P_3, PI-3,4,5-P_3 is produced and recruits downstream proteins by binding to pleckstrin homology (PH) domain [5]. AKT is a serine/threonine kinase which can phosphorylate numerous downstream targets and activate several pathways. Interaction between PI-3,4,5-P_3 and PH domain on AKT lead to its recruitment to cell membrane and conformational change, which allows the phosphorylation of AKT (Figure 2). Only one phosphorylation on threonine 308 in AKT is not able to completely activate AKT unless there is also phosphorylation on serine 473.

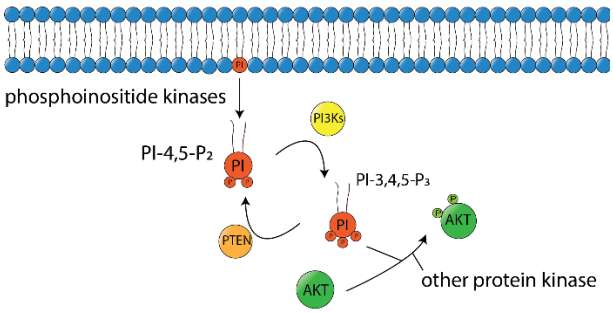


Figure 2. PI3K-AKT pathway and function of PTEN

2.2.2. AKT downstream targets

Once activated, AKT regulate downstream pathways in a phosphorylation-dependent manner. The most discussed is mTOR, a protein kinase regulating variety of cell activities. Since AKT can upregulate mTOR by activate various transcriptional factors, activated mTOR is capable of hyperactivate AKT by phosphorylation of Ser473 [11]. It has been reported that AKT can phosphorylate FKHRL1, a transcriptional factor, to prevent cell death [12]. Apart from FKHRL1, many other transcriptional factors can also be phosphorylated by AKT. IKK can be activated to phosphorylate IκB by AKT, leading to NF-κB pathway activation [13], which is also a transcriptional factor that promote transcription of multiple oncogenes. Mammalian forkhead members of the class O (FOXO) transcription factors takes an important role in cell cycle regulatory, acting as a tumour suppresser. While activated AKT has negative regulatory on FOXO families by phosphorylation [14]. Glycogen synthase kinase-3(GSK-3) is a kinase participate in cell cycle and cell proliferation. GSK-3 regulate cell growth by phosphorylate various factors, like c-Myc and cyclin D1. AKT can phosphorylate GSK-3 to inhibit its regulatory and promote cell growth [15]. In conclusion, PI3K/PI-3,4,5-P_3/AKT pathway occupy an indispensable place in cell cycle, cell growth and cell survival.

2.2.3. Negative regulators of PI3K-AKT pathway

PI3K-AKT pathway plays an important role in cell activities and is under strict regulation. At rest state, concentration of PI-3,4,5-P_3 is too low to be detectable. However, once activated, PI3Ks can elevate the concentration more than 500 folds. To make it under control, PTEN plays an essential role in downregulating the concentration of PI-3,4,5-P_3 [16]. PTEN is a phosphatase which can remove the phosphorylation of PI-3,4,5-P_3, like an eraser. (Figure 2) The balance between PTEN and PI3K make sure cell signalling transmitted precisely. As a negative regulator of PI3Ks, mutation of *PTEN* gene and inhibited function of PTEN were observed in many cancer to promote overactivation of PI3Ks and accelerate tumorigenesis [17]. PHLPP is a phosphatase that can dephosphorylate the phosphorylation on Ser473 of AKT and AKT phosphorylation is elevated by inhibited PHLPP in cancer cells [18].

3. Targeting the PI3K/AKT/mTOR Pathway via gastrointestinal stomal tumor Therapeutics (isoform-specific drugs)

3.1. Pure PI3K Inhibitors

In phase I clinical trials of Imatinib and sunitinib refractory Gastrointestinal Stromal Tumor (GIST) patients were to be employed; and they would be tested with KM120 (NCT01468688) and BYL719 (NCT01735968) in combination with imatinib treatment. These research is aimed to find out the highest dose of BKM120 or BYL719 which in the combination with imatinib to treat patients with refractory GIST [19].

3.2. AKT Inhibitors

In a Phase I or II study, a combination of peri-lobe glycoside and imatinib is used to treat patients with imatinib-resistant metastatic GIST, most of whom experienced a variety of adverse effects, typically ophthalmic toxicity and ulcerative keratitis [20].

