Targeting PI3K in cancer: mechanisms and advances in clinical trials

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Abstract
Phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling is one of the most important intracellular pathways, which can be considered as a master regulator for cancer. Enormous efforts have been dedicated to the development of drugs targeting PI3K signaling, many of which are currently employed in clinical trials evaluation, and it is becoming increasingly clear that PI3K inhibitors are effective in inhibiting tumor progression. PI3K inhibitors are subdivided into dual PI3K/mTOR inhibitors, pan-PI3K inhibitors and isoform-specific inhibitors. In this review, we performed a critical review to summarize the role of the PI3K pathway in tumor development, recent PI3K inhibitors development based on clinical trials, and the mechanisms of resistance to PI3K inhibition.

Keywords: PI3K, mTOR, Cancer, Target therapy

Highlights
Activation of the PI3K pathway contributes to the development of tumor PI3K is an attractive therapeutic direction in the treatment of cancer. Inhibition of PI3K signaling is effective in the treatment of several types of cancer. Intrinsic and acquired resistance limits the therapeutic efficacy of PI3K inhibitors.

Introduction
Phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling is one of the most important intracellular pathways, which regulates cell growth, motility, survival, metabolism, and angiogenesis [1, 2]. Activation of the PI3K/AKT/mTOR pathway contributes to the development of tumor and resistance to anticancer therapies [3]. MicroRNA (miRNA) and long non-coding RNA (lncRNA), the two most studied classes of non-coding RNA (ncRNA), are crucial regulators of gene expression [4]. These two types of ncRNA and PI3K/AKT/mTOR pathway are in tight conjunction during oncogenesis [5, 6]. The PI3K/AKT/mTOR pathway has been found to be dysregulated almost in all human cancers, such as breast cancer, colorectal cancer, and hematologic malignancies, which emphasizes the value of targeting this pathway as a potential therapeutic direction in the treatment of cancer [7]. Inhibition of PI3K can result in both decreased cellular proliferation and increased cellular death [8]. Small molecule inhibitors of PI3K include PI3K/mTOR inhibitors, pan-PI3K inhibitors, and isoform-selective PI3K inhibitors. The safety and efficacy of these therapeutic approaches have been investigated in a wide range of preclinical and clinical trials, and it is becoming increasingly clear that PI3K inhibitors are effective in inhibiting tumor progression. For example, PI3K delta-specific inhibitor idelalisib is the first PI3Ki compound approved by United States Food and Drug Administration (FDA) and is proved to be effective in the cancer treatment [9]. In this review, we summarized the role of the PI3K signaling in tumor progression, recent PI3K inhibitors development based on clinical trials, and the mechanisms of resistance to PI3K inhibition.

PI3K signal pathway
Signal transduction pathways
PI3K is a group of plasma membrane-associated lipid kinases, consisting of three subunits: p85 regulatory subunit, p55 regulatory subunit, and p110 catalytic subunit [10]. According to their different structures and specific substrates, PI3K is divided into 3 classes: classes I, II, and III [1, 2]. Class I PI3Ks comprised of class IA and class IB PI3Ks. Class IA PI3K, a heterodimer of p85
regulatory subunit and p110 catalytic subunit, is the type most clearly implicated in human cancer [11]. Class IA PI3K contains p110α, p110β and p110δ catalytic subunits produced from different genes (PIK3CA, PIK3CB and PIK3CD, respectively), while p110γ produced by PIK3CG represents the only catalytic subunit in class IB PI3K [12]. The p85 regulatory subunit is composed of p85α (p85α, p55α and p50α splice variants), p85b and p55g, which are encoded by the genes PIK3R1, PIK3R2 and PIK3R3, respectively [2]. As an integration point for p110 activation and downstream molecular, p85 regulatory subunit binds and integrates signals from various transmembrane and intracellular proteins, including tyrosine kinase-linked receptors, protein kinase C (PKC), Src homology 2 domain-containing protein tyrosine phosphatase 1 (SHP1), Rac, Rho, hormonal receptors, Src, as well as mutated Ras [8]. The overview of PI3K/AKT/mTOR signaling pathway was shown in Fig. 1.

**Activation of PI3K signaling**

Under baseline conditions, the p110 catalytic subunit is stabilized by dimerization with regulatory p85 subunit. In physiologic conditions, PI3K is normally activated by a variety of extracellular stimuli, such as growth factors, cytokines, and hormones [13]. Upon activation, PI3K catalyzes the phosphorylation of PtdIns(4,5) P2(PIP2) to produce PtdIns(3,4,5) P3(PIP3), a second messenger that binds and recruits a subset of pleckstrin-homology (PH), FYVE, Phox (PX), C1, C2 or other lipid-binding domains of downstream targets to the cell membrane. A variety of signaling proteins, such as kinases AKT and PDK1 can bind to the lipid products of PI3K and thereby localize to the cell membrane to activate cell growth and cell survival pathways [14]. Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) regulates the pathway by dephosphorylating PIP3 to PIP2 and thus prevents activation of downstream kinases [8].

In the last decade or so, ncRNAs have emerged as important regulators of a wide range of genes and PI3K/AKT/mTOR pathway [5, 6]. ncRNAs function as both upstream mediators and downstream effectors to affect PI3K pathway activities. Of importance, ncRNAs have been reported to directly or indirectly target multiple key components (PI3K, AKT, mTOR and PTEN) in the PI3K pathway, regulating the activity of PI3K signaling. However, the exact mechanisms through which IncRNAs...
PI3K signaling in human cancer

Over the past decades, PI3K signaling pathway is believed to be deregulated in a wide spectrum of human cancers. Mutations of the kinases and/or decreased expression of PTEN lead to neoplastic transformation, underscoring its central role in human carcinogenesis [8, 15]. PI3K pathway is deregulated through a variety of mechanisms, including loss or inactivation of the tumor suppressor PTEN, mutation or amplification of PI3K, as well as activation of tyrosine kinase growth factor receptors or oncogenes upstream of PI3K [16–18].

Loss or inactivation of PTEN

PTEN, a negative regulator of PI3K pathway, acts as a direct antagonist of PI3K action through dephosphorylation of PIP3. Dimeric PTEN complexes have higher activity than PTEN monomers in PIP3 dephosphorylation and PI3K signaling regulation [19, 20]. PTEN is a well characterized tumor suppressor with growth, survival and metabolic regulatory functions, and its loss or inactivation of function is frequently observed in both heritable and sporadic malignances, including brain cancer, breast cancer, and prostate cancer [21–23]. Furthermore, it has been shown that small changes in PTEN expression contribute to major consequences for normal cellular function [24]. In PTEN knock-in mice harboring two cancer-associated PTEN mutations, PTENC1245S and PTENG129E inhibit the PTEN lipid-phosphatase activity in a dominant negative manner, leading to increased activation of PI3K signaling and tumorigenesis [20]. Moreover, in PTEN-deficient cancer, the main carcinogenic driving force is the overactivation of AKT caused by the loss of PTEN lipid phosphatase function [20, 25].

Mutation or amplification of PI3K

PIK3CA (phosphatidylinositol 3-kinase, catalytic, α-polypeptide), the gene encoding the p110α subunit, are frequently mutated or amplified in the most common human cancers, such as breast cancers, colon cancer, gastric cancer, cervical cancer, prostate cancer, and lung cancer [26–31]. Most mutations cluster around two hotspots: E545K (exon 9) in the helical phosphatidylinositol kinase homology domain, which reduces inhibition of p110α by the regulatory subunit p85; H1047 (exon 20) near the end of the catalytic domain, which increases interaction of p110α with lipid membranes [32, 33]. E542K is also one of the most frequently observed PIK3CA mutations [33, 34]. In colorectal cancer, exon 9 plays a more important role than exon 20, whereas in endometrial cancer, the opposite pattern was described, suggesting that different mutations of PIK3CA may have specific effects on downstream carcinogenic signals [35]. It is worth noting that the coexistence of mutations in helical domain and kinase domain leads to synergistic enhancement of p110 activity and enhancement of the tumorigenicity effects [35]. In addition to the two hotspot mutations, mutations on C2 domain are also important components of PIK3CA mutations [36]. Such deregulation of PI3K pathway promotes cell proliferation and migration, glucose transport and catabolism, cytoskeletal rearrangements, and angiogenesis, playing an important role in tumor initiation, progression, and maintenance [27]. In addition, the tumorigenic potential of these mutations was confirmed in experimental research using genetically engineered mouse models (GEMMs) [37–39].

In contrast, mutations in the other catalytic subunits p110β, p110γ and p110δ are rare, and overexpression of these wild-type catalytic subunits is sufficient to induce an oncogenic phenotype in cultured cells [34, 40]. Subunit p110β plays an important role in stimulating cell proliferation, invasiveness, as well as tumorigenesis in prostate and breast cancer [41–43]. The precise mechanisms of p110β activation in cancer are still not well established. However, it has been reported that it can occur through G protein-coupled receptor (GPCRs) [44]. E633K, a p110β helical domain mutation, was first reported in a HER2-positive breast cancer patient [45]. E633K might enhance p110β’s basal association with membranes and thus activates p110β [43]. The p110β has been suggested to be responsible for the reaccumulation of PIP3 and reactivation of AKT in HER2-amplified cancers treated with a p110α-specific inhibitor, and concomitant inhibition of p110α and p110β induces greater antitumor efficacy in HER2-amplified and PIK3CA mutant breast cancers. In endometrial cancer, occurrence of PIK3CB mutations (D1067V and A1048V within the kinase domain) has been reported [46, 47]. P110δ is primarily expressed in the cells of hematopoietic lineage and is activated by cytokine receptors, antigen receptors, growth factor receptors and costimulatory receptors [48, 49]. PI3Kδ is important in T and B cells development and activation. PI3Kδ blockade increases genomic instability by an activation-induced cytidine deaminase (AID)-dependent mechanism in B cells [50]. Gain-of-function (GOF) mutations in PI3Kδ result in a range of developmental and functional deficiencies of B and T cell that compromise host defense. Loss-of-function (LOF) mutations lead to much more severe B cell lymphopenia and agammaglobulinemia, but not T cell senescence [51]. In acute myeloid leukemia (AML), PI3Kδ is critical in activation of AKT and cell proliferation [52]. Point mutations of p110δ have been described in a panel of diffuse large B-cell lymphomas [53]. Moreover, p110δ protein has been detected in cells of melanocytic or breast origin and it has been reported to regulate cell migration in breast
cancer lines and tumor progression [54]. PI3Kγ is abundantly expressed in immune cells of myeloid origin but not cancer cells, which regulates innate immunity in both inflammation and cancer [55]. PI10γ contributes to chemotactic responses, as well as reactive oxygen species production in neutrophils [56]. PI3Kγ may possibly be able to promote solid tumor neovascularization indirectly by regulating the immune-suppressive TAM subset, which is a major source of VEGFα [57].

