The PI3K Pathway Targeted Inhibitors and Their Anti-tumor Effects

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Abstract: The PI3K signaling pathway is one of the important signal transduction pathways in cells, and it is also a common abnormal expression signal pathway in cancer cells. Cell proliferation, differentiation, death, glucose transport, and other cell processes are all regulated by the PI3K signaling system. Because of this, both the occurrence and development of a range of tumors are thought to be inextricably linked to PI3K. In recent years, the study of anti-tumor regulatory mechanisms with PI3K as a molecular target has attracted much attention. According to the different regulatory mechanisms of the PI3K signaling pathway, Pan-PI3K Inhibitors, Dual PI3K/mTOR Inhibitors, and Isoform-specific PI3K Inhibitors are the three types of inhibitors. At present, many studies have found a variety of effective inhibitors, and these inhibitors provide more directions and options for the treatment of various tumors. Research on PI3K inhibitors is ongoing. This article reviews the research progress of PI3K pathway inhibitors in anti-tumor aspects in recent years.

1. Introduction

The phosphatidylinositol 3'-kinase (PI3K) signaling pathway is one of the most important intracellular signaling pathways in mammals which is essential for a variety of important physiological functions such as cell cycle, cell growth, protein synthesis, metabolisms, and angiogenesis [1]. It is directly related to as many as 71 of the signaling pathways, most of which are vital in human diseases. The signal transduction cascade formed by PI3K and its downstream signal molecules such as the protein kinase B (Akt) and the mammalian target of rapamycin (mTOR) plays an important role in tumorigenesis and metastasis of various hematological and solid tumors [2]. As a result, the PI3K signaling pathway has become a major focus of targeted therapies in cancer treatment.

PI3K is a family of enzymes with a heterodimer structure composed of a catalytic subunit and a regulatory subunit. The regulatory subunit contains an SH2 (SrcHomology2) domain that can combine with the phosphorylated tyrosine residues on the corresponding target proteins for interactions [3]. The PI3K family can be generally classified into Class I, II and III based on its specific structure and substrate specificity. Among them, Class I PI3K is most relevant to human cancer while Class II and Class III PI3K mainly play a role in transmembrane and intracellular transport. Class I PI3K can be further classified into Class IA and Class IB. Class IA PI3K includes PI3Kα, PI3Kβ and PI3Kδ which consists of a corresponding catalytic subunit p110 (p110α, p110β, p110δ) and a regulatory subunits p85. Class IB (PI3Kγ) is composed of a catalytic subunit p110γ and a regulatory subunit p101 or p87. The p110α and p110β PI3K are universally expressed, while the expressions of p110γ and p110δ PI3K are enriched in immune cells.

The researches on PI3K began in the 1980s, and the first PI3K inhibitor was developed in 1994[4]. The first PI3K inhibitor on the market was Idelalisib, after which other PI3K inhibitors such as Copanlisib also came into the market. By the end of 2021, there have been 5 drugs targeting the PI3K pathway on the market. Many other drugs are still in clinical trials or are waiting for marketing

authorization. Overall, PI3K inhibitors can be classified into three categories – Pan-PI3K inhibitors, dual PI3K/mTOR inhibitors and isoform-specific PI3K Inhibitors. In this review, we separately summarized the research progress of these three categories of PI3K inhibitors in recent years.

2. Pan-PI3K Inhibitors

Pan-PI3K inhibitors target all the four isoforms of class I PI3K. This type of inhibitor through competitively binding to ATP to inhibit hyper-activation of PI3K. Inhibit PI3K phosphorylate phosphatidylinositol 4,5-bisphosphate, PIP2, to phosphatidylinositol 3,4,5 trisphosphate (PIP3) which inhibits a cascade of downstream reactions of the PI3K signaling pathway. The development of this non-selective reversible inhibitor is limited by lack of specificity, causes adverse effects, off-target and on-target toxicity. According to our search on PubMed, many studies and clinical trials of Pan-PI3K inhibitors have been suspended in recent years such as Pilaralisib, PX-866. To date, only Copanlisib has been approved by the U.S. Food and Drug Administration (FDA). Three drugs in this category that have been studied extensively are selected for a detailed introduction.