3.3. mTOR Inhibitors

In following clinical studies, there were a Phase I and a Phase II study about the efficacy and safety of the combination of RAD001 and imatinib for Imatinib-resistant patients with GIST and all patients had tolerance of this treatment [21]. In the Phase I study, the combination of the ideal dose of imatinib (600 / 800 mg / day) with 20 mg per week or 2.5 / 5.0 mg per day of RAD001 was most suitable for Imatinib-resistant PATIENTS WITH GIST. In another phase II trial, patients with advanced imatinib-resistant GIST are treated most effectively with imatinib 600 mg per day combined with RAD001 2.5 mg per day. Therefore, the combined use of rapamycin analogues with imatinib for imatinib-resistant GIST deserves further study [19].

3.4. Dual PI3K/mTOR Inhibitors

In a Phase I study with approximately 40 experimenters with B-cell malignancies and developed solid tumors, one patient with GIST who had resistance to tisirololimus and had disease for more than a year received SF1126 and had improved disease for more than one year, which may suggest that SF1126 was effective against mTORC1 [22]. In other Phase I study, three patients who have similar conditions treated with GDC-980 with GIST reduced FDG intake by more than 25 percent. One of the patients had a decrease in FDG intake, suggesting that GDC-980 had antitumor activity [23].

3.5. Clinical trials in PI3K Inhibitor-Based Therapies

Some current and finished clinical trials of PI3K for Pan-PI3K inhibitors contain Buparlisib/ NVPBKM120/ BKM120, Pilaralisib/XL147/SAR245408, Copanlisib, TG-100-115. Their aims and progress are collected in Table 1, as well as the adverse events that investigated in clinical trials.

Table 1. Clinical trials of PI3K inhibitor-based therapies [24]

Treatment	Phase and NCT	Outcome and aims
Bupalixib in combination with tyrosine kinase inhibitors, imatinib.	NCT01468688	This combination fails to provide additional benefit (n = 60) compared to therapies currently available for these patients.
Buparlisib/NVP-BKM120/BKM120		To determine the maximum tolerated dose and dose limit toxicity of this drug combination.
Pilaralisib/XL147/SAR245408	Phase I	To study the effectiveness of the combination of MTD and RP2D.
Pilaralisib and MSC1936369B	Phase I dose-escalation trial	To study Polaralisib as a monotherapy.
Copanlisib (Cop) in developed solid tumors	NCT00962611	There is a positive correlation between transient hyperglycemia after infusion. The side effects include CR, PR, endometrial carcinoma, mutations of PIK3CA and PTEN.
TG-100-115	Phase I and Phase II	TG 100-115 was proved to be an effective TRPM7 kinase inhibitor.

CR = Canrenone, PR = partially response, PI3KCA = phosphatidylinositol 3-kinase, PTEN = phosphatase and tension homolog

4. PI3K inhibitor resistance

4.1. The effects of PTEN Activity

PTEN is dephosphorized by dephosphorization of inositol-3,4,5-triphosphate (PIP3). A rise in PI3K presenting and tumorigenesis was observed in mice with the PTEN mutation gene, so the absence of PTEN lipid phosphatase activity trigger to activate AKT in PTEN-null cancers [25]. Another research suggested that the absence of PTEN causes resistance to the PI3K inhibitor Allpelisib in tumors of breast cancer [26].

4.2. Mutations of PI3K

Some patients with PI3K mutation exhibited PI3K inhibitor resistance, such as the PIK3CAE545K helix PI3K homologous domain in exon 9, which inhibits the inhibition of p85 regulatory subunits on p110α. Another type of mutation is PIK3CAH1047, which appears in the exon 20, that exaggerates the mutual effects between the lipid membrane and p110α [27].

4.3. Toxic effects produced by the drug are continuously inhibited by the target.

Pan-PI3K inhibitors have common dose-related toxicity, including diarrhea, fatigue, hyperglycemia and rash. Normally dual PI3K inhibitors have higher susceptibility to toxicity than pan-PI3K or isoform inhibitors. However, isoform-specific PI3Kδ inhibitors are more effective in B-cell malignancies than pan- or bi-PI3K inhibitors because they are less susceptible to toxicity [28].