Non-coding RNA and other factors in regulation of PI3K pathway

In addition to inherent aberrations in members of the PI3K pathway, pathologic signaling through this pathway can also occur in other ways, including tyrosine kinase growth factor receptors (e.g. human epidermal growth factor receptor 2 and insulin-like growth factor 1 receptor), cell adhesion molecules (e.g. integrins, GPCR), and oncogenes (e.g. RAS) [1, 58, 59]. The interactions between ncRNAs and PI3K signaling in cancer have been studied. For example, the IncRNA CRNDE which promote cell proliferation through activating PI3K signaling, is highly expressed in patients with non-small cell lung cancer, colorectal cancer, gastric cancer, cervical cancer, hepatocellular carcinoma and gallbladder cancer [60–65]. In addition to activating PI3K pathway, some ncRNAs have been reported to inhibit the activity of PI3K signaling. IncRNA GAS5 expression is lower in tumor cells compared to normal cells; its over-expression inhibits tumor cell proliferation and migration while treatment with PI3K activator reduces the inhibitory effects [66–72]. Table 1 shows the examples of ncRNA that interact with PI3K signaling in different types of cancer.

PI3K inhibitors

PI3K are believed to be one of the key therapeutic targets for cancer treatment based on the observation that hyperactivity of PI3K signaling is significantly correlated with human tumor progression, increased tumor microvessel density and enhanced chemotaxis and invasive potential of cancer cells. Enormous efforts have been dedicated to the development of drugs targeting PI3K signaling, many of which are currently employed in clinical trials evaluation. Important ongoing clinical trials with PI3K-targeted therapies were summarized in Table 2. PI3K inhibitors are subdivided into dual PI3K/mTOR inhibitors, pan-PI3K inhibitors and isoform-specific inhibitors. The drugs targeting PI3K in clinical trial were shown in Table 3 and Fig. 2.

Dual PI3K/mTOR inhibitors

**NVP-BEZ235 (Dactolisib)**

NVP BEZ235 (dactolisib) is a dual PI3K/mTOR inhibitor and is currently in Phase I/II clinical trials. It is an imidazo[4,5-c] quinoline derivative compound that binds to the ATP-binding cleft of PI3K and mTOR kinase, inhibiting their catalytic activities [25]. BEZ235 exhibited satisfactory anticancer effects in preclinical studies in several types of cancer, including the following: triple-negative breast cancer, lung cancer, melanoma, colorectal cancer, renal cancer, prostate cancer, lymphoma, and mucinous adenocarcinoma of the ovary [73–85]. However, the clinical trials of BEZ235 were not satisfactory. A phase I study investigated maximum tolerated dose (MTD), recommended dose for expansion (RDE), safety and antitumor activity of BEZ235, in combination with abiraterone acetate [86]. In this study, dose escalation was stopped after 200 mg bid due to challenging safety and tolerability profile; the most common adverse events (AEs) were diarrhea (78%), nausea (61%) and stomatitis (39%). Moreover, no objective response and few prostate specific antigen (PSA) decreases were reported. Limited efficacy and poor tolerance of BEZ235 combined with everolimus (BEZ235: 200, 400, or 800 mg daily; everolimus: 2.5 mg daily; 28-day cycles) in patients with advanced solid malignancies were reported in a phase Ib trial [87].

In a Phase II Study, BEZ235 was poorly tolerated by patients with everolimus-resistant pancreatic neuroendocrine tumor at 400 or 300 mg bid doses, and the estimated 16-week progression-free survival (PFS) rate was 51.6% [88]. Treatment-related grade 3/4 AEs including hyperglycaemia, nausea, diarrhoea, and vomiting occurred in 72.7% patients at 400 mg and 40.0% patients at 300 mg; 95.0% of the patients in the 300 mg group and all patients in the 400 mg group experienced at least one AE relating to the treatment [88]. Treatment with BEZ235 in mTOR inhibitor-naïve patients with advanced pancreatic neuroendocrine tumors demonstrated poorer efficacy and tolerability compared with everolimus in another Phase II study [89]. Phase I studies of BEZ235 in patients with advanced breast cancer and advanced renal cancer, reported that BEZ235 was not enough to achieve a satisfactory antitumor effect with a favorable safety profile. Currently, several clinical studies of BEZ235 among patients with relapsed or refractory acute leukemia and patients with metastatic breast cancer are ongoing.

**GDC-0980 (Apitolisib, RG7422)**

GDC-0980 (apitolisib, RG7422) is a potent, orally bioavailable inhibitor of class I PI3K and mTOR kinase (TORC1/2). Several preclinical studies have assessed this agent’s activity in a variety of solid tumors. A phase I trial assessed the safety, tolerability, and preliminary antitumor effects of GDC-0980 in patients with solid tumors [90]. In this study, 2–70 mg daily GDC-0980 was administered to patients for days 1–21 or 1–28 of 28-day cycles. The main AEs from this agent were hyperglycemia, rash, liver dysfunction and diarrhea. This phase I study concluded that GDC-0980 has a narrow therapeutic window, and dose of 40 mg 28/28 days was reasonably tolerated. More recently,
| LncRNAs | Up- or down-regulation | Cancer type | Affected biological process (Involved factors) | References |
|---------|------------------------|-------------|------------------------------------------------|------------|
| CRNDE   | Up                     | Gallbladder carcinoma; Non-small cell lung carcinoma; Colorectal cancer; Gastric cancer; Cervical cancer; Hepatocellular cancer | Cell proliferation, growth, migration, invasion and apoptosis; glucose and lipid metabolism (Gene expression in PI3K pathway: MMP-9, JUK-1, ERK and AKT) | [60–65] |
| OIP5-AS1| Up                     | Multiple myeloma; Osteosarcoma | Cell proliferation, cycle and apoptosis; cisplatin resistance; (miRNA-410, miRNA-340-5p and expression of lysophosphatidic acid acyltransferase) | [201, 213] |
| CCAT1   | Up                     | Thyroid carcinoma; Squamous cell carcinomas | Cell proliferation, migration, and invasion (miRNA-143; EGFR expression) | [214, 215] |
| H19     | Up                     | Retinoblastoma, Melanoma | Cell viability, migration, invasion, and apoptosis (miRNA-143, RUNX2, Phosphorylation of key kinases) | [216, 217] |
| HOTAIR  | UP                     | Gastric cancer; Adenocarcinoma of esophagogastric junction; Leukemia; Melanoma; Gliomas | Cell proliferation, metastasis and apoptosis; cisplatin resistance; acquired multidrug resistance to imatinib (miRNA-143, miRNA-34a, miRNA-152-3p, miRNA-126, miRNA-326, FGF1) | [202, 203, 218–222] |
| NEAT1   | Up                     | Myeloma; Cervical carcinoma; Gastric cancer | Cell proliferation, viability, migration, invasion, apoptosis, and cell cycle. (microRNA-17) | [223–226] |
| HULC    | Up                     | Bladder cancer; Leukemia; Gliomas; Osteosarcoma; Liver cancer; Gastric cancer | Cell viability, growth, migration, invasion and autophagy (PTEN, miRNA15a, autophagy-P62, miRNA-122) | [227–232] |
| AB073614| Up                     | Colorectal cancer | Cell cycle, proliferation, migration, and invasion | [233] |
| PTTG3P  | Up                     | Hepatocellular carcinoma | Cell proliferation, migration, invasion, tumorigenesis and metastasis | [234] |
| MALAT1  | Up                     | Cervical cancer; Epithelial ovarian cancer; Breast cancer; Osteosarcoma; Cholangiocarcinoma; Non-small cell lung carcinoma; Hepatocellular carcinoma; Renal cell carcinoma | Cell proliferation, invasion, metastasis, viability and mobility; stemness-related factor activation; epithelial-to-mesenchymal transition; cisplatin resistance (PI3Kp85α, miRNA-22-3p, miRNA-195, miRNA-124, miRNA-101-3p, miRNA-129-5p) | [235–245] |
| ATB     | Up                     | Bladder cancer; Prostate carcinoma | Cell proliferation, migration and invasion; mitogenic; epithelial-mesenchymal transition (microRNA-126, KRAS) | [246, 247] |
| BC0878S8| Up                     | Non-small-cell lung cancer | Cells invasion; resistance to EGFR-TKIs (ZEB1, Snai1) | [248] |
| Linc00659| Up                   | Colorectal cancer | Cell growth inhibition and apoptosis | [249] |
| Linc00152| Up                   | Lung cancer; Gallbladder cancer | Cell proliferation, invasion, migration, apoptosis, and G1 phase rates | [250, 251] |
| Linc00462| Up                   | Hepatocellular carcinoma | Cell proliferation, invasion and migration | [252] |
| Linc01296| Up                   | Prostate cancer; Colorectal cancer | Tumorigenesis, cell proliferation, migration, invasion, and liver metastasis; epithelial-mesenchymal transition; chemoresistance to 5-fluorouracil (miRNA-26a, mucin1, GALNT3) | [253, 254] |
| Linc003121| Down                | Thyroid cancer | Cell proliferation, Invasion, and tumorigenicity | [255] |
| UCA1    | Up                     | Gastric cancer; Bladder cancer | Cell proliferation, migration, invasion, apoptosis and cell cycle | [256–259] |
| ecCEBPA | Up                     | Gastric cancer; Hepatic cancer | Disease progression | [257, 260] |
| Ftx     | Up                     | Hepatocellular carcinoma | Cell growth (miRNA-545, RIG-I) | [261] |
| RMEL3   | Up                     | Melanoma | Cell survival and proliferation (PTEN) | [262] |
a single arm, open-label trial phase II study in recurrent or persistent endometrial carcinoma patients reported that anti-tumor activity of 40 mg GDC-0980 daily was limited by tolerability, especially in diabetic patients, and patients with mutations of PI3K pathway may benefit more from GDC-0980 [91].

In another phase II study, 85 patients with metastatic renal cell carcinoma were randomly assigned to apitolisib 40 mg QD or to everolimus 10 mg QD. Patients receiving GDC-0980 were shown to have poorer median PFS (3.7 vs 6.1 months; hazard ratio (HR) 2.12; \( p < 0.01 \)) than patients receiving everolimus, while median overall survival (OS) was not significantly different but trended in favor of patients receiving everolimus (16.5 vs 22.8 months; HR 1.77; \( p = 0.06 \)) [92, 93]. However, GDC-0980 was reported to be well tolerated and to have early signs of anti-tumor activity in patients with advanced solid tumors or non-Hodgkin lymphoma, with an 80% decrease in measurable tumor marker [90]. A Phase/II study of GDC-0980 in patients with prostate cancer is ongoing.

In a phase Ib study of GDC-0980 in combination with capecitabine, 19 patients with advanced solid tumors and colorectal cancer were enrolled [94]. Confirmed partial responses (PR) were observed in one head and neck squamous cell cancer patient and one colorectal cancer patient with PIK3CA and KRAS mutations, which indicated preliminary anti-tumor activity of GDC-0980 in combination with capecitabine. GDC-0980 combined with fluoropyrimidine-based regimens was also demonstrated to be well tolerated, with confirmed antitumor activity [95].

