Therapeutic Potency of PI3K Pharmacological Inhibitors of Gastrointestinal Cancer

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ABSTRACT

Therapeutic targeting of phosphatidylinositol 3-kinase (PI3K) is considered as a possible strategy in several types of cancer, including gastrointestinal ones. In vitro and in vivo studies indicated the significance of proapoptotic and antiproliferative inhibition of PI3K. Although there are many phase 1 and 2 clinical trials on PI3K inhibitors in patients with gastrointestinal cancer, the molecular mechanism of PI3K targeting PI3K/mTOR pathway is not clear. Panclass I, isoformselective, and dual PI3K/mTOR inhibitors are under investigation. This review aimed to indicate PI3K-dependent targeting mechanisms in gastrointestinal cancer and the evaluation of related clinical data.

KEYWORDS: Gastrointestinal cancer, PI3K pharmacological inhibitors, Clinical trials

INTRODUCTION

Phosphatidylinositol 3-kinase (PI3K), an intracellular lipid kinase, plays an important role in cell function and cancer development. PI3K phosphorylates phosphatidylinositol 4,5 biphosphate (PIP2) to phosphatidylinositol 3,4,5 triphosphate (PIP3) and subsequently PIP3 leads to phosphorylation of Protein Kinase B (AKT) by Phosphoinositide-dependent kinase 1 (PDK1) and Mammalian target of rapamycin complex 2 (mTORC2). Phosphatase and tensin homologue protein (PTEN), a tumor suppressor molecule, dephosphorylates PIP3 to PIP2. PI3Ks has three classes based on structure and function. Class Ia, the most important PI3K in human cancer, comprised of regulatory (p85) and catalytic (p110) subunits. Phosphoinositide-3-Kinase Regulatory Subunits 1,2,3 (PIK3R1,2,3) genes encode different isoforms of p85 regulatory subunit, whereas the catalytic subunits p110α, p110β, and p110γ are products of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), beta (PIK3CB) and delta (PIK3CD), respectively. Common somatic mutations of PIK3CA and PIK3CB in cancer cells induce activation of PI3K. Many clinical trials are done on PI3K inhibitors in solid tumors, including gastrointestinal (GI) cancer (table 1), but it is not known how various forms of PI3K targeting alter the molecular mechanisms of PI3K/mTOR pathway. This review aimed at indicating the targeting PI3K-dependent mechanisms in GI cancer and evaluating the correlated clinical data.
| Compound name | Cancer type | Mechanism of action | Phase | Arm | Status | Reference |
|---------------|-------------|---------------------|-------|-----|--------|-----------|
| **BKM120** (Buparlisib) | Advanced solid tumors | Pan-PI3K inhibitor | I | BKM120 | Completed | Bendell et al. 20 |
| | Advanced solid tumors | Pan-PI3K inhibitor | I | BKM120 | Completed | Baselga et al. 21 |
| | Gastrointestinal stromal tumor | Pan-PI3K inhibitor + TK inhibitor | Ib | BKM120 + imatinib | Completed | NCT01468688 23 |
| | Advanced colorectal cancer | Pan-PI3K inhibitor + EGFR inhibitor | I | Irinotecan + BKM120 | Completed | NCT01304602 24 |
| | Metastatic or advanced colorectal cancer | Pan-PI3K inhibitor + Topoisomerase 1 inhibitor | Ib | BKM120 + irinotecan | Recruiting | NCT01591421 25 |
| | Recurrent or metastatic advanced solid tumors | Pan-PI3K inhibitor + DNA synthesis inhibitor + microtubule polymer stabilizer | I | BEZ235-paclitaxel + BKM120-paclitaxel | Ongoing (no longer recruiting) | NCT01285466 26 |
| | Metastatic adenocarcinoma of the colon or rectum | Pan-PI3K inhibitor + Topoisomerase 1 inhibitor | I | BKM120 + irinotecan | Recruiting | NCT01540253 27 |
| | Metastatic or advanced solid tumors | mTOR/PI3K inhibitor + Pan-PI3K inhibitor + microtubule polymer stabilizer | Ib | BEZ235-paclitaxel + BKM120-paclitaxel | Ongoing (no longer recruiting) | NCT01285466 26 |
| | Advanced solid tumors | Pan-PI3K inhibitor + hedgehog pathway inhibitor | Ib | BKM120 + erismodigib | Recruiting | NCT01576666 29 |
| | Advanced solid malignancies | Pan-PI3K inhibitor + mTORC1 inhibitor | I/II | BKM120 + everolimus | Recruiting | NCT01470209 30 |
| | PI3K activated tumors | Pan-PI3K inhibitor | II | BKM120 | Recruiting | NCT01833169 31 |
| | Esophageal cancer | Pan-PI3K inhibitor | II | BKM120 | Recruiting | NCT01806649 32 |
| | Advanced solid tumors | Pan-PI3K inhibitor + MEK inhibitor | Ib | BKM120 + binimetinib | Recruiting | NCT01363232 33 |
| | Advanced solid tumors | Pan-PI3K inhibitor + MEK inhibitor | I | BKM120 + GSK1120212 | Completed | NCT01155453 34 |
| | Advanced solid tumors | Pan-PI3K inhibitor + Topoisomerase 1 inhibitor | I | BKM120 + irinotecan | Completed | NCT01068483 35 |
| | PX-866 | Advanced solid tumors | Pan-PI3K inhibitor | I | PX-866 | Completed | Hong et al. 36 |
| | Advanced solid tumors | Pan-PI3K inhibitor | I | PX-866 | Completed | NCT00726583 37 |
| | ZSTK474 | Advanced solid malignancies | Pan-PI3K inhibitor | I | ZSTK474 | Completed | NCT01682473 38 |
| | Advanced solid malignancies | Pan-PI3K inhibitor | I | ZSTK474 | Completed | NCT01280487 39 |
| | Advanced solid tumors | Pan-PI3K inhibitor | I | GDC-0941 | Completed | Wagner et al. 40 |
| | Advanced or metastatic solid tumors | Pan-PI3K inhibitor | I | GDC-0941 | Completed | NCT00876109 41 |
| | GDC-0941 (Pictilisib) | Advanced or metastatic solid tumors | MEK inhibitor + Pan-PI3K inhibitor | Ib | Cobimetinib + GDC-0941 | Active, not recruiting | NCT00996892 42 |
| | Advanced or metastatic solid tumors | Pan-PI3K inhibitor + EGFR inhibitor | I | GDC-0941 + erlotinib | Active, not recruiting | NCT00975182 43 |
| | Advanced solid tumors | PI3K inhibitor + MEK inhibitor | Ib | GDC-0941 + GDC-0973 | Completed | Shapiro et al. 44 |
| | BAY80-6946 (Copanlisib) | Advanced solid malignancy | pan-PI3K inhibitor + microtubule polymer stabilizer | I | BAY80-6946 + paclitaxel | Completed | NCT01411410 45 |
| | Advanced solid malignancy | Pan-PI3K inhibitor + nucleic acid synthesis inhibitor | I | BAY80-6946 + gemcitabine or cisplatin + gemcitabine | Completed | NCT01460537 46 |
| | Advanced solid malignancy | Pan-PI3K inhibitor | I | BAY80-6946 | Completed | NCT00962611 47 |
Mechanism of PI3K inhibitors