4.4. Selection of the patient population

Selecting an appropriate patient population with an active PIK3CA mutation is of great help to test whether PI3K inhibitors are effective. For instance, in one Phase I research, the clinical benefit rate

of PI3K inhibitor Allelisib in PIK3CA hotspot mutant tumors was 44%, but it was a fifth of patients with WT PIK3CA [29].

4.5. Miscellaneous Resistance Mechanisms

KRAS and HRAS mutations make PI3K inhibitors less sensitive. The sensitivity of PI3K inhibitors increases when these mutations are reduced [30, 31]. Additionally, there are other factors that lead to the resistance of PI3K inhibitor mechanisms. First, factors including a large number of purine-related metabolites, mitochondrial signaling imbalances, and elevated glycolysis caused the expression of PPP2R2B and PTEN to respond to dual PI3K/mTOR inhibitors [32]. Second, macrophages which are in the tumor conditions may cause the resistance of PI3K inhibitors through the NFkB pathway. Moreover, there is currently a lack of PI3K mutation-specific inhibitors [33].

5. Application of PI3K inhibitors

The PI3K signaling pathway is known to activate human cancers, and almost mediates the occurrence of 50% of malignant tumors. Currently, Many PI3K inhibitors have entered clinical studies or have been approved for marketing (Table 2). Pan-pi3k inhibitors, such as Buparlisib, Pictilisb (GDC-0941), Copanlisib, etc. Pan-pi3k inhibitors can act on all type I PI3K subtypes, so the side effects and toxicity are large, making their clinical progress slow. Inhibitors that selectively act on a subtype of PI3K have less toxic side effects, and some selective PI3K inhibitors have been approved for marketing.

5.1. PI3K signaling pathway in solid tumor

PI3K inhibitors can be used to treat solid tumors, such as liver, breast, prostate, and colon. PI3K regulates the growth, metabolism, differentiation and proliferation of normal tissues and organs. Studies have shown that the PI3K signaling pathway is also activated in most ovarian cancers [34]. This signaling pathway can also be activated in patients with advanced gastric cancer [35].
PI3K was over-expressed in ovary and cervical cancer, and mutations were observed in breast cancer. Moreover, the PTEN/PI3K/Akt pathway plays an important role in maintaining the original cells of prostate cancer stem cells, and the targeted PI3K signal can complete the clearance of prostate cancer stem cell-like cells, which has important implications for the therapy of prostate cancer [34].

5.1.1. PI3K inhibitors and breast cancer

Alpelisib is the first developed oral PI3K inhibitor that inhibits the P110α subunit of HER-2 negative breast cancer. It was shown tolerable toxicity and good efficacy both in preclinical and phase I clinical studies [36]. As an important part of a Phase III clinical research of post-menopausal HR/HER2, patients with advanced breast cancer with PI3K mutations, Alpelisib versus placebo combined with flurvestrant showed predictive value for Alpelisib in both tissue and circulating tumor DNA PI3K mutations. In PI3K mutated patients, Alpelisib in combination with flulvesant significantly prolonged PFS. However, treatment-related adverse events (hyperglycemia and rash) led to a slightly higher discontinuation rate of about 25% [35]. In May 2019, the Alpelisib in conjunction with flurvistrine to treat advanced breast cancer in post-menopausal men and women with $HR^+/HER2^-$ and PI3K mutations was approved by the FDA. A similar study comparing the Alpelisib or Buparlisib phase III clinical trial or placebo combined with Letrozole recruited post-menopause patients with $HR^+/HER2^-$ with stage T1-T3C operable breast cancer. There was no statistical difference in ORR and pathological CR between Alpelisib group and placebo combined with Letrozole group. The Buparlisib combined with letrozole regimen was shut down due to an unacceptable adverse reaction in the patient [37].

In addition, other PI3K inhibitors, whether pan-PI3K inhibitors or selective PI3K subunit inhibitors, including Buparlis-Ib, Pictilisib and Taselisib, although they have shown good anti-tumor effects in basic and pre-clinical studies of breast cancer, they cannot bring significant clinical benefits to breast cancer patients in clinical studies. Clinical phase studies of Pictilisib associated with

chemotherapy. (paclitaxel in conjunction with Pictilisib and placebo) or endocrine therapy (flulvesant combined with Pictilisib or placebo) failed to bring clinical benefit to breast cancer patients, so subsequent clinical studies of Pictilisib were stopped [38].