**Table 1 Important long non-coding RNA that interact with PI3K signaling in different cancer (Continued)**

| LncRNAs    | Up- or down-regulation | Cancer type                     | Affected biological process (Involved factors)                                                                 | References          |
|------------|------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------|
| LncARSR    | Up                     | Hepatocellular Carcinoma        | Doxorubicin resistance (PTEN)                                                                                     | [206]               |
| BDLNR      | Up                     | Cervical cancer                 | Cell proliferation, migration, and death; anti-cancer effects of baicalein (YB1, PIK3CA promoter)                | [263]               |
| ANRIL      | Up                     | Cervical cancer; Osteosarcoma; Gliomas | Cell proliferation, migration, invasion, and apoptosis (miRNA-34a, Sirt1)                                            | [264–266]          |
| ROR        | Up                     | Non-small-cell lung cancer      | Cell proliferation, migration, and invasion; cisplatin resistance                                                                                                | [267]               |
| PlncRNA-1  | Up                     | Colorectal cancer               | Cell proliferation, migration, invasion, and apoptosis                                                            | [268]               |
| MYD88      | Up                     | Hepatocellular carcinoma;       | Cell proliferation and metastasis (H3K27Ac)                                                                 | [269]               |
| RP4        | Down                   | Colorectal cancer               | Cell proliferation, growth, and early apoptosis (SH3GLB1, miRNA-7-5p)                                             | [270]               |
| OIPS-AS1   | Down                   | Osteosarcoma, myeloma           | Cell growth; cisplatin resistance (miRNA-340-5p, LPAATbeta, miRNA-410, KLF10)                                    | [201, 213]          |
| MEG3       | Down                   | Endometrial carcinoma; Breast cancer; Cervical cancer; Pancreatic cancer; Lymphoma; Gliomas | Cell proliferation, migration, metastasis, and apoptosis; autophagy; glycolysis; epithelial-mesenchymal transition; chemoresistance (Combine directly with PI3K, miRNA-21, cytomembrane translocation of AKT) | [271–277]          |
| GASS       | Down                   | Colorectal cancer; Esophageal squamous cell carcinoma; Breast cancer; Malignant pleural mesothelioma; Osteosarcoma; Prostate cancer | Cell proliferation and migration, viability, migration and invasion; apoptotic responses to conventional chemotherapies (miRNA-203a, TIMP2, miRNA-196a-5p, FOXO1) | [66–72]            |
| RNA-422    | Up                     | Colorectal cancer               | Cell proliferation, migration, and invasion                                                                 | [278]               |

**PF-04691502 and PF-05212384 (Gedatolisib, PKI-587)**

PF-04691502 and PF-05212384 (gedatolisib, PKI-587) are potent ATP competitive dual class-I PI3K/ mTOR kinases inhibitors. Preclinical studies demonstrated that PI3K-mTOR inhibition with PF-04691502 can enhance TP53/p73 expression and significantly inhibit tumor growth in head and neck squamous cell carcinomas [96]. In cancer cell lines with PI3Ka mutation and PTEN deletion, PF-04691502 can reduce phosphorylation of AKT and S6RP, thus inhibit cell proliferation [97]. PF-05212384 were reported to suppress a negative feedback loop mediated by mTORC2, leading to MEK/ERK over-activation in pancreatic cancer cells [98]. PF-05212384 causes strong attenuation of cell cycle and G0/G1 arrest, as well as induction of apoptosis in neuroendocrine tumor cells [99].

Phase I study of PF-04691502 in 23 patients with advanced solid tumors recommended that 8 mg orally once
## Table 2 Important ongoing clinical trials with PI3K-targeted therapies

| Conditions | Sample size | Design | Phase | Status | Trial number |
|------------|-------------|--------|-------|--------|--------------|
| NVP-BEZ235 (BEZ235, Dactolisib) Dual PI3K/mTOR inhibitor | | | | | |
| Acute Lymphoblastic Leukemia; Acute Chronic Myelogenous Leukemia With Crisis of Blast Cells | 23 | BEZ235 | I | Active not recruiting | NCT01756118 |
| GDC-0084 (RG7666) Dual PI3K/mTOR inhibitor | | | | | |
| Glioblastoma, Adult | 66 | GDC-0084 | II | Recruiting | NCT03522298 |
| Brain and Central Nervous System Tumors | 41 | Radiation therapy+ GDC-0084 | I | Not yet recruiting | NCT03696355 |
| GDC-0980 (Apitolisib, RG7422) Dual PI3K/mTOR inhibitor | | | | | |
| Prostate Cancer | 273 | Abiraterone Acetate +/- (GDC-0980/Ipatasertib) | I/II | Active not recruiting | NCT01485861 |
| LY3023414 Dual PI3K/mTOR inhibitor | | | | | |
| Endometrial Cancer; Recurrent Endometrial Cancer | 25 | LY3023414 | II | Recruiting | NCT02549989 |
| Advanced Malignant Solid Neoplasm; Ann Arbor Stage III/IV Childhood Non-Hodgkin Lymphoma | | | | | |
| Metastatic Colorectal Neoplasm; Metastatic Breast Cancer | 205 | Prexarsertib+Cisplatin/Cetuximab/ Pemetrexed/S-FU/LY3023414 | I | Recruiting | NCT02124148 |
| Advanced or Metastatic Solid Tumors | 163 | LY3023414 +/− (GDC-0980/Ipatasertib) + Abemaciclib/Cisplatin/Gemcitabine/Carboplatin | I | Recruiting | NCT02784795 |
| NSCLC | 150 | Abemaciclib+LY3023414/Pemetrexed/Gemcitabine/Ramucirumab/Pembrolizumab | I | Active not recruiting | NCT02079636 |
| Prostate Cancer Metastatic | 144 | Enzalutamide +/- LY3023414 | II | Recruiting | NCT02407054 |
| Advanced Non-Hodgkin Lymphoma; Metastatic Breast Cancer; Advanced Mesothelioma; Advanced NSCLC | 130 | LY3023414 +/− (GDC-0980/Ipatasertib) + Abemaciclib + Letrozole | I | Recruiting | NCT01655225 |
| Pancreatic Ductal Adenocarcinoma | 231 | Abemaciclib +/- LY3023414 VS Gemcitabine/Capece 

Note: The table continues with additional information regarding various conditions, sample sizes, designs, phases, statuses, and trial numbers.
| Conditions | Sample size | Design | Phase | Status | Trial number |
|------------|-------------|--------|-------|--------|--------------|
| PQR309 (Bimiralisib) Dual PI3K/mTOR inhibitor | | | | | |
| Lymphoma | 72 | PQR309 | I/II | Recruiting | NCT02249429 |
| Lymphoma; Non-Hodgkin Lymphoma | 72 | PQR309 | II | Recruiting | NCT03127020 |
| Primary Central Nervous System Lymphoma | 21 | PQR309 | II | Not yet recruiting | NCT03120000 |
| Metastatic Breast Cancer | 60 | PQR309 + Eribulin | I/II | Recruiting | NCT02723877 |
| P7170 Dual PI3K/mTOR inhibitor | | | | | |
| Advanced Refractory Solid Tumors | 60 | P7170 | I | Suspended | NCT01762410 |
| SF-1126 Dual PI3K/mTOR inhibitor | | | | | |
| Advanced Hepatocellular Carcinoma | 14 | SF-1126 | I | Recruiting | NCT03059147 |
| Advanced Castrate-resistant Prostate Cancer; Squamous NSCLC; Triple Negative Breast Cancer | 180 | AZD8186+/-Abiraterone Acetate/AZD2014 | I | Recruiting | NCT01884285 |
| Copanlisib (BAY 80–6946) PI3Kδ/α inhibitor | | | | | |
| Recurrent Endometrial, Ovarian, Primary Peritoneal, or Fallopian Tube Cancer | 44 | Copanlisib+Niraparib | I | Not yet recruiting | NCT03586661 |
| Head and Neck Squamous Cell Carcinomas | 32 | Copanlisib+Cetuximab | I/II | Recruiting | NCT02822482 |
| Endometrial cancer | 84 | Copanlisib | II | Suspended | NCT02728258 |
| HR+, HER2-, Stage I-IV Breast Cancer | 102 | Copanlisib+Letrozole+/-Palbociclib | I/II | Recruiting | NCT03128619 |
| HER2+ Breast Cancer | 19 | Copanlisib +Trastuzumab | I | Recruiting | NCT02705859 |
| Non-Hodgkin Lymphoma | 25 | Copanlisib | I/II | Active not recruiting | NCT02342665 |
| Mature T-Cell and NK-Cell Neoplasm | 36 | Copanlisib+Gemcitabine | I/II | Recruiting | NCT03052933 |
| Advanced or Metastatic Solid Tumor | 65 | Copanlisib+Rogaratinib | I | Recruiting | NCT03517956 |
| Medical Oncology | 51 | Copanlisib+/-Itraconazole/ Rifampin | I | Active not recruiting | NCT02253420 |
| Mixed Tumor, Malignant | 130 | Copanlisib | I/II | Recruiting | NCT03458728 |
| Biliary Carcinoma; Gall Bladder Carcinoma; Cholangiocarcinoma; Gastrointestinal Tumor | 25 | Copanlisib+Gemcitabine+Ciaplatin | II | Recruiting | NCT02631590 |
| Refractory/Recurrent Primary Central Nervous System Lymphoma | 45 | Copanlisib+Ibrutinib | I/II | Not yet recruiting | NCT03581942 |
| Marginal Zone Lymphoma | 56 | Copanlisib+Rituximab | II | Not yet recruiting | NCT03474744 |
| Large B-Cell Lymphoma | 99 | Copanlisib+Nivolumab | II | Not yet recruiting | NCT03484819 |
| Ann Arbor Stage III/IV Lymphoma; Metastatic Malignant; Solid Neoplasm | 50 | Copanlisib+Nivolumab | I | Recruiting | NCT03502733 |
| Non-Hodgkin Lymphoma | 450 | Rituximab+Copanlisib/Placebo | III | Recruiting | NCT02367040 |
| Non-Hodgkin Lymphoma | 227 | Copanlisib | II | Active not recruiting | NCT01660451 |
| Non-Hodgkin Lymphoma | 25 | Copanlisib | III | Active not recruiting | NCT02369016 |
| Non-Hodgkin Lymphoma | 12 | Copanlisib | I | Recruiting | NCT03498430 |
| Non-Hodgkin Lymphoma | 546 | Standard Immunochemotherapy+/- Copanlisib | III | Recruiting | NCT02626455 |
| Buparlisib (BKM120 NVP-BKM120) Class I PI3K inhibitor | | | | | |
| Metastatic Transitional Cell Carcinoma of the Urothelium | 35 | Buparlisib | II | Active not recruiting | NCT01551030 |
| Metastatic Squamous Neck Cancer With Occult Primary Squamous Cell Carcinoma; | 30 | Buparlisib+Cetuximab | I/II | Active not recruiting | NCT01816984 |
Table 2: Important ongoing clinical trials with PI3K-targeted therapies (Continued)