Based on the pharmacokinetic properties and selectivity for the ATP binding cleft on PI3K, PI3K inhibitors can be divided into three classes: pan-class I, isoform selective, and dual PI3K/mTOR inhibitors. These molecules mostly demonstrate cytostatic effects, resulting in desirable anti-cancer effects in vivo as well as G1 phase arrest in vitro. Figure 1 depicts the PI3K pharmacological inhibitors’ mechanism in GI cancer.

Pan-Class I inhibitors

Panclass I inhibitors have inhibitory effects against each isoform of p110 (PIK3CA). Based on early phase trial data it is unlikely that pan-class I PI3K inhibitors have significant activity as single agents. Rational combinations with either cytotoxics or other molecularly targeted agents are therefore being explored and are likely to be more effective in GI cancer. Of the main limitations of pan-class I inhibitors are the wide range of side effects including hyperglycemia, rash, and fatigue, which potentially limit dose escalation leading to sub-optimal inhibition of PI3K. The first report of a molecular agent inhibiting PI3K was about quercetin, which was a nonspecific kinase inhibitor. Eventually, more specific panclass I inhibitors were identified, such as Wortmannin and a quercetin analogue, LY294002.
Both LY294002 and Wortmannin showed strong PI3K inhibitory properties. Nevertheless, they had considerable limitations for application in clinical trials.\textsuperscript{11,12} LY294002 exhibited toxicity, a short half-life, and nonspecific targeting in vivo,\textsuperscript{13,14} whereas the limitations of Wortmannin included a short half-life and lack of biological stability.\textsuperscript{15} Preclinical and clinical studies have extensively assessed pan-class I inhibitors, including NVP-BKM120, PX-866, ZSTK474, GDC-0941, and BAY80-6946.