In breast cancer with positive HER-2, HER-2 signaling almost entirely passes through the P110α subkeynote of PI3K. PI3K signaling pathway may have a synergistic effect with HER-2 inhibitors to some extent. Unfortunately, relevant clinical studies have shown that it fails to bring benefits patients [39].

PI3K inhibitors continue to be in the early stages of developing triple negative breast cancer. Researchers used paclitaxel in combination with an AKT inhibitor to treat metastatic triple-negative breast cancer, PTEN gene deletion and INPP4B phosphorylation are closely related to AKT phosphorylation. These early clinical trial results are encouraging [40].

5.1.2. PI3K inhibitors and other solid tumors

In preclinical studies of ovarian cancer, PI3K inhibitors can significantly kill ovarian cancer cells, especially in the presence of PI3K mutation or PTEN deletion. Preclinical studies suggested that PARP inhibitors combined with PI3K inhibitors showed stronger antitumor effect in ovarian cancer cells. However, The effectiveness of the combined PARP inhibitors was not predicted by the PI3K mutations, and the results of early clinical trials have been unsatisfactory [39].

The phenomenon of high frequency mutations in genes or loci related to the PI3K signaling pathway in patients with head and neck cancer has been reported by many studies. The PI3K inhibitor Alpelisib has shown good anti-tumor properties in basic studies and has been well tolerated with small treatment-related adverse reactions in clinical phase I/II trials [41]. Buparlisib has been shown different anti-tumor effects in several tumor species in basic studies. Buparlisib combined with AZD1775, a cell cycle inhibitor, also significantly enhanced the cytotoxic antitumor effect. Other PI3K inhibitors, including dual-targeted inhibitors such as Dactolisib and Gedatolisib in combination with mTOR, have shown modest efficacy in clinical trials involving head and neck tumours [42].

5.2. Application of PI3K inhibitors to lymphatic hematological system tumors

5.2.1. Application to chronic lymphocytic leukemia

PI3Kγ can be expressed directly in CLL cells and play a nonredundant role in cell migration and adherence. Therefore, inhibition of PI3Kγ may play an antitumor role by disrupting the pro-survival signals of T cells in the CLL microenvironment [43].

Idelalisib is a PI3K inhibitor that can be used to treat CLL. A Phase III randomized controlled trial 116 compared idelalisib rituximab with placebo-rituximab in patients with R/R type CLL ineligible for cytotoxic chemotherapy. Idelalisib-rituximab may confer superior ORR and median progression-free survival in patients with CLL. [44].

Duvelisib is also an oral inhibitor, studies have shown that PI3K inhibitors can reduce immune escape of bone marrow cells associated with tumor microenvironment and slow tumor cell proliferation [45]. The FDA approved Duvelisib in September 2018, it is mainly used to treat patients with second-line or higher relapsed/refractory CLL/ small lymphocytic lymphoma (SLL), it has been determined to be effective in about 35% of patients who have discontinuation due to adverse reactions [46].

5.2.2. Application to non- Hodgkin's lymphoma

The objective response rate for idelalisib in the Non-Hodgkin's lymphoma phase I clinical trials was about 47%. In the phase II single-arm clinical study, which was the same as the subtype of lymphoma enrolled in Phase I (mainly follicular lymphoma and SLL), the study found that the drug was safe and treatment-related adverse reactions could be tolerated [47].

The clinical research of Copanlisb in relapsed follicular lymphoma showed not only tolerable treaty-related adverse reactions, but also considerable objective response rate through an improved Copanlisib administration regimen. In a later Phase II clinical investigation, relapsed/refractory inactivated non-Hodgkin lymphoma (mainly relapsed/refractory follicular lymphoma) was enrolled,

and the objective response rate was like that of Idelalisib (ORR about 59%, PFS about 11 months), with a higher CR rate in patients with relapsed/refractory follicular lymphoma [48]. In addition, in non-Hodgkin's lymphoma, Copanlisib has shown promising efficacy in patients with relapsed clost-cell lymphoma, the clinical trials were being conducted to combine Copanlisib and Ibrutinib to treat diseases of are ongoing. PI3K inhibitors are relatively poorly studied in non-Hodgkin's lymphoma (NHL), and included in a clinical trial of relapsed/refractory indolent T-cell NHL (primarily peripheral and cutaneous T-cell lymphatic), adverse events were well tolerated by patients [34].