| Conditions                        | Sample size | Design                          | Phase | Status                      | Trial number               |
|-----------------------------------|-------------|---------------------------------|-------|-----------------------------|----------------------------|
| Head and Neck Cancer              | 170         | Buparlisib                      | II    | Recruiting                 | NCT01737450               |
| NSCLC                             | 37          | Buparlisib+Erlotinib            | II    | Active not recruiting       | NCT01487265               |
| NSCLC                             | 38          | Buparlisib+Gefitinib            |       |                             | NCT01570296               |
| Advanced Squamous Cell Cancer of Head and Neck | 23          | Radiotherapy+Buparlisib+Cisplatin | I     | Active not recruiting       | NCT02113878               |
| Breast Cancer                     | 106         | Buparlisib+lapatinib            | I/II  | Suspended (Data analysis)   | NCT01589861               |
| Breast Cancer                     | 1149        | Buparlisib/Placebo+Fulvestrant | III   | Active not recruiting       | NCT01610284               |
| Breast Cancer                     | 110         | Buparlisib                      | II    | Active not recruiting       | NCT01790932               |
| Metastatic Breast Cancer          | 47          | Buparlisib+Capcitabine+/- (Trastuzumab/Lapatinib) OR BYL719+ Capcitabine | I     | Active not recruiting       | NCT01300962               |
| Breast Cancer Patients With Brain Metastases | 10         | Buparlisib/Capcitabine          | II    | Active not recruiting       | NCT02000882               |
| Pre-menopausal Breast Cancer      | 40          | Buparlisib/BYL719 + Tamoxifen+ Goserelin Acetate | I     | Active not recruiting       | NCT02058381               |
| Ovarian Cancer; Breast Cancer     | 118         | Buparlisib/BYL719+ Olaparib     | I     | Active not recruiting       | NCT01623349               |
| Glioblastoma Multiforme           | 88          | Buparlisib+Bevacizumab          | I/II  | Active not recruiting       | NCT01349660               |
| Glioblastoma                      | 65          | Buparlisib+/-Surgery            | II    | Active not recruiting       | NCT01339052               |
| Thyroid Cancers                   | 47          | Buparlisib                      | II    | Active not recruiting       | NCT01830504               |
| Thymoma                           | 14          | Buparlisib                      | II    | Active not recruiting       | NCT02220855               |
| Malignant Melanoma; Metastases    | 22          | Buparlisib                      | II    | Recruiting                 | NCT02452294               |
| Melanoma                          | 140         | LGX818 + MEK162+/- (Buparlisib/ LEE011/ BGJ398/ INC280) | II    | Active not recruiting       | NCT02159066               |
| Metastatic Colorectal Cancer      | 22          | Buparlisib+Panitumumab          | I/II  | Active not recruiting       | NCT01591421               |
| Relapsed or Refractory Indolent B-Cell Lymphoma | 18          | Buparlisib+Rituximab            | I     | Active not recruiting       | NCT02049541               |
| Chronic Lymphocytic Leukemia      | 14          | Buparlisib                      | II    | Active not recruiting       | NCT02340780               |
| Recurrent/ Refractory Chronic Lymphocytic Leukemia; Recurrent/ Refractory Small Lymphocytic Lymphoma | 1 | Buparlisib+Ofatumumab/Ibrutinib | I     | Active not recruiting       | NCT02614508               |
| Mantle Cell Lymphoma; Follicular Lymphoma; Diffuse Large B Cell Lymphoma | 37 | Buparlisib+Ibrutinib | I     | Active not recruiting       | NCT02756247               |
| Duvelisib (IPI-145) PI3Kδ/γ inhibitor |              |                                 |       |                             |                           |
| Indolent Non-Hodgkin Lymphoma     | 129         | Duvelisib                       | II    | Active not recruiting       | NCT01882803               |
| Relapsed/Refractory T-cell Lymphomas | 88         | Duvelisib+Romidepsin/ Bortezomib | I     | Recruiting                 | NCT02783625               |
| Peripheral T-cell Lymphoma        | 120         | Duvelisib                       | II    | Recruiting                 | NCT03372057               |
| Chronic Lymphocytic Leukemia      | 47          | Duvelisib+Venetoclax            | I/II  | Recruiting                 | NCT03534323               |
| Hematologic Malignancy            | 500         | Duvelisib                       | II    | Active not recruiting       | NCT02711852               |
| Conditions | Sample size | Design | Phase | Status | Trial number |
|------------|-------------|--------|-------|--------|--------------|
| Chronic Lymphocytic Leukemia; Small Lymphocytic Lymphoma | 150 | Duvelisib VS Ofatumumab | III | Enrolling by invitation | NCT02049515 |
| Chronic Lymphocytic Leukemia; Small Lymphocytic Lymphoma | 300 | Duvelisib VS Ofatumumab | III | Active not recruiting | NCT02004522 |
| Chronic Lymphocytic Leukemia | 50 | Duvelisib | II | Recruiting | NCT03370185 |
| Chronic Lymphocytic Leukemia | 32 | Duvelisib+Fludarabine+Cyclophosphamide+Rituximab | I/II | Active not recruiting | NCT02158091 |
| RP6530 (Tenalisib) PI3Kδ/γ inhibitor | 58 | RP6530 | I | Active not recruiting | NCT02567656 |
| Classical Hodgkin Lymphoma | 57 | RP6530 + Pembrolizumab | I | Recruiting | NCT03471351 |
| Taselisib (GDC-0032) PI3Kα/β/γ inhibitor | 59 | Taselisib | II | Active not recruiting | NCT02785913 |
| Metastatic Breast Cancer; Recurrent Breast Cancer | 76 | Taselisib+Trastuzumab emtansine +/- Pertuzumab OR Pertuzumab+Trastuzumab+/- Paclitaxel | I | Recruiting | NCT02390427 |
| Androgen Receptor Positive Triple Negative Metastatic Breast Cancer | 73 | Taselisib+Enzalutamide | I/II | Active not recruiting | NCT02457910 |
| Breast Cancer | 290 | Tamoxifen+ Taselisib/Placebo | I/II | Recruiting | NCT02285179 |
| Breast Cancer | 631 | Fulvestrant+ Taselisib/Placebo | III | Active not recruiting | NCT02340221 |
| PIK3CA-Related Overgrowth | 30 | Taselisib | I/II | Recruiting | NCT03290902 |
| Solid Cancers; Non-Hodgkin Lymphoma | 724 | Taselisib+/-Fulvestrant/Letrozole/ Midazolam/ Fulvestrant | I | Active not recruiting | NCT01296555 |
| Advanced Refractory Solid Tumors; Lymphomas; Multiple Myeloma | 6452 | Molecular Analysis for Therapy Choice Screening Trial | II | Recruiting | NCT02465060 |
| KA2237 PI3Kβ/γ inhibitor | 53 | KA2237 | I | Recruiting | NCT02679196 |
| B Cell Lymphoma | 90 | BYL719 VS Chemotherapy | II | Recruiting | NCT03386162 |
| PIK3CA Mutated Advanced Breast Cancer | 23 | BYL719 + LJM716+ Trastuzumab | I | Active not recruiting | NCT02167854 |
| Breast Cancer | 44 | BYL719 + Nab-Paclitaxel | I/II | Active not recruiting | NCT02379247 |
| HER2+ Metastatic Breast Cancer | 17 | BYL719 + Ado-Trastuzumab Emtramsine | I | Active not recruiting | NCT02038010 |
| Metastatic Breast Cancer | 34 | BYL719 | II | Recruiting | NCT02506556 |
| Malignant Neoplasm of Breast | 28 | BYL719 + Enzalutamide | I | Not yet recruiting | NCT03207529 |
| Pancreatic Cancer | 15 | BYL719 + Gemcitabine+(Nab)-Paclitaxel | I | Active not recruiting | NCT02155088 |
| Breast Cancer | 572 | Fulvestrant+ BYL719/Placebo | III | Active not recruiting | NCT02437318 |
| Premenopausal Patients With HR+, HER2- Locally Advanced or Metastatic Breast Cancer | 40 | BYL719/BKM120 + Tamoxifen+ Goserelin Acetate | I | Active not recruiting | NCT02058381 |
| Advanced or Metastatic ER+ Breast Cancer | 312 | LSZ102+/- LEE011/BYL719 | I | Recruiting | NCT02734615 |
| Metastatic or Locally-advanced Unresectable Breast Cancer | 52 | BYL719 + Letrozole/Exemestane | I | Active not recruiting | NCT01870505 |
Table 2: Important ongoing clinical trials with PI3K-targeted therapies (Continued)

| Conditions                                                                 | Sample size | Design                                                                 | Phase | Status               | Trial number     |
|---------------------------------------------------------------------------|-------------|------------------------------------------------------------------------|-------|----------------------|------------------|
| Breast Cancer                                                             | 160         | BYL-719 + Fulvestrant/Letrozole                                         | II    | Recruiting           | NCT03056755     |
| ER+ Breast Cancer; HER2-negative Breast Cancer; Invasive Ductal Breast Carcinoma | 46          | BYL-719 + Letrozole                                                   | I     | Active not recruiting| NCT01791478     |
| Breast Cancer                                                             | 253         | Letrozole+BYL719/LEE011/ Both                                          | I     | Recruiting           | NCT01872260     |
| Metastatic Breast Cancer                                                 | 47          | BMK120 + Capecitabine+/- Trastuzumab/ Lapatinib OR BYL719+ Capecitabine| I     | Active not recruiting| NCT01300962     |
| Head and Neck Cancer and Esophageal Cancer Patient                        | 259         | BYL719/Poziotinib/Nintedanib/Abemaciclib/ (Duvralumab+Tremelimumab)      | II    | Recruiting           | NCT03292250     |
| Head and Neck Squamous Cell Cancer                                       | 30          | BYL719                                                             | N/A   | Recruiting           | NCT03138070     |
| Recurrent or Metastatic Squamous Cell Carcinoma of Head and Neck          | 43          | BYL719                                                             | II    | Recruiting           | NCT02145312     |
| Head and Neck Squamous Cell Cancer                                       | 16          | BYL719 + Cetuximab+MRT (Intensity-Modulated Radiation Therapy)         | I     | Active not recruiting| NCT02282371     |
| Locoregionally Advanced Squamous Cell Carcinoma of Head and Neck          | 36          | BYL719 + Cisplatin+Radiation (Intensity modulated radiation therapy)   | I     | Recruiting           | NCT02537223     |
| Uveal Melanoma                                                           | 30          | BYL719 + AEB071                                                      | I     | Active not recruiting| NCT02273219     |
| Rectal Cancer                                                             | 24          | BYL719 + Capecitabine+Radiation                                       | I     | Recruiting           | NCT02550743     |
| Colorectal Cancer                                                         | 150         | LGX818 + Cetuximab+/- BYL719                                         | I/II  | Active not recruiting| NCT01719380     |
| Patients With Gastrointestinal Stromal Tumor                              | 56          | BYL719 + ST571                                                      | I     | Active not recruiting| NCT01735968     |
| Adenocarcinoma Lung Cancer; Squamous Cell Lung Carcinoma                  | 67          | BYL719/AUY922/INC280/LDK378/MEX162                                     | II    | Active not recruiting| NCT02276027     |
| CDKN2A-p16+; Human Papillomavirus+Oropharyngeal Squamous Cell Carcinoma   | 14          | BYL719 + Surgery                                                    | II    | Not yet recruiting   | NCT03601507     |
| Breast Neoplasms; Kidney Neoplasms; Pancreatic Neuroendocrine Neoplasms   | 79          | BYL719 + Everolimus/Exemestane/Both                                  | I     | Active not recruiting| NCT02077933     |
| Advanced Solid Tumors With an Alteration of the PIK3CA Gene; ER+ Breast Cancer | 221        | BYL719+/-Fulvestrant                                                | I     | Active not recruiting| NCT01219699     |
| Solid Tumors                                                             | 41          | BYL719 + Cisplatin                                                  | I     | Recruiting           | NCT02620839     |
| Ovarian Cancer; Breast Cancer                                             | 118         | Olaparib+BYL719/BKM120                                               | I     | Active not recruiting| NCT01623349     |
| Meningioma                                                               | 25          | BYL719 + Trametinib                                                | I     | Not yet recruiting   | NCT03631953     |
| CAL-101 (GS-1101, Idelalisib) PI3Kδ inhibitor                             |             |                                                                     |       |                      |                  |
| Metastasis/Recurrence NSCLC                                               | 40          | CAL-101 + Pembrolizumab                                             | I/II  | Recruiting           | NCT03257722     |
| Waldenstrom Macroglobulinemia                                             | 50          | Obinutuzumab                                                   | II    | Active not recruiting| NCT02962401     |
| Chronic Lymphocytic Leucemia                                             | 62          | CAL-101 + Bendamustine+GA101                                        | II    | Recruiting           | NCT02445131     |
| Chronic Lymphocytic LeukemiaSmall Lymphocytic Lymphoma                    | 50          | CAL-101 + Ofatumumab                                               | II    | Suspended            | NCT02135133     |
| Follicular Non-Hodgkin Lymphoma Refractory                                | 260         | CAL-101                                                           | N/A   | Recruiting           | NCT03568929     |
| Chronic Lymphocytic Leukemia                                             | 42          | CAL-101 + Rituximab+Venetoclax                                    | I     | Not yet recruiting   | NCT03639324     |
| Chronic Lymphocytic Leukemia                                             | 104         | CAL-101 + Rituximab                                               | N/A   | Not yet recruiting   | NCT03545035     |
| Diffuse Large B-Cell                                                     | 36          | CAL-101 + (Rituximab+Ifosfa mide+Carboplatin+Etoposide) (RICE)       | I     | Recruiting           | NCT03349346     |
Table 2 Important ongoing clinical trials with PI3K-targeted therapies (Continued)