**a- NVP-BKM120 (buparlisib):** NVPBKM120 (buparlisib) is a potent panclass I PI3K inhibitor with its activity in nano-molar ranges for all the isoforms of class I PI3K. Preclinical investigations have revealed its effectiveness in a diverse range of cancer cell lines, with increased sensitivity in tumors harboring PIK3CA mutations.\textsuperscript{16} Similar results were also observed in a panel of GI cancer cell lines.\textsuperscript{17} In the study, the synergistic efficacy of NVP-BKM120, demonstrated that dual PI3K and STAT3 blockade showed a synergism in Kirsten rat sarcoma virus (KRAS) mutant gastric cancer cells. The synergistic effect was not seen in KRAS wild-type cells. Together, these findings suggest that the dual inhibition of PI3K and STAT3 signaling may be an effective therapeutic strategy for KRAS mutant gastric cancer patients.\textsuperscript{18} Although preclinical studies on BKM120 in GI cancer are still ongoing, it has reached phase I and II clinical trials for other solid cancers such as gastric and colorectal carcinomas.\textsuperscript{19} A phase I clinical trial showed that BKM120 was a safe and well tolerated drug, with a favorable pharmacokinetic profile, evidence of target inhibition, and preliminary antitumor activity.\textsuperscript{20} In phase I trial, BKM120 broadly activated class I PI3K inhibitor and lack of anti-mTOR activity was tolerable at doses to inhibit enzyme activity in blood, skin, or tumor cells.\textsuperscript{21} Buparlisib in combination with imatinib has antitumor and antiapoptotic activity in imatinib-resistant KIT exon 11+17 mutant tumors,\textsuperscript{22} and is being evaluated as third-line therapy in a phase 1/2 dose-escalation and dose-expansion clinical trial.\textsuperscript{23} Two studies of BKM120 in patients with colorectal cancer are underway, one in combination with irinotecan and another in combination with panitumumab.\textsuperscript{24,25} In other studies, BKM120 was administrated with paclitaxel, docetaxel, LDE225 and everolimus to treat patients with advanced solid tumor or esophageal squamous cell carcinoma.\textsuperscript{26-32} Some studies have shown the safety, pharmacokinetics, and pharmacodynamics of BKM120 in patients with solid tumors.\textsuperscript{33-35}

**b- PX-866:** PX866 is a semisynthetic panclass I, Wortmannin analogue with inhibitory concentrations in nano-molar ranges and better efficacy and a safer pharmacokinetic profile than Wortmannin. Preclinical studies have shown its anticancer effect against several xenograft models of various cancers.\textsuperscript{36} PX866 has also recently come under limelight for a multicenter trial for advanced solid tumors including gastric tumors. Data from the trial show that PX866 can be administered with endurable toxicity for patients with advanced solid tumors.\textsuperscript{37,38}

**c- ZSTK474:** ZSTK474, a panclass I PI3K inhibitor inhibits all the four isoforms of PI3K and exhibits antitumor activity in vivo against human tumor xenograft models.\textsuperscript{39-41} In vitro studies in gastric cancer cell lines suggest combination therapy of ZST474 and Insulin-like growth factor receptor (IGFR) inhibitors for treating IGFRpositive cancers to overcome any intrinsic resistance to inhibition of PI3K/Akt/mTOR signaling, since overexpression of IGFR correlated with increased tyrosine phosphorylation on insulin receptor substrate, leading to increased PI3K activation. Hence, combination therapy with both ZST474 and IGFR inhibitors on gastric cells with high IGFR expression exerted a superior therapeutic response.\textsuperscript{42} Studies have shown safety of ZSTK474 in patients with advanced solid malignancies.\textsuperscript{43,44}