Table 2. Clinical application of PI3K inhibitors

Drug	PI3K inhibitor class	Disease indication	Monotherapy or combination	References
Alpelisib	PI3Kα inhibitor	PIK 3CA-mutated, hormone receptor-positive, human EGFR2-negative ABC	Combination with Fluvestrant (ER inhibitor)	[49]
Idelalisib	PI3Kδ inhibitor	Two prior systemic treatments for FL; two prior systemic treatments for SLL	Rituximab therapy alone is considered the most effective treatment in patients with other comorbidities	[50]
Umbralisib	PI3Kδ inhibitor	FL, CLL, MZ lymphoma	Combination of anti-CD20 antibody and ublituximab for CLL, FL, MZ lymphoma	[9]
Duvelisib	PI3Kδ or PI3Kγ inhibitor	Two piror systemic treatments for CLL; two prior systemic treatments for SLL and FL	Monotherapy	[51]
Copanlisib	Pan-PI3K inhibitor	Two systemic treatments for FL	Monotherapy	[52]

PI3K = Phosphatidylinositol-3-kinase; ER = Estrogen Receptor; EGFR = Epidermal Growth Factor Receptor; FL = Follicular Lymphoma; CLL = Chronic Lymphocytic Leukemia; SLL = Small Lymphocytic Lymphoma; MZL = Marginal Zone Lymphoma; ABC = Advanced Breast Cancer.

6. CONCLUSION

The mechanism of PI3K inhibitor includes its function in the phosphatidylinositol-3-kinase (PI3K), PI3K downstream and PI3K-AKT's role in tumorigenesis. Besides, advances and difficulties of PI3K drugs applied in clinical trials are listed. In addition, PI3K inhibitors are widely used in treatments of hematologic malignancies, squamous cell lung carcinoma, fibroblast-like synoviocytes in osteoarthritis, leukemia and breast cancer. Moreover, some new drugs such as TG-100-115 and RIDR-PI-103 still require more clinical trials. Furthermore, some new P13K inhibitors, like TG-100-115, B591 and RIDR-PI-103 have deficiency *in vivo* and *in vitro* research and require further exploration using PK and PD models for clinical application.