| Conditions                                                                 | Sample size | Design                                      | Phase | Status               | Trail number        |
|---------------------------------------------------------------------------|-------------|---------------------------------------------|-------|----------------------|---------------------|
| Chronic Lymphocytic Leukemia                                              | 35          | CAL-101 + Tirabrutinib +/- Obinutuzumab      | II    | Recruiting           | NCT02968563        |
| Chronic Lymphocytic Leukemia; Small Lymphocytic Lymphoma                 | 24          | MOR00208 + CAL-101 / Venetoclax             | II    | Recruiting           | NCT02639910        |
| Chronic Lymphocytic Leukemia                                             | 308         | Acalabrutinib VS Rituximab + CAL-101/Bendamustine | III   | Recruiting           | NCT02970318        |
| Recurrent Chronic Lymphocytic Leukemia; Extramedullary Marginal Zone Lymphoma; Follicular Lymphoma | 68         | Pembrolizumab +/- CAL-101/Ibrutinib         | II    | Recruiting           | NCT02332980        |
| B-cell Malignancies                                                      | 197         | Tirabrutinib +/- CAL-101/Entospletinib +/- Obinutuzumab | I     | Active not recruiting | NCT02457598        |
| Chronic Lymphocytic Leukemia; Peripheral T-cell Lymphoma                 | 123         | TRU-016 + Rituximab/Obinutuzumab/Ibrutinib/Bendamustine OR TRU-016 + Rituximab+CAL-101 | I     | Recruiting           | NCT01644253        |
| Acute Lymphoblastic Leukemia; Acute Myeloid Leukemia                     | 24          | Personalized Kinase Inhibitor Therapy Combined With Chemotherapy | I     | Recruiting           | NCT02779283        |
| Non-Hodgkin Lymphoma                                                     | 30          | CAL-101                                    | N/A   | Recruiting           | NCT02928510        |
| Hematological Malignancies                                               | 150         | CAL-101 VS Ibrutinib (Side Effects)         | N/A   | Recruiting           | NCT02824159        |
| Recurrent Chronic Lymphoid Leukemia                                      | 3           | ACY-1215+ CAL-101/Ibrutinib                 | I     | Active not recruiting | NCT02787369        |
| Chronic Lymphocytic Leukemia                                             | 416         | Rituximab+Bendamustine+ Placebo/ CAL-101    | III   | Active not recruiting | NCT01569295        |
| Follicular Lymphoma                                                      | 240         | CAL-101                                    | III   | Recruiting           | NCT02536300        |
| B-Cells-Tumors; B Cell Chronic Lymphocytic Leukemia; Follicular Lymphoma; Mantle Cell Lymphoma; Large B-Cell Diffuse Lymphoma | 60          | CAL-101 VS Placebo                         | I     | Recruiting           | NCT03151057        |
| Chronic Lymphocytic Leukemia; Small Lymphocytic Lymphoma                 | 24          | MOR00208 + CAL-101/ Venetoclax             | II    | Active not recruiting | NCT02639910        |
| Diffuse Large B Cell Lymphoma                                            | 72          | CAL-101                                    | II    | Recruiting           | NCT03576443        |
| B-Cell Non-Hodgkin Lymphoma                                              | 34          | CAL-101                                    | II    | Recruiting           | NCT03133221        |
| Chronic Lymphocytic Leukemia                                             | 20          | CAL-101 + Rituximab                        | N/A   | Recruiting           | NCT02993526        |
| Chronic Lymphocytic Leukaemia                                            | 150         | CAL-101 + Rituximab                        | N/A   | Not yet recruiting   | NCT03582098        |
| GSK2636771 PI3Kβ inhibitor                                               |             |                                             |       |                      |                     |
| Gastric Cancer                                                           | 400         | Biomarker Screening                        | N/A   | Recruiting           | NCT02951091        |
| Advanced Gastric Adenocarcinoma                                          | 66          | GSK2636771+ Paclitaxel                     | I/II  | Recruiting           | NCT02615730        |
| Metastatic Castration-Resistant Prostate Cancer                          | 64          | GSK2636771+ Enzalutamide                   | I     | Recruiting           | NCT02215096        |
| Melanoma and Other Malignant Neoplasms of Skin; Metastatic Melanoma       | 41          | GSK2636771 + Pembrolizumab                 | I/II  | Recruiting           | NCT03131908        |
| Advanced Malignant Solid Neoplasm                                        |             |                                             |       |                      |                     |
| Patients with PTEN mutation, deletion, expression or loss were given GSK2636771 |             |                                             |       |                      |                     |
| INCBO5046S (Parsacilisib) PI3Kδ inhibitor                                 |             |                                             |       |                      |                     |
| MPN (Myeloproliferative Neoplasms)                                       | 78          | INCB050465 + Ruxolitinib                   | II    | Recruiting           | NCT02718300        |
| Advanced Solid Tumors                                                    | 237         | Pembrolizumab + Itacitinib/ INCB050465     | I     | Recruiting           | NCT02646748        |
| Advanced Solid Tumors                                                    | 159         | Itacitinib + Epacadostat/ INCB050465       | I     | Active, not recruiting | NCT02559492        |
| Solid Tumors; Advanced Malignancies; Metastatic Cancer                    | 80          | lla:INCB052793 + (Gemcitabine+Nab-Paclitaxel+Dexamethasone+Carfilzomib+Bortezomib+Lenalidomide+Azacitidine+INCB052793 + Pomalidomide+INCB050465) II:INCB052793 + Azacitidine+ INCBO39110 | II/II | Active not recruiting | NCT02265510        |
| Conditions | Sample size | Design | Phase | Status | Trial number |
|------------|-------------|--------|-------|--------|--------------|
| Unresectable or Metastatic Solid Tumors | 100 | INCMGA00012 + Epacadostat / INCB050465 | I | Recruiting | NCT03589651 |
| Primary Sjögren’s Syndrome | 12 | INCB050465 | II | Not yet recruiting | NCT03627065 |
| Lymphoma | 120 | INCB050465 | II | Recruiting | NCT03235544 |
| Lymphoma | 120 | INCB050465 +/- CITADEL-204 | II | Recruiting | NCT03144674 |
| Lymphoma | 60 | INCB050465 | II | Active not recruiting | NCT02998476 |
| Lymphoma | 18 | INCB050465 | I | Recruiting | NCT03314922 |
| Lymphoma | 45 | INCB050465 + Bendamustine + Obinutuzumab | I | Recruiting | NCT03039114 |
| Lymphoma | 100 | INCB050465 | II | Recruiting | NCT03126019 |
| Lymphoma | 25 | INCB050465 + INCB053914 | I | Not yet recruiting | NCT03688152 |
| Lymphoma | 81 | INCB050465 + Rituximab +/- Bendamustine OR INCB050465+ Ibrutinib | I | Recruiting | NCT03424122 |
| B-Cell Malignancies | 88 | Serabelisib+TAK-228+ Paclitaxel | I | Not yet recruiting | NCT03154294 |
| Clear-cell Metastatic Renal Cell Carcinoma | 96 | MLN0128 +/- Serabelisib VS Everolimus | II | Active not recruiting | NCT02724020 |
| Endometrial Neoplasms | 242 | Paclitaxel +/- MLN0128 OR MLN0128 +/- Serabelisib | II | Recruiting | NCT02725268 |
| Triple Negative Breast Cancer | 20 | TAK-228 + Serabelisib+ Cisplatin+Nab Paclitaxel | II | Recruiting | NCT03193853 |
| Chronic Lymphocytic Leukemia (CLL) Small Lymphocytic Lymphoma (SLL), B-cell Non-Hodgkin Lymphoma | 133 | ME401 +/- Rituximab | I | Recruiting | NCT02914938 |
| Marginal Zone Lymphoma; Waldenstrom Macroglobulinemia | 30 | Ublituximab + Umbralisib | I | Recruiting | NCT03364231 |
| Chronic Lymphocytic Leukemia | 30 | Ublituximab + Umbralisib + Venetoclax | I/II | Recruiting | NCT03379051 |
| Follicular Lymphoma | 150 | Obinutuzumab + Umbralisib / lenalidomide/Chemotherapy | II | Recruiting | NCT03269669 |
| Non-Hodgkin Lymphoma; Chronic Lymphocytic Leukemia | 50 | TG-1701 +/- (Ublituximab + Umbralisib) | I | Recruiting | NCT03671590 |
| Chronic Lymphocytic Leukemia; B-cell Non-Hodgkin Lymphoma | 36 | Umbralisib + Pemtrolizumab | I | Recruiting | NCT03283137 |
| Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; Mantle Cell Lymphoma | 45 | Umbralisib + Ibrutinib | I | Active not recruiting | NCT02268851 |
| Relapsed and/or Refractory Diffuse Large B-cell Lymphoma Including With Myc Alterations | 60 | CUDC-907 | I | Recruiting | NCT02307240 |
| Lymphoma; Neuroblastoma; Brain Tumor; Solid Tumor | 44 | CUDC-907 | I | Recruiting | NCT02909777 |
| Multiple Myeloma; Lymphoma | 88 | CUDC-907 | I | Active not recruiting | NCT01742988 |
| Relapsed and/or Refractory Diffuse Large B-cell Lymphoma Including With Myc Alterations | 200 | CUDC-907 | II | Recruiting | NCT02674750 |
daily was tolerable, but objective anti-tumor responses were not observed in these patients [100]. The most frequent treatment-related AEs in the study population were fatigue, decreased appetite, nausea, hyperglycemia and rash. Maximum tolerated dose (MTD) for PF-05212384 was estimated to be 154 mg weekly in a phase II trial; the most common AEs were mucosal inflammation, stomatitis, nausea, decreased appetite, vomiting and fatigue [101]. Clinical benefits were noted in 11 of 78 patients, with 2 confirmed PR, 1 unconfirmed PR, and 8 long-lasting stable (> 6 months) [101].