2.1 Buparlisib

It is an oral reversible pan-PI3K inhibitor. It combined with Fulvestrant, as the second or third line, to treat postmenopausal patients with HR+/HER2- metastatic breast cancer [5]. The Safety was assessed in phase III clinical trial, compared with the control group, fulvestrant with placebo, the possibility of each adverse effect is increased. Hyperglycaemia (43%), increased ALT (41%), nausea (39%), diarrhea (35%) and fatigue (32%) are all common adverse effects [5]. Buparlisib can cross the blood-brain barrier, this could explain the symptoms of depression (27%) and anxiety (22%) that patients experience during treatment [5]. Although the efficacy of Buparlisib met the primary endpoint, there is no significant difference in progression-free survival between two groups in non-PIK3CA mutant [5]. In this case, identifying specific biomarkers and gene mutation seems to significantly improve the effect of Buparlisib. In recent years, many clinical trials have focused on the efficacy and safety of the coadministration of Buparlisib and Paclitaxel in the treatment of various types of tumors such as HER2- advanced breast cancer and squamous cell carcinoma of the head and neck (SCCHN). Unfortunately, this coadministration shows no improvement in HER2- advanced breast cancer, the clinical trial was stopped at phase ii [6]. Coadministration with Paclitaxel has been shown to improve the efficacy of SCCHN treatment in phase II clinical trials compare to Paclitaxel alone and the safety is also management [7]. The combination of Buparlisib with Paclitaxel showed no significant difference in the incidence of adverse effects and drug toxicity compared with Paclitaxel mono-therapy [7]. The company is also conducting phase II trials for follicular lymphoma, gastrointestinal stromal tumor, mantal cell lymphoma, diffuse large B-cell lymphoma, non-small cell lung cancer.

2.2 Pictilisib

Pictilisib is an oral PI3K α/δ inhibitor. The coadministration of Pictilisib and Fulvestrant to patients with HR+/HER2- metastatic breast cancer was enrolled in the phase II trial [8]. Similar to Buparlisib, the toxicity of Pictilisib might limit the efficacy. In an open-label, phase Ib study, Pictilisible combined with cobimetinib was evaluated in patients with advanced or metastatic solid tumors, to identify the confirm the dose-limiting toxicities (DLTs) and the maximum tolerated doses (MTDs) [9]. After 2020, there are no clinical trials in progressing on Pictilisib.

2.3 Copanlisib (approved by FDA)

Copanlisib is an intravenous Pan-PI3K inhibitor. Copanlisib (ALIQOPA) is the first Pan-PI3K inhibitor approved by the FDA for the treatment of relapsed follicular lymphoma. The FDA recommends the dose of copanlisib is 60mg intravenous, every seven days on a twenty-eight-day cycle until the patients develop severe toxicity [10]. According to the clinical phase ii study, nearly 50% of patients have transient hypertension during treatment. This is the most common treatment-

related adverse effect, except transient hypertension, about 30% of patients experience diarrhea, fatigue, nausea, fever or on-target effect hyperglycemia [10]. The phase iii coadministration of Copanlisib and rituximab used in patients with relapsed indolent non-Hodgkin lymphoma shows effect improvement compared with rituximab monotherapy [4]. There was a significant increase in toxicity and adverse effects compared with rituximab monotherapy. The incidence of adverse events in coadministration is similar to that in copanlisib monotherapy and no new adverse events appear [11].

3. Dual PI3K/mTOR Inhibitors

Dual PI3K/mTOR inhibitors target both the PI3K and the mTOR pathways. Single PI3K or mTOR inhibitors can easily lead to drug resistance. For example, Rapamycin and its derivatives, which are representative drugs of mTOR inhibitors, will cause feedback activation of Akt when they inhibit mTOR, leading to reactivation of the PI3K signaling pathway. Single PI3K inhibitors will cause drug resistance once the p110α is mutated [12]. Although using inhibitors of other signaling molecules in the PI3K signaling pathway such as PKB inhibitors can effectively block the PI3K/mTOR signaling pathway, it will cause an imbalance in insulin and glucose metabolism since the PI3K signaling pathway is also associated with various other diseases in addition to cancer involving glucose metabolism, inflammation and immunity. Moreover, other factors such as nutrient intake and growth factors can directly activate Akt and mTOR bypassing PI3K, and mTOR can also act on PI3K as feedback [13]. Overall, the development of the PI3K/mTOR dual inhibitors can help to reduce the occurrence of drug resistance and prevent the activation of PI3K pathway by other factors without causing an imbalance in glucose metabolism. Therefore, PI3K/mTOR dual inhibitors have become one of the hot spots in the research and development of anti-tumor drugs in recent years.