REFERENCES

[1] M. Whitman, D.R. Kaplan, B. Schaffhausen, et al., Association of phosphatidylinositol kinase activity with polyoma middle-t competent for transformation. Nature, 1985, pp. 239-242. DOI: https://dx.doi.org/10.1038/315239a0
[2] L. Zhao and P.K. Vogt, Class i pi3k in oncogenic cellular transformation. Oncogene, 2008, pp. 5486-5496. DOI: https://dx.doi.org/10.1038/onc.2008.244
[3] J. Bertacchini, N. Heidari, L. Mediani, et al., Targeting pi3k/akt/mtor network for treatment of leukemia. Cell Mol Life Sci, 2015, pp. 2337-2347. DOI: https://dx.doi.org/10.1007/s00018-015-1867-5
[4] H.A. Blair, Duvelisib: First global approval. Drugs, 2018, pp. 1847-1853. DOI: https://dx.doi.org/10.1007/s40265-018-1013-4
[5] R.D. Riehle, S. Cornea, and A. Degterev, Role of phosphatidylinositol 3,4,5-trisphosphate in cell signaling. Adv Exp Med Biol, 2013, pp. 105-139. DOI: https://dx.doi.org/10.1007/978-94-007-6331-9_7
[6] M.D. Goncalves, B.D. Hopkins, and L.C. Cantley, Phosphatidylinositol 3-kinase, growth disorders, and cancer. N Engl J Med, 2018, pp. 2052-2062. DOI: https://dx.doi.org/10.1056/NEJMra1704560
[7] B.T. Hennessy, D.L. Smith, P.T. Ram, et al., Exploiting the pi3k/akt pathway for cancer drug discovery. Nat Rev Drug Discov, 2005, pp. 988-1004. DOI: https://dx.doi.org/10.1038/nrd1902
[8] J. Vallejo-Diaz, M. Chagoyen, M. Olazabal-Moran, et al., The opposing roles of pik3r1/p85alpha and pik3r2/p85beta in cancer. Trends Cancer, 2019, pp. 233-244. DOI: https://dx.doi.org/10.1016/j.trecan.2019.02.009
[9] N.H. Fowler, F. Samaniego, W. Jurczak, et al., Umbralisib, a dual pi3kδ/ck1ε inhibitor in patients with relapsed or refractory indolent lymphoma. J Clin Oncol, 2021, pp. 1609-1618. DOI: https://dx.doi.org/10.1200/jco.20.03433
[10] M.R. Fruman DA, Cantley LC., Phosphoinositide kinases. Annu Rev Biochem, 1998. DOI: https://dx.doi.org/10.1146/annurev.biochem.67.1.481
[11] A.S. Alzahrani, Pi3k/akt/mtor inhibitors in cancer: At the bench and bedside. Semin Cancer Biol, 2019, pp. 125-132. DOI: https://dx.doi.org/10.1016/j.semcancer.2019.07.009
[12] A. Brunet, A. Bonni, M.J. Zigmond, et al., Akt promotes cell survival by phosphorylating and inhibiting a forkhead transcription factor. Cell, 1999, pp. 857-868. DOI: https://dx.doi.org/10.1016/s0092-8674(00)80595-4
[13] R.J. Shaw and L.C. Cantley, Ras, pi(3)k and mtor signalling controls tumour cell growth. Nature, 2006, pp. 424-430. DOI: https://dx.doi.org/10.1038/nature04869
[14] Y. Furukawa-Hibi, Y. Kobayashi, C. Chen, et al., Foxo transcription factors in cell-cycle regulation and the response to oxidative stress. Antioxid Redox Signal, 2005, pp. 752-760. DOI: https://dx.doi.org/10.1089/ars.2005.7.752
[15] S. Frame and P. Cohen, Gsk3 takes centre stage more than 20 years after its discovery. Biochem J, 2001, pp. 1-16. DOI: https://dx.doi.org/10.1042/0264-6021:3590001
[16] H. Sun, R. Lesche, D.M. Li, et al., Pten modulates cell cycle progression and cell survival by regulating phosphatidylinositol 3,4,5,-trisphosphate and akt/protein kinase b signaling pathway. Proc Natl Acad Sci U S A, 1999, pp. 6199-6204. DOI: https://dx.doi.org/10.1073/pnas.96.11.6199
[17] M.L. D Bonneau Mutations of the human pten gene. HUMAN MUTATION, 2000. DOI: https://dx.doi.org/ 10.1002/1098-1004(200008)16:2<109::AID-HUMU3>3.0.CO;2-0
[18] T. Gao, F. Furnari, and A.C. Newton, Phlpp: A phosphatase that directly dephosphorylates akt, promotes apoptosis, and suppresses tumor growth. Mol Cell, 2005, pp. 13-24. DOI: https://dx.doi.org/10.1016/j.molcel.2005.03.008
[19] Y. Duan, J. Haybaeck, and Z. Yang, Therapeutic potential of pi3k/akt/mtor pathway in gastrointestinal stromal tumors: Rationale and progress. Cancers (Basel), 2020. DOI: https://dx.doi.org/10.3390/cancers12102972
[20] D. Shome, J. Trent, L. Espandar, et al., Ulcerative keratitis in gastrointestinal stromal tumor patients treated with perifosine. Ophthalmology, 2008, pp. 483-487. DOI: https://dx.doi.org/10.1016/j.ophtha.2007.11.016
[21] P. Schöffski, P. Reichardt, J.Y. Blay, et al., A phase i-ii study of everolimus (rad001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Ann Oncol, 2010, pp. 1990-1998. DOI: https://dx.doi.org/10.1093/annonc/mdq076