A multi-arm phase I study evaluated dose-limiting toxicity, safety, pharmacokinetics and preliminary antitumor activity of the PF-04691502 and PF-05212384 plus irinotecan or the MEK inhibitor PD-0325901 in advanced cancer [102]. In this clinical study, MTD for PF-05212384 plus irinotecan (180 mg/m2) was estimated to be 110 mg weekly, and for PF-05212384 plus PD-0325901 (4 mg BID) was not reached at the highest dose at PF-05212384 154 mg weekly; the PF-04691502 (4 mg/6 mg, QD) combination arms were terminated early due to poor tolerability. Further preliminary evidence of clinical activity was observed in

| Conditions | Sample size | Design | Phase | Status | Trial number |
|------------|-------------|--------|-------|--------|--------------|
| Rigosertib (ON-01910) PI3K and PIk-1 inhibitor | Leukemia; Myelofibrosis; Anemia; Splenomegaly | 35 | Rigosertib | II | Recruiting | NCT00730884 |
| Myelodysplastic Syndromes | 36 | Rigosertib | I | Suspended | NCT02075034 |
| Myelodysplastic Syndromes | 45 | Rigosertib | II | Active not recruiting | NCT01904682 |
| Myelodysplastic Syndromes; MDS; RAEB; Chronic Myelomonocytic Leukemia | 299 | Rigosertib | III | Active not recruiting | NCT01241500 |
| Myelodysplastic Syndromes; Refractory Anemia With Excess Blasts; Chronic Myelomonocytic Leukemia; Cytopenia | 67 | Rigosertib | III | Active not recruiting | NCT01928537 |
| Myelodysplastic Syndromes | 12 | Rigosertib | I | Recruiting | NCT03495167 |
| Myelodysplastic Syndrome; Acute Myeloid Leukemia; Chronic Myelomonocytic Leukemia | 45 | Rigosertib+Azacitidine | I/II | Active not recruiting | NCT01926587 |
| Myelodysplastic Syndrome; MDS; Refractory Anemia With Excess Blasts; RAEB | 360 | Rigosertib VS. Any approved or standard-of-care therapy | III | Recruiting | NCT02562443 |

Abbreviations: NSCLC Non-small cell lung cancer, SCLC Small cell lung cancer, ER Estrogen Receptor, PR Progesterone receptor

Table 3 Drugs targeting PI3K in clinical trial

| Compound | Terminated | Phase I | Phase II | Phase III | FDA approved |
|----------|------------|---------|----------|-----------|--------------|
| Dual PI3K/mTOR inhibitor | BGT-226 (Novartis) | GSK468/Omipalisib (GlaxoSmithKline) | BEZ235/Dactolisib (Novartis) | PF-05212384/gedatolisib/PKI-587 (Pfizer) | |
| | DS-7423 (Daichi Sankyo) | P7170 (Piramal) | GDC-0980/Aprotinisib (Genentech) | | |
| | P04691502 (Pfizer) | SB2343/VS-SS84 (Verastem) | LY3023414 (Eli Lilly) | | |
| | PKI-179 (Pfizer) | | PQR309/Bimarisib (PQUR Therapeutics) | | |
| Pan-PI3K inhibitor | GDC-0941/Pictilisib (Genentech) | CHS132799 (TohokuNipponPharm) | XL147/ Pilaralisib (Sanofi) | BKM-120/Buparlisib (Novartis) | BAY80–6946/Copanlisib (Bayer) |
| | PX-866 (Oncothryon) | | ZSTK474 (Zenyaku Kogyo) | | |
| | TG100-115 (Sanofi) | | | | |
| Isoform-specific PI3K inhibitor | AZD8835 (AstraZeneca) | AZD8186 (AstraZeneca) β/δ | AMG 319 (Amgen) δ | GDC-0032/Taselisib (Genentech) α/6/γ | Duvelisib/IPI-145 (Infinity) δ/γ |
| | δ/α | KA2237 (Karus Therapeutics) /δ/β | GSK2636771 (GlaxoSmithKline) β | INC0056045/Parsaclisib (Incyte) δ | CAL-101/delalisib (Gilead) δ |
| | WX-037 (Wilex) α | GS-9820/CAL-120 (Gilead) /β/δ | INCB050465/Parsaclisib (Incyte) δ | Serabelisib/INK-1117 (Takeda) α | BYL719/Alpelisib (Novartis) α |
| | | ME401/PWT-143 (MEI Pharma) δ | Umbralisib/TGR-1202 (TG Therapeutics) δ | | |
| Others | CUDC-907/Fimepinostat (Curis) | | | Rigosertib/ON-01910 (Onconova Therapeutics) | |
PF-05212384 combination arms. Similar results were also reported in a phase II study, which demonstrated poor tolerability of PF-04691502, whilst also demonstrating acceptable tolerability and moderate anti-tumor activity of PF-05212384 in patients with recurrent endometrial cancer [103]. Ongoing clinical studies are exploring efficacy of PF-05212384 alone and in combination in breast cancer, lung cancer, head and neck cancer, ovary cancer, endometrial cancer, and pancreatic cancer.

Pan-PI3K inhibitors

**BKM120 (NVP-BKM120, Buparlisib)**

BKM120 (buparlisib) is an orally pan-class I, reversible inhibitor of PI3K. In vitro, buparlisib demonstrates potent antiproliferative effect in human cancer cell lines. In vivo, buparlisib exhibits good oral bioavailability and significant antitumor activity in human tumor xenograft models at tolerated doses [104]. In the first-in-human, phase I, dose-escalation study of buparlisib in western patients with advanced solid tumors, MTD was established at 100 mg daily [105], which was confirmed in the dose-expansion part of another study [106]. The most common treatment-related AEs included rash, hyperglycemia, diarrhea, anorexia, mood alteration, decreased appetite, nausea and abnormal hepatic function [105, 106]. Phase I studies of buparlisib in Japanese and Chinese patients with advanced solid tumors also established a recommended dose of 100 mg daily [107, 108]. The MTD was 80 mg/d in a phase I study of buparlisib in patients with advanced acute leukemias [109].

A phase I trial in patients with advanced solid tumors suggested that the MTD of buparlisib in combination with standard doses of mFOLFOX6 (every 2 weeks of a 28-day cycle) was 40 mg daily; increased toxicity was observed compared to that expected from either buparlisib or mFOLFOX6 alone [110]. This trial concluded that further studies of buparlisib in combination with mFOLFOX6 are not recommended in gastrointestinal tumor. In a phase Ib clinical trial, addition of buparlisib (100 mg/day) to carboplatin + paclitaxel was well tolerated in patients with advanced solid tumors [111]. Confirmed objective response was observed in 5 of 25 patients with measurable disease, in particularly, all 3 patients with loss of PTEN expression benefitted clinically from treatment [111]. Interestingly, in the dose expansion study, this combination was revealed to show no significant clinical activity amongst the group of PTEN deficient tumors [112].

In combination with trametinib (MEK inhibitor), buparlisib 60 mg daily plus trametinib 1.5 mg daily displayed promising antitumor activity in patients with KRAS-mutant ovarian cancer; however, modest antitumor activity was observed in patients with non–small cell lung cancer and
pancreatic cancer [113]. In a phase I dose escalation study, the MTD of combining buparlisib with olaparib (PARP inhibitor) was determined to be BKM120 50 mg daily and olaparib 300 mg daily. Anticancer activity was observed in patients with breast cancer and ovarian cancer [114]. However, in a phase II study, buparlisib was associated with a poor safety profile and minimal antitumor activity in advanced or recurrent endometrial carcinoma [115]. In patients with metastatic renal cell carcinoma progressing on vascular endothelial growth factor (VEGF) targeted therapies, buparlisib (80 mg/day) with bevacizumab (10 mg/kg every 2 weeks), was shown to be a tolerable regimen with preliminary activity [116]. In patients with castration-resistant prostate cancer, buparlisib did not demonstrate significant activity in a phase II trial, furthermore, the combination of buparlisib with abiraterone acetate was not recommended as a phase Ib study reported [86, 117].

Several clinical trials investigated the use of buparlisib in patients with breast cancer. The combination of buparlisib with capcitabine in patients with metastatic breast cancer was suggested to be well-tolerated in patients with metastatic breast cancer, with 5 of 17 patients demonstrating complete responses (CR) or PR [118]. The combination of buparlisib (100 mg/day) and trastuzumab (2 mg/kg every week) was well tolerated, and preliminary signs of antitumor activity were observed in patients with HER2-positive advanced breast cancer resistant to trastuzumab-based therapy [119]. A randomized adaptive phase II/III study (BELLE-4) suggested that addition of buparlisib to paclitaxel did not improve PFS of patients with HER2 negative advanced breast cancer [120]. In a placebo-controlled phase II trial (NeoPHOEBE), addition of the pan-PI3K inhibitor buparlisib to taxane-trastuzumab-based therapy in HER2 positive early breast cancer was revealed to be unfeasible [121].

Combination trials of buparlisib with endocrine therapy were conducted. MTD was estimated as buparlisib 100 mg daily plus fulvestrant in patients with metastatic estrogen receptor positive breast cancer in a phase I trial [122]. The most common AEs included fatigue, transaminases elevation, rash, and diarrhea. In a phase 3, randomized, placebo-controlled trial (BELLE-2), the addition of buparlisib to fulvestrant significantly prolonged PFS (6.9 vs 5.0 months, HR0.78, one-sided \( p = 0.00021 \)) compared with the placebo plus fulvestrant group in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer [123]. Prespecified exploratory analyses in BELLE-2 showed that the combination regimen resulted in meaningful clinical benefits in the patients with circulating tumor DNA (ctDNA) PIK3CA mutant. Serious AEs were reported in 134 (23%) of 573 patients in the buparlisib group compared with 90 (16%) of 570 patients in the placebo group. Based on these findings, BELLE-3 was to assess the efficacy of buparlisib or placebo in combination with fulvestrant in hormone-receptor-positive, HER2-negative, advanced breast cancer patients with PIK3CA-mutant and wild-type status detected in ctDNA [124]. Buparlisib group was shown to have better PFS than the placebo group (3.9 vs 1.8 months, HR0.67, one-sided \( p = 0.00030 \)), but serious AEs were more frequently reported in the buparlisib group (22% vs. 16%).

**BAY 80–6946 (Copanlisib)**

BAY 80–6946 (copanlisib) is an intravenous, potent, highly selective and reversible pan-class I PI3K inhibitor with predominant activity against the p110\(\alpha\) and p110\(\delta\) isoforms, currently in clinical development [125]. The first-in-human phase I study of copanlisib monotherapy in patients with advanced solid tumors and non-Hodgkin lymphomas determined the MTD to be 0.8 mg/kg (dosed intermittently on days 1, 8, and 15 of a 28-day cycle), and promising anti-tumor activity was observed, especially in patients with non-Hodgkin lymphoma [126]. The most common treatment-related AEs included nausea and transient hyperglycemia [126]. In a phase I study among Japanese patients with advanced or refractory solid tumor, MTD of 0.8 mg/kg was also observed; the most frequent AEs were hyperglycemia, hypertension, and constipation [127]. A phase I, dose-escalation study of copanlisib in combination with gemicitabine or cisplatin plus gemicitabine (CisGem) recommended copanlisib 0.8 mg/kg for patients with advanced cancer. Copanlisib plus CisGem demonstrated favorable clinical response than CisGem [128].