A series of researches have been conducted on PI3K/mTOR dual inhibitors, and some of the PI3K/mTOR dual inhibitors have entered the phase of clinical studies as anti-tumor drugs. Few drugs have been approved by the FDA for clinical use due to their obvious toxicity characteristics. Recently, researchers have discovered some PI3K/mTOR dual inhibitors with various structures, the most representative of which are those with arylurea and 5-pyridyl heterocyclic structures. The dual inhibitors with the triazines, sulfonamides, benzofurans and others structures are also under development. Notably, it was found that the introduction of the morpholino group greatly increased the activity of the compound on PI3K/mTOR [14]. Molecular model studies also suggested that a hydrogen bond formed between the oxygen on the morpholine ring and Va1851 in the catalytic center of PI3Kα. Furthermore, the amino acid (Phe961Leu) in the catalytic center of mTOR forms a deeper pocket than PI3K, which binds to the morpholine ring and forms a hydrogen bond with the oxygen on the II-5 morpholine ring [15]. In addition, in order to develop oral drugs by improving the solubility, the structures are still being redesigned and modified. There are several dual PI3K/mTOR inhibitors as below which have been or have not been tested in various stages of human clinical trials.

Dactolisib/BEZ-235/NVP-BEZ235 is an imidazole [4,5-c] quinoline derivative which targets the ATP binding cleft of p110α/ß/γ/δ and mTOR kinase inhibitor to inhibit the catalytic activity of mTORC1 and mTORC2[16]. It has shown satisfactory antitumor effects in preclinical studies on triple-negative breast cancer, lung cancer, melanoma, colorectal cancer, kidney cancer, prostate cancer, lymphoma and ovarian mucinous adenocarcinoma. However, due to the high variability of PK and its inevitable toxicity characteristics, it may cause side effects such as diarrhea (78%), nausea (61%) and stomatitis (39%), hyperglycemia, nausea, diarrhea and vomiting. Therefore, it stopped clinical trials in 2015[17]. Other inhibitors are summarized in the table below (Table 1).

Table 1. Types and clinical research progress of dual PI3K/mTOR Inhibitors.

Inhibitor	Target	Cancer type	Phase
Apitolisib/GDC-0980/RG7422	class I PI3K α/β/δ/γ isoforms	monotherapy for R/R solid tumors or NHL	phase I/II studies
Gedatolisib/PF-05212384/PKI-587	PI3Kα/γ and mTOR		phase I/II studies
SF1126	all PI3K class IA isoforms		phase I/II studies
Omipalisib/GSK458/GSK2126458	PI3Kα	solid tumors and lymphomas	phase I/II studies
Samotolisib/LY3023414	PI3Kα mTOR		phase I/II studies combined with chemotherapy
Bimiralisib/PQR309	pan-I PI3K mTORC1 and mTORC2	R/R primary central nervous system lymphoma (PCNSL) advanced lymphoma	phase I/II studies
Voxtalisib/SAR245409/XL765	PI3K p110γ, DNA-PK and the mTOR		phase I/II studies monotherapy or combination regimen

4. Isoform-specific PI3K Inhibitors

Isoform-Specific PI3K inhibitors are intended to be as effective as or more effective than Pan-PI3K inhibitors and Dual PI3K/mTOR inhibitors, while reducing adverse side effects. More and more researchers realize that the different isoforms of the PI3K family play a non-redundant role in physiological regulation and tumor development, which has prompted the development of Isoform-Specific inhibitors for different isoforms of the PI3K pathway. With a better understanding of the various functions of PI3K isoforms in various kinds of cancer, Isoform-Specific PI3K inhibitors have attracted more and more interest from researchers in precise cancer treatment. PI3K consist of the regulatory subunit p85 and the catalytic subunit p110. There are four types of catalytic subunits, namely p110α, β, δ, γ, while δ and γ are only found in white blood cells and the rest are found in a variety of cells. Isoform-Specific PI3K inhibitors can be selective Inhibit the four PI3K subtypes of α/β/γ or δ [17]. Among many isoform-Specific drugs, Idelalisib was the first PI3K Isoform-Specific inhibitor approved for the treatment of cancer [18], and then Alpelisib, Umbralisib and Duvelisib also stood out and received FDA approval [17]. We will elaborate on these four Isoform-Specific PI3K inhibitors.