[22] D. Mahadevan, E.G. Chiorean, W. Harris, et al., Phase i study of the multikinase prodrug sf1126 in solid tumors and b-cell malignancies. Journal of Clinical Oncology, 2011, pp. 3015-3015. DOI: https://dx.doi.org/10.1200/jco.2011.29.15_suppl.3015
[23] S. Dolly, A.J. Wagner, J.C. Bendell, et al., A first-in-human, phase l study to evaluate the dual pi3k/mtor inhibitor gdc-0980 administered qd in patients with advanced solid tumors or non-hodgkin's lymphoma. Journal of Clinical Oncology, 2010, pp. 3079-3079. DOI: https://dx.doi.org/10.1200/jco.2010.28.15_suppl.3079
[24] R. Mishra, H. Patel, S. Alanazi, et al., Pi3k inhibitors in cancer: Clinical implications and adverse effects. Int J Mol Sci, 2021. DOI: https://dx.doi.org/10.3390/ijms22073464
[25] A. Papa, L. Wan, M. Bonora, et al., Cancer-associated pten mutants act in a dominant-negative manner to suppress pten protein function. Cell, 2014, pp. 595-610. DOI: https://dx.doi.org/10.1016/j.cell.2014.03.027
[26] D. Juric, P. Castel, M. Griffith, et al., Convergent loss of pten leads to clinical resistance to a pi(3)kα inhibitor. Nature, 2015, pp. 240-244. DOI: https://dx.doi.org/10.1038/nature13948
[27] W. Jiang, T. He, S. Liu, et al., The pik3ca e542k and e545k mutations promote glycolysis and proliferation via induction of the β-catenin/sirt3 signaling pathway in cervical cancer. J Hematol Oncol, 2018, pp. 139. DOI: https://dx.doi.org/10.1186/s13045-018-0674-5
[28] A.B. Hanker, V. Kaklamani, and C.L. Arteaga, Challenges for the clinical development of pi3k inhibitors: Strategies to improve their impact in solid tumors. Cancer Discov, 2019, pp. 482-491. DOI: https://dx.doi.org/10.1158/2159-8290.Cd-18-1175
[29] D. Juric, J. Rodon, J. Tabernero, et al., Phosphatidylinositol 3-kinase α-selective inhibition with alpelisib (byl719) in pik3ca-altered solid tumors: Results from the first-in-human study. J Clin Oncol, 2018, pp. 1291-1299. DOI: https://dx.doi.org/10.1200/jco.2017.72.7107
[30] K.M. Ruicci, N. Pinto, M.I. Khan, et al., Erk-tsc2 signalling in constitutively-active hras mutant hnscc cells promotes resistance to pi3k inhibition. Oral Oncol, 2018, pp. 95-103. DOI: https://dx.doi.org/10.1016/j.oraloncology.2018.07.010
[31] J.A. Engelman, L. Chen, X. Tan, et al., Effective use of pi3k and mek inhibitors to treat mutant kras g12d and pik3ca h1047r murine lung cancers. Nat Med, 2008, pp. 1351-1356. DOI: https://dx.doi.org/10.1038/nm.1890
[32] H. Makinoshima, S. Umemura, A. Suzuki, et al., Metabolic determinants of sensitivity to phosphatidylinositol 3-kinase pathway inhibitor in small-cell lung carcinoma. Cancer Res, 2018, pp. 2179-2190. DOI: https://dx.doi.org/10.1158/0008-5472.Can-17-2109
[33] M.W. Usman, J. Gao, T. Zheng, et al., Author correction: Macrophages confer resistance to pi3k inhibitor gdc-0941 in breast cancer through the activation of nf-κb signaling. Cell Death Dis, 2019, pp. 501. DOI: https://dx.doi.org/10.1038/s41419-019-1692-0
[34] P. Xia and X.Y. Xu, Pi3k/akt/mtor signaling pathway in cancer stem cells: From basic research to clinical application. Am J Cancer Res, 2015, pp. 1602-1609.
[35] F. André, E. Ciruelos, G. Rubovszky, et al., Alpelisib for pik3ca-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med, 2019, pp. 1929-1940. DOI: https://dx.doi.org/10.1056/NEJMoa1813904
[36] F. André, E.M. Ciruelos, D. Juric, 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, pp. 208-217. DOI: https://dx.doi.org/10.1016/j.annonc.2020.11.011
[37] W. Wu, J. Chen, H. Deng, et al., Neoadjuvant everolimus plus letrozole versus fluorouracil, epirubicin and cyclophosphamide for er-positive, her2-negative breast cancer: A randomized pilot trial. BMC Cancer, 2021, pp. 862. DOI: https://dx.doi.org/10.1186/s12885-021-08612-y
[38] J. Baselga, S.A. Im, H. Iwata, 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, pp. 904-916. DOI: https://dx.doi.org/10.1016/s1470-2045(17)30376-5
[39] S. Ebrahimi, M. Hosseini, S. Shahidsales, et al., Targeting the akt/pi3k signaling pathway as a potential therapeutic strategy for the treatment of pancreatic cancer. 2017, pp. 1321-1331. DOI: https://dx.doi.org/10.2174/0929867324666170206142658
[40] S. Jain, A.N. Shah, C.A. Santa-Maria, et al., Phase i study of alpelisib (byl-719) and trastuzumab emtansine (t-dm1) in her2-positive metastatic breast cancer (mbc) after trastuzumab and taxane therapy. Breast Cancer Res Treat, 2018, pp. 371-381. DOI: https://dx.doi.org/10.1007/s10549-018-4792-0