In a phase II study of copanlisib in different subtypes of indolent or aggressive lymphoma, the objective response rate was 44% (14/32) in indolent lymphoma and 27% (13/48) in the aggressive lymphoma. In this trial, enhanced anti-tumor effects were observed in tumors with upregulated PI3K pathway gene expression [129]. Based on this trial, another phase II trial was conducted with participants suffering from relapsed or refractory indolent B-cell lymphoma; overall response rates (ORR) of 59% (84/142) and CR rates of 12% were observed, leading to accelerated approval of copanlisib for relapsed follicular lymphoma [130, 131]. Clinical trials of copanlisib are ongoing, including several phase III trials in patients with non-Hodgkin lymphoma.

**IPI-145 (Duvelisib)**

IPI-145 (duvelisib) is an oral dual inhibitor of PI3K-\(\gamma\) and PI3K-\(\delta\) currently in clinical development. Preclinical studies revealed that IPI-145 causes direct killing in primary chronic lymphocytic leukemia cells in a dose- and time-dependent manner, whereas not bring direct cytotoxicity to normal human B cells [132]. In a phase I, open-label study of duvelisib, the ORR in patients with relapsed/refractory peripheral T-cell lymphoma and cutaneous T-cell lymphoma were 50% (8/16) and 31.6% (6/19) respectively [133]. The most frequently reported AEs were transaminase increases,
maculopapular rash, and neutropenia. Moreover, a phase II study is planned to further evaluate the efficacy and safety of duvelisib in patients with relapsed and refractory peripheral T-cell lymphoma. The samples of patients with chronic lymphocytic leukemia of this trial were obtained, and the gene-expression studies demonstrated that expression of anti-apoptotic protein BCL2 and several BH3-only pro-apoptotic genes were upregulated on duvelisib therapy [134]. In vitro, the combination of duvelisib and BCL2 inhibitor venetoclax resulted in enhanced apoptosis in chronic lymphocytic leukemia cells [134].

A phase I dose-escalation study in patients with relapsed/refractory indolent non-Hodgkin lymphoma reported the antitumor activity of duvelisib, with an ORR of 65% including CR in 25% of responding patients [135]. The phase II Dynamo study enrolled 129 patients with relapsed/refractory indolent non-Hodgkin lymphoma, and the ORR was 46%, with acceptable safety profile. The response rate across the disease subtypes was 41, 68, and 33% for patients with follicular lymphoma, small lymphocytic lymphoma, and marginal zone lymphoma, respectively [136]. More recently, in the randomized phase III DUO trial of duvelisib versus ofatumumab monotherapy, patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma were randomized to oral duvelisib 25 mg BID (n = 160) or ofatumumab intravenous (n = 159) [137]. Compared with ofatumumab group, patients who received duvelisib were shown to have significantly improving median PFS (13.3 months vs. 9.9 months; HR 0.52; p < 0.0001). The ORR was significantly higher with duvelisib (74% vs. 45%; p < 0.0001) regardless of del(17p) status. In September 2018, the FDA granted regular approval to duvelisib for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma after at least two prior therapies. In addition, duvelisib received accelerated approval for adult relapsed or refractory follicular lymphoma patients who received at least two prior systemic therapies.

**GDC-0941 (Pictilisib)**

GDC-0941 (pictilisib) is a potent, orally class I pan-PI3K inhibitor, which is currently in clinical development [138, 139]. Pictilisib has demonstrated antitumor activity in human tumor xenograft murine models [140, 141]. Pictilisib exhibited favorable tolerability with potential clinical antitumor activity in the first-in-human phase I study of advanced solid tumor, and the MDT was 330 mg/day [142]. The most common drug-related toxicities were nausea, fatigue, diarrhea, vomiting, dysgeusia and decreased appetite [142]. Pictilisib demonstrated a favorable safety profile in Japanese patients with advanced solid tumor or non-squamous non-small cell lung cancer in a phase Ia/lb study; no objective anti-tumor responses were observed in patients with advanced solid tumor while partial anti-tumor responses were observed in patients with non-squamous non-small cell lung cancer [143]. The MDT was determined to be 340 mg/day for monotherapy and was 260 mg/day for combination with carboplatin-paclitaxel and bevacizumab [143]. In patients with advanced solid tumors, another phase I dose-escalation study indicated that combination of pictilisib with EGFR tyrosine kinase inhibitor erlotinib was feasible [144]. In this study, modest antitumor effects were observed, that 2 (3.5%) of 57 patients experienced PR and 19 (33.3%) had stable disease [144]. A phase Ib dose-escalation study in patients with advanced non-small cell lung cancer assessed the tolerability and pharmacokinetics of pictilisib in combination with eitherpaclitaxel and carboplatin or pemetrexed and cisplatin, with or without bevacizumab [145]. In this study, pictilisib combination with various treatment regimens demonstrated promising efficacy and manageable toxicity, and preliminary antitumor activity was observed [145].

In a randomized, double-blind, placebo-controlled phase II study (FERGI) of oestrogen receptor-positive, aromatase inhibitor resistant advanced breast cancer, patients were randomly allocated (1:1 in part 1 and 2:1 in part 2) to pictilisib (340 mg daily in part 1 and 260 mg daily in part 2) or placebo, plus intramuscular fulvestrant 500 mg. As a result, the addition of pictilisib to fulvestrant did not significantly improve PFS; it may be that the dose of pictilisib was limited by toxicity, potentially limiting its efficacy [146]. A phase II randomized PEGGY study in patients with hormone receptor-positive, HER2-negative, locally recurrent, or metastatic breast cancer revealed that adding pictilisib to paclitaxel did not prolong PFS of the patients [147]. In a randomized phase II study, patients with newly diagnosed estrogen receptor–positive, HER2 negative breast cancers were randomized to anastrozole or pictilisib plus anastrozole group [148]. The antitumor effects were measured by change of Ki-67 protein expression between tumor legions taken before and at the end of treatment [148]. Patients receiving the combination therapy showed greater geometric mean Ki-67 suppression from 66.0 to 83.8%. Further, significant Ki-67 response was observed for patients with luminal B tumor, but not for patients with luminal A tumor [148].

**GDC-0032 (Taselisib)**

GDC-0032 (taselisib) is a potent and selective inhibitor of p110α, p110β, and p110γ isoforms of class IA PI3K, with 31 folds less potency for the p110β isoform. Taselisib was progressed to clinical trials as a potential treatment for human cancer. A phase I study in Japanese patients showed that taselisib was well tolerated at 6 mg daily in patients with advanced solid tumor, and 4 mg daily in combination with fulvestrant in patients with HR-positive, HER2-negative advanced/recurrent breast cancer [149]. The most frequent treatment-related AEs were rash, diarrhea, and stomatitis. PR were observed in 2/9 patients
receiving monotherapy, and in 1/6 patients receiving combination therapy [149]. All patients with PR had PIK3CA-mutated tumor, which suggested that taselisib is expected to be effective in patients with PIK3CA-mutated solid tumor [149]. In another phase I dose escalation study of taselisib, 34 patients with locally advanced or metastatic solid tumor were given 3–16 mg taselisib once daily [150]. Dose limiting toxicities (DLT) were observed in patients receiving 12 and 16 mg dose levels. Pharmacodynamic findings of patient tumor sample showed that PI3K pathway was inhibited at dose ≥3 mg/d. Confirmed response was observed in 5/14 of PIK3CA-mutant tumor patients, and in 0/15 patients with tumors without known PIK3CA mutations [150]. A randomized phase III study of taselisib plus fulvestrant versus placebo plus fulvestrant in patients with metastatic breast cancer is ongoing.

Isoform-specific inhibitors

**BYL719 (Alpelisib)**

BYL719 (alpelisib), an oral selective PI3Kα isoform inhibitor, exhibited dose-dependent antitumor activity in tumor xenograft models, particularly models with mutated or amplified PIK3CA, highlighting the potential antitumor activity of alpelisib in patients with PIK3CA-altered tumors [151, 152]. The first-in-human phase Ia study of alpelisib, demonstrated a tolerable safety profile and declared its MTD as 400 mg daily and 150 mg twice daily [153]. The most frequent treatment-related AEs included hyperglycemia, nausea, decreased appetite, diarrhea, and vomiting [153]. Among 134 patients with PIK3CA-altered advanced solid tumor who received treatment, stable disease was achieved in 70 (52.2%) patients, PR was achieved in 7 (5.2%) patients, and CR was achieved in 1 (0.7%) patient [153]. In patients with ER-positive, HER2-negative metastatic breast cancer refractory to endocrine therapy, MTD of alpelisib in combination with letrozole was 300 mg/d [154]. In this phase Ib study, the clinical antitumor activity was observed in 44% patients with PIK3CA mutated and 20% in PIK3CA wild-type tumors [154]. In trastuzumab- and taxane-resistant HER2-positive metastatic breast cancer, the combination of alpelisib and trastuzumab emtansine was tolerable and activity was observed, therefore further studies of the combination are expected to perform [155]. The triple-combination therapy of encorafenib (RAF kinase inhibitor), cetuximab (monoclonal antibody targeting EGFR) and alpelisib demonstrated promising clinical activity and tolerability in metastatic BRAF-mutant colorectal cancer patients [156]. A phase III study of alpelisib and fulvestrant is ongoing.

**CAL-101 (GS-1101, Idelalisib)**

CAL-101 (GS-1101, idelalisib) is an oral and specific inhibitor of the δ isoform of PI3K [122, 123]. It has been shown that idelalisib has therapeutic effects without inhibiting PI3K signaling essential for normal function of healthy cells [157, 158]. Idelalisib is the first FDA-approved PI3K inhibitor for use in combination with rituximab for the treatment of relapsed or refractory chronic lymphocytic leukemia, or as monotherapy for relapsed small lymphocytic lymphoma and follicular lymphoma previously treated with two or more prior systemic therapies.

In a phase Ib dose-escalation and extension studies of idelalisib, 64 patients with relapsed/refractory B-cell malignancies were assigned to one of eight regimens; idelalisib was taken once or twice a day at doses ranging from 50 to 350 mg [159]. The ORR was 47% (30/64), with 1 patient had a CR (1.6%). The median duration of response was 18.4 months, and the PFS was 7.6 months [159]. AEs were reported in 20% or more patients, including diarrhea, fatigue, nausea, and rash [159]. In this 48-week phase I clinical trial, the results of 40 patients with relapsed/refractory mantle cell lymphoma were reported in another article. Among this population, it was reported that the ORR was 40% (16/40), with CR in 5% (2/40) patients. The median duration of response was 2.7 months, and the median PFS was 3.7 month [160]. In patients with relapsed/refractory chronic lymphocytic leukemia, acceptable safety profile and antitumor activity of idelalisib were also reported [161]. A phase II trial in patients with chronic lymphocytic leukemia found that idelalisib used as upfront therapy caused an early, severe hepatotoxicity, particularly in younger subjects who have not received prior disease-specific therapy [162]. A single-group, open-label, phase II trial evaluating patients with relapsed (after receipt of rituximab and an alkylating agent) indolent non-Hodgkin lymphomas demonstrated similar findings; 125 patients were administered idelalisib 150 mg twice daily [157]. The ORR was 57% (71/125), and 6% (7/125) met the criteria for CR, leading to FDA approval [9, 157, 163]. The median duration of response was 12.5 months, and the median PFS was 11 months [157]. Moreover, in patients with relapsed/refractory classical Hodgkin lymphoma, idelalisib was tolerable and had modest single-agent activity, with an ORR of 20% (5/25) [164].