4.1 Idelalisib/CAL-101/GS-1101/Zydelig

Idelalisib is a PI3K inhibitor that is taken orally and has a cell-free IC50 of 2.5nM. It is the first isoform-specific PI3K inhibitor approved by the FDA for clinical use. Mainly used to treat the following three diseases, they are relapsed chronic lymphocytic leukemia (CLL), follicular B cell

non-Hodgkin lymphoma (FL), and small lymphocytic lymphoma (SLL) [19]. PI3K, unlike other isoforms of PI3K, is found predominantly in the hematopoietic lineage. Idelalisib has been shown in studies to have a therapeutic effect, but it does not inhibit PI3K signaling, which is required for healthy cells to function normally [20]. Idelalisib can inhibit the production of phosphatidylinositol-3,4,5-triphosphate (PIP3), the second messenger prevents the activation of the tumor PI3K signaling pathway and inhibits the proliferation, movement and survival of tumor cells.

Idelalisib and BCL 201 (selective BH3 mimic inhibitor of Bcl-2) were investigated in a Novartis Pharmaceuticals-sponsored Phase Ib research in dose escalation trials in patients with recurrent follicular B-cell non-Hodgkin's lymphoma (FL) and mantle cell lymphoma (MCL). The significant motivation behind this research was to assess the drug mix's security and decency [21]. Furthermore, numerous researchers are doing active non-recruitment studies on Idelalisib. In a phase I clinical trial, for example, in a phase I clinical trial, a combination therapy study of idelalisib is ongoing. For individuals with R/R CLL. Idelalisib is co-treated with a histone deacetylase inhibitor called ACY-1215/Ricolinostat. This is a collaboration supported and initiated by the Dana-Farber Cancer Institute and Acetylon Pharmaceuticals [22]. Tiralutinib is in clinical phase II. It is a Bruton tyrosine kinase (BTK) inhibitor, which can be taken orally. The BTK inhibitor, Idelalisib and rituximab are undergoing Phase I testing and studies in combination with TRU-016, a CD37-targeting monoclonal antibody [23. Idelalisib is being tested in individuals with recurrent DLBCL in a phase II clinical study (ILIAD) [24]. Another Phase II clinical study (COSMO) is evaluating the safety and efficacy of R/R CLL/SLL patients previously treated with a BTK inhibitor. The approach used was a combination of MOR00208 with either Idelalisib or Venetoclax [25].

4.2 Alpelisib/BYL719/Piqray

Alpelisib is an effective PI3Kα inhibitor, and it can be taken orally. Studies have shown that Alpelisib can target cancers with PIK3CA mutations [26]. The FDA has authorized Alpelisib for clinical use. Mainly for advanced breast cancer with PIK3CA mutation, HR+, and HER2[27]. Furthermore, other studies are continuously being conducted to investigate the therapeutic benefits of Alpelisib in various malignancies. A phase I clinical trial of Alpelisib is going on. In a phase Ib study comprising dosage escalation of Alpelisib, Imatinib (an RTK inhibitor) and Sunitinib (an RTK inhibitor) were used to treat tumor recurrence in people suffering from gastrointestinal stromal tumor (GIST) [28]. In a phase Ib/II study, the effects of Alpelisib and HER3 monoclonal antibody, which is called LJM716, as well as Taxane or Irinotecan, on previously treated patients with esophageal squamous cell carcinoma were investigated. The maximum tolerated dose of this medication combination was determined by this study as well as the Phase II clinical study's recommended dose (RP2D) [29]. Abelicide and an oral pan-PIM kinase inhibitor (LGH447/PIM447) were evaluated in a Phase Ib/II study. The therapy in this study was primarily targeted at patients with relapsed myeloma, and the aim was to find out the MTD and RP2D of this combination [30].