[41] K.L. Reckamp, G. Giaccone, D.R. Camidge, et al., A phase 2 trial of dacomitinib (pf-00299804), an oral, irreversible pan-her (human epidermal growth factor receptor) inhibitor, in patients with advanced non-small cell lung cancer after failure of prior chemotherapy and erlotinib. Cancer, 2014, pp. 1145-1154. DOI: https://dx.doi.org/10.1002/cncr.28561
[42] M.J. Lee, N. Jin, J.R. Grandis, et al., Alterations and molecular targeting of the gsk-3 regulator, pi3k, in head and neck cancer. Biochim Biophys Acta Mol Cell Res, 2020, pp. 118679. DOI: https://dx.doi.org/10.1016/j.bbamcr.2020.118679
[43] K. Patel and J.M. Pagel, Exploring a future for pi3k inhibitors in chronic lymphocytic leukemia. Curr Hematol Malig Rep, 2019, pp. 292-301. DOI: https://dx.doi.org/10.1007/s11899-019-00525-9
[44] R.R. Furman, J.P. Sharman, S.E. Coutre, et al., Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med, 2014, pp. 997-1007. DOI: https://dx.doi.org/10.1056/NEJMoa1315226
[45] Duvelisib, in Drugs and lactation database (lactmed). 2006, National Library of Medicine (US): Bethesda (MD).
[46] I.W. Flinn, S. O'Brien, B. Kahl, et al., Duvelisib, a novel oral dual inhibitor of pi3k-δ,γ, is clinically active in advanced hematologic malignancies. Blood, 2018, pp. 877-887. DOI: https://dx.doi.org/10.1182/blood-2017-05-786566
[47] A.K. Gopal, M.A. Fanale, C.H. Moskowitz, et al., Phase ii study of idelalisib, a selective inhibitor of pi3kδ, for relapsed/refractory classical hodgkin lymphoma. Ann Oncol, 2017, pp. 1057-1063. DOI: https://dx.doi.org/10.1093/annonc/mdx028
[48] A.K. Gopal, B.S. Kahl, S. de Vos, et al., Pi3kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med, 2014, pp. 1008-1018. DOI: https://dx.doi.org/10.1056/NEJMoa1314583
[49] C. Vernieri, F. Corti, F. Nichetti, et al., Everolimus versus alpelisib in advanced hormone receptor-positive her2-negative breast cancer: Targeting different nodes of the pi3k/akt/mtorc1 pathway with different clinical implications. Breast Cancer Res, 2020, pp. 33. DOI: https://dx.doi.org/10.1186/s13058-020-01271-0
[50] P. Ghia, A. Pluta, M. Wach, et al., Ascend: Phase iii, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol, 2020, pp. 2849-2861. DOI: https://dx.doi.org/10.1200/jco.19.03355
[51] S.M. Horwitz, R. Koch, P. Porcu, et al., Activity of the pi3k-δ,γ inhibitor duvelisib in a phase 1 trial and preclinical models of t-cell lymphoma. Blood, 2018, pp. 888-898. DOI: https://dx.doi.org/10.1182/blood-2017-08-802470
[52] A. Kumar, R. Bhatia, P. Chawla, et al., Copanlisib: Novel pi3k inhibitor for the treatment of lymphoma. Anticancer Agents Med Chem, 2020, pp. 1158-1172. DOI: https://dx.doi.org/10.2174/1871520620666200317105207