The safety and efficacy of combined therapy with idelalisib and rituximab was evaluated in several clinical trials. In a phase II study of idelalisib plus rituximab, 64 treatment-naive older patients with chronic lymphocytic leukemia received rituximab 375 mg/m² weekly and idelalisib 150 mg twice daily; the ORR was 97% (62/64), including 19% (12/64) CR [165]. Notably, the ORR was 100% in patients with del(17p)/TP53 mutations. As compared with placebo and rituximab, this combined treatment significantly improved ORR (81% vs. 13%; OR, 29.92; P < 0.001), PFS (HR, 0.15; P < 0.001), and OS at 12 months (92% vs. 80%; HR, 0.28; P = 0.02) among chronic lymphocytic leukemia patients who are less able to undergo standard chemotherapy [166]. However, the
combination of idelisib, lenalidomide and rituximab were not recommended for that excessively toxicity of this triplet regimen was reported in patients with relapsed and refractory lymphoma in a phase I trial [163]. In a global, randomised, phase III trial, idelisib plus atumumab (a second-generation anti-CD20 antibody) resulted in better PFS (16.3 months vs. 8.0 months, HR 0.27, p < 0.0001) compared with atumumab alone in patients with relapsed chronic lymphocytic leukaemia progressing less than 24 months from the last therapy [167].

Resistances
The complexity of the PI3K/AKT/mTOR signaling network involves numerous feedback loops, extensive crosstalk nodes with other signaling pathways and compensatory pathways, providing ample opportunities for circumventing the effects of PI3K inhibition. Although small-molecule inhibitors of PI3K have exhibited promising clinical efficacy against human cancers, intrinsic and acquired resistance limits their therapeutic efficacy. Therefore, elucidating the mechanisms underlying resistance to PI3K inhibitor can provide rationale for combination therapies and alternative therapies. The specific mechanism is not completely defined; however, recent studies have described several possible resistance mechanisms, including PI3K reactivation, activation of parallel pathway, and tumor microenvironment.

Acquired amplification and mutation of PIK3CA and PIK3CB, which resulted in a marked upregulation of the PI3K signaling itself, have been shown to cause resistance to selective PI3K inhibitors [168, 169]. As suggested previously, in the absence of PTEN, proliferation of cancer cells became dependent mostly on the activity of the p110β isoform [170, 171]. The impact of PTEN loss on PI3K inhibitor resistance has been proposed [172]. The loss of PTEN alone was not able to induce resistance to inhibitor of class I PI3K (GDC-0941), however, amphiregulin enhanced the resistance, which resulted in increased EGFR/MAPK signaling. As a PI3K regulatory subunit, the phosphorylation of p85 has also been suggested to play a role in the development of resistance to PI3K inhibitors; presence of a regulatory loop between PI3K p85 and Sra has also suggested contributing to resistance against PI3K inhibitors [173]. Intrinsic resistance to PI3K p110α Inhibitors was correlated with sustained mTORC1 activity; growth factors such as insulin-like growth factor 1 and neuregulin 1 can activate mTOR and thus mediate resistance to p110α inhibitors [152].

The RAS-RAF-MEK-ERK signaling pathway is highly interconnected with PI3K signaling [174]. Mutation and overexpression of HRAS which belongs to the RAS family has been shown to reduced susceptibility to PI3K inhibitor, while knockdown improved sensitivity [175]. Further, interactions between NEK9 and MAP2K4 have been proposed to mediate cancer cell proliferation and resistance to PI3K inhibitors [176]. PI3K inhibition with the pan-PI3K inhibitor GDC0941/ XL-147 or the dual PI3K/mTOR inhibitor BEZ235 has been shown to induce increased HER2/3 expression and lead to compensatory activation of the ERK signaling pathway [177, 178]. Activation of STAT5 and expression of Pim kinases through STAT5 also conferred resistance to PI3K/AKT inhibitors by enhancing the mTORC1/Mcl-1 pathway [179]. Dual inhibition of PI3K and m-TOR has been found to elicit a positive feedback response and lead to increases activation of JAK2/STAT5 and secretion of IL-8, thus contributing to drug resistance [180]. Moreover, IL6-STAT3 loop triggered epithelial–mesenchymal transition and expanded action cancer stem cells population, which have been proposed as one of the mechanisms [181]. Aberrant regulation of WNT/β-catenin signaling and activation of GSK3β were correlated with resistance to the dual PI3K/mTOR inhibitor; nuclear β-catenin conferred resistance to the FOXO3a-mediated apoptosis provoked by PI3K and AKT inhibitors [182, 183].

Dual PI3K/mTOR inhibition led to activation of the NOTCH-MYC pathway [184]. NOTCH pathway and downstream induction of c-MYC were conferred resistance to PI3K inhibitors, whereas overexpression of the NOTCH canonical target genes HES1, HEY1 or HEY2 were not correlated with PI3K pathway inhibitor resistance [37, 184, 185]. The MYC was involved in growth, proliferation, differentiation, and metabolism of malignant cells, and knockdown of MYC reversed the resistance to dual PI3K/mTOR inhibitor [184]. Previous studies have also indicated that amplification of both MYC and eIF4E can mediate resistance to PI3K/m-TOR inhibitors [186]. eIF4E is an established MYC regulated target, indicate that interactions between MYC and eIF4E in regulating resistance mechanism is a possibility [184].

Proviral Integration site for Moloney murine leukemic virus (PIM) which overexpress in multiple malignancies has been shown to confer resistance by maintaining activation of downstream PI3K effectors in an AKT-independent manner [187]. In addition, PIM has been reported to modulate the activity of elf4B and mTORC1 to enhance NRF2/ARE activity, and to decrease ROS production to diminish the cytotoxicity of PI3K/AKT inhibitors [188]. S-phase kinase-associated protein 2 (Skp2) could promote the activation of AKT, and it has been reported to correlate with the resistance of PI3K inhibition [189]. Amplification or overexpression of RSK3 (Ribosomal S6 kinases RPS6KA2), RSK4 (Ribosomal S6 kinases RPS6KA4), PAK1, CDK 4/6, MSK1 (mitogen- and stress-activated protein kinase 1), KDM6B, and IGFBP5 have also been shown to confer resistance to PI3K inhibitors [168, 190–192].

High amounts of purine-related aqueous metabolites like hypoxanthine, and high levels of the mRNA encoding hypoxanthine phosphoribosyl transferase 1 (one of the key components of the purine salvage pathway), have
been found to be associated with resistance of PI3K pathway inhibition [193]. In consideration of the fact that ncRNA have been reported to regulate PI3K signaling and other parallel pathways (e.g. WNT/β-catenin, RAS/ERK/MAPK, JAK/STAT, NOTCH), we believe ncRNA may also play a role in the resistance of PI3K inhibitors [194–199]. Not surprisingly, more and more researches have suggested that deviant ncRNA expression is powerfully concerned about tumor drug resistance [200–208]. Recent studies have indicated potential mechanism of acquired resistance to dual PI3K/mTOR inhibitors, including elevated glycolysis accompanied with depletion of mitochondrial DNA, and upregulated DNA methyltransferases which Reduce PTEN and PPP2R2B expression [209, 210]. Novel roles of the tumor microenvironment have introduced in regulating drug resistance, and macrophages in microenvironment have been proposed as factors contributing to the resistances of PI3K inhibitors through the activation of NF-kB signaling [211].

Conclusions
The PI3K signaling pathway plays an important role in cell growth, proliferation and survival, making PI3K inhibition an attractive target for anticancer therapy. However, clinical trials with PI3K inhibitors used as a monotherapy have shown limited clinical activity, possibly as a consequence of resistance to PI3K inhibition and poor tolerability of PI3K inhibitors. Dual PI3K/mTOR and pan-PI3K inhibitors have made their way into clinical trials with limited efficacy as monotherapy, and relatively high rates of side effects were reported. As it has been increasingly recognized that different isoforms of PI3K play non-redundant roles in particular tumor types, isoform-selective inhibitors were developed. Isoform-selective PI3K inhibitors demonstrate improved specificity and reduced toxicity over dual PI3K/mTOR and pan-PI3K inhibitors, which have shown promising success in several clinical trials for both solid and hematological malignancies.

Several studies showed that PI3K inhibitors were more effective in patients with PI3K pathway mutations, however, some patients without documented PI3K mutations benefited from PI3K inhibitors and some patients with PIK3CA or other mutations not experienced benefit. As a result, strong correlations between PI3K mutations and response to therapy still have not been established in preclinical and clinical studies. It is important to identify reliable biomarkers that can guide patient selection, and to determine which tumor type and genetic profiles will benefit from PI3K inhibition. It is reported the value of pharmacodynamic biomarkers and functional imaging monitoring biomarker in guiding the selection of patients who are most likely to respond to PI3K inhibition, but the precision is still controversial [212]. To date, the mechanism of PI3K inhibitors has not been well established. The precise mechanism needs to be extensively and systematically studied, so that it will allow us to monitor efficacy and side effects, and to make personalized therapeutic decisions.

Preliminary clinical data indicated that the use of single-agent PI3K pathway inhibitors achieved modest responses and was unlikely to be a curative therapy for diverse cancers. The efficacy of PI3K inhibitors is limited for their narrow therapeutic window and frequent treatment-related toxicities. The drugs recommended are more likely to be optimally used in combination with other therapeutic modalities, such as surgery, hormonal therapies and other anticancer agents. Introduction of tumor suppressive or knockdown of oncogenic ncRNAs would be a feasible approach to inhibit the PI3K pathway. The combination of PI3K inhibitors with ncRNAs or inhibitors against other cross-talk pathways might yield promising therapeutic effects. AEs, including nausea, vomiting, diarrhea, hyperglycemia, fatigue, rash, anorexia, and abnormal hepatic function were frequently reported. These combination strategies may also decrease the rates of AEs and minimize the risk of the development of resistance.

Overall, PI3K inhibition is being investigated as a potential strategy to develop novel therapeutics for cancer management. Although we move forward with the clinical development of PI3K inhibitors, maximizing the utility of these agents in the treatment of patients remains challenging. Certainly, understanding the precise mechanisms of PI3K signaling and PI3K inhibition will be critical. Optimization of the patient selection strategies and combination approaches will help increase the practical efficacy of these agents. Continued work to clarify the resistance mechanisms and the novel strategies to overcome resistance will also be important.

Abbreviations
AEs: Adverse events; CR: Complete responses; ctDNA: Circulating tumor DNA; FDA: Food and Drug Administration; HR: Hazard ratio; LncRNA: Long non-coding RNA; mRNA: MicroRNA; MTD: Maximum tolerated dose; mTOR: Mammalian target of rapamycin; ncRNA: Non-coding RNA; ORR: Overall response rates; OS: Overall survival; PFS: Progression-free survival; PI3K: Phosphatidylinositol-3-kinase; PIP2: Phosphorylation of Phosphatidylinositol-3,4,5-phosphates; PI3Kδ: Phosphorylation of Phosphatidylinositol-3,4-phosphates; PIP3: Phosphorylation of Phosphatidylinositol-3,4,5-phosphates; P3; PR: Partial responses; PTEN: Phosphatase and tensin homologue deleted on chromosome 10; RDE: Recommended dose for expansion

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JY Data curation; Formal analysis; Writing - original draft. JN Data curation; Formal analysis; Writing - original draft. XM Writing - review & editing. JN Writing - review & editing.

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