In addition, there are several active non-recruitment studies on various phases of clinical trials of Alpelisib. Phase II study of patients with advanced breast cancer (SAFIR PI3K) is ongoing. A Phase I clinical trial is underway. The current Alpelisib and an effective oral bioavailability selective estrogen receptor degradation agent (SERD) LSZ102, ER + combined with the treatment of metastatic breast cancer. The goal of this study was to establish the combination scheme's safety, tolerability, pharmacokinetics (PK), and anticancer efficacy [31]. Another phase I trial is looking into Alpelisib in combination with cisplatin and radiation to treat squamous cell head and neck cancers (LA-SCCHN) [32].

4.3 Umbralisib/TGR1202/RP5264

Umbralisib is a second-generation, highly selective inhibitor of PI3K isoform. Like other inhibitors, it can be taken orally. The FDA has authorized umbralisib for the treatment of individuals who are suffering from R/R marginal zone lymphoma (MZL) [33]. Numerous researchers are testing Umbalisib. There is a Phase I study evaluating the stability, safety, and efficacy of umbralisib as a monotherapy in combination with other agents in patients with relapsed or refractory solid tumors

[34]. Another phase I trial looked at how well Umbralisib and Brentuximab vedotin worked together. An anti-CD30 antibody-drug conjugate (ADC) which is called Brentuximab vedotin can be utilized in the treatment of Hodgkin's lymphoma (HL) In patients, it has a high effectiveness rate [35]. In addition, Umbralisib is being tested as a monotherapy in phase II/III research for patients with non-follicular indolent non-Hodgkin's lymphoma (non-Follicular iNHL) [36].

4.4 Duvelisib/ IPI-145/ INK1197

Duvelisib is an isoform-specific PI3K inhibitors that is taken orally. Like other FDA-approved drugs, it is also highly selective. In both dose-dependent and time-dependent manners, Duvelisib has been clinically proven to directly kill primary chronic lymphocytic leukemia (CLL) cells, but not normal human B cells [37]. In adult patients with these disorders, including relapsed or refractory chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and relapsed or refractory follicular lymphoma (FL), the FDA has authorized Duvelisib for the treatment [38]. Duvelisib's effectiveness and safety in patients with relapsed and refractory peripheral T-cell lymphoma will be studied further in a phase II trial. This study relied on samples donated by patients with chronic lymphocytic leukemia. According to gene expression analysis, through an administration of Duvelisib, both the anti-apoptotic proteins BCL2's expression and BH3-only pro-apoptotic genes' expression have been increased [39]. In a recent phase II research, through efficacy trial of Duvelisib in patients with hematological malignancies, it has been confirmed that it has clinical efficacy and long-term safety, and the survival rate of patients has also been guaranteed [40].

5. Conclusions

The hyper-activation of the PI3K signaling pathway caused by mutation of the *PIK3CA* gene or inactivation of the *PTEN* tumor suppressor gene can be observed in nearly half of cancer patients. Pan-inhibitor, which targets all the four isomers in class I, is effective against many different types of tumors. For example, many studies have been done on buparlisib in combination with other drugs for the treatment of HR+/ HER2-breast cancer patients. Dual PI3K/mTOR inhibitor can inhibit both PI3K and mTOR targets at the same time, which can effectively avoid drug resistance and adverse reactions caused by the feedback mechanism of the PI3K signaling pathway and improve the clinical effect. It is important to determine specific biomarker and which gene mutation cause PI3K hyperactivation, it makes clearer that the inhibitor is more sensitive to which type of gene mutation or isoform, and the activation level is higher. This will significantly improve the efficacy of the inhibitor. In addition, it has stronger specificity than the other two, so they are better in drug toxicity control and drug effects than the other two. The PI3K pathway seems to have a good effect on lymphatic system-related cancers. In addition, the PI3K pathway is closely related to the *HER2* gene, gynecological cancer and breast cancer. In recent five years, there have been a lot of clinical trials progress in this area (clinicaltrials.gov). Despite the severe drug toxicity, inhibitors such as Alpelisib and Buparlisib also show high clinical activity and are potent in breast cancer treatment.

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