**GDC-0941(pictilisib):** Pictilisib (GDC-0941) is a potent inhibitor of PI3Kα/δ in cell-free assays, with modest selectivity against p110β and p110y. In a study, the combination of NU6102 (CDK2 inhibitor) and pictilisib (pan-PI3K inhibitor) resulted in
synergistic growth inhibition, and enhanced cytotoxicity in HT-29 cells in vitro and in vivo. These studies identified a novel series of mixed CDK2/PI3K inhibitors and demonstrated that dual targeting of CDK2 and PI3K can result in enhanced antitumor activity.\textsuperscript{45} A phase 1 dose-escalation trial of pan-PI3K inhibitor, GDC-0941, is in progress.\textsuperscript{46} In some studies, GDC-0941 was administered with cobimetinib (Mitogen-activated protein kinase kinase [MEK] inhibitor) and erlotinib (Epidermal growth factor receptor [EGFR] inhibitor) in treating patients with advanced or metastatic solid tumors.\textsuperscript{47-49} In a recent phase 1 trial, the combination of the PI3K and MEK inhibitors GDC-0941 and GDC-0973 was effective against advanced solid tumors at doses that were tolerable for patients.\textsuperscript{50}

**d- BAY80-6946 (copanlisib):** Copanlisib (BAY 80-6946) is a potent pan-class I PI3K for PI3Kα/β/γ/δ in cell-free assays. In some studies, BAY80-6946 was administered with paclitaxel and gemcitabine in treating patients with advanced solid tumor.\textsuperscript{51-53}

**Isoform specific PI3K inhibitors**

PI3K isoform specific inhibitors were designed with an aim to provide comparable or superior efficacy than panclass I inhibitors. One potential advantage of isoform-specific antagonists over broad-spectrum inhibitors is that they can be matched more closely to their single target, yielding increased potency, fewer off-target effects, and improved tolerability. Specific inhibitors of p110α are expected to inhibit PI3K-AKT signaling in tumors with PIK3CA mutations and might also be effective against tumors that express activated Receptor tyrosine kinases (RTKs) or other oncopgenes, such as KRAS. P110β plays a key role in PI3K signaling in some Phosphatase and tensin homolog (PTEN)-deficient tumors, so p110β-specific inhibitors might be effective in patients with these particular tumors. One limitation for the use of PI3K inhibitors is that they may fail to block AKT activation in tumors that have gene amplifications, AKT2 mutations, or the AKT1 E17K mutation. Consequently, isoform-specific PI3K inhibitors are currently studied for an enhanced toxicity profile and more complete target inhibition.\textsuperscript{54,55} As noted below, preclinical and clinical studies have extensively examined isoform-specific PI3K inhibitors such as BYL719, INK1117, WX-037, and XL147.

**a- BYL719 (alpelisib):** BYL719 (alpelisib) is an α-isoform specific PI3K inhibitor working at nano-molar concentrations with minimal activity against other PI3K isoforms.\textsuperscript{56} BYL719 exhibited its inhibitory effects in synergy with another inhibitor LJM716, a ligand dependent as well as independent HER3 inhibitor, in gastric cancer xenograft models.\textsuperscript{57} Interestingly, a combination study was done on Human epidermal growth factor receptor 2 (HER2) positive gastric cancer cell lines, suggesting the sensitivity of this drug towards HER amplifications. BYL719 also recently completed phase 1b clinical trial for advanced stage gastric cancer in a combinational study with the HSP90 inhibitor AUY922 in patients whose tumors either harbour molecular alterations of PIK3CA or HER2 amplification.\textsuperscript{58} Another study showed pharmacological inhibition of PI3K pathway in tumor-bearing KitV558Δ/+ mice with the dual PI3K/mTOR inhibitor voxtalisib, the pan-PI3K inhibitor pilaralisib, and the PI3Kα inhibitor alpelisib each diminished tumor proliferation. Moreover, it has been shown that PI3K inhibition was effective against imatinib-resistant KitV558Δ;T669I/+ tumors.\textsuperscript{59} The highly selective PI3Kα inhibitor (Wild type and mutant forms) alpelisib (BYL719) showed strong single-agent activity in PIK3CA mutant tumor models and greater antitumor activity in Gastrointestinal stromal tumors (GIST)-specific models when combined with imatinib.\textsuperscript{60} The antitumor effect of the combination therapy was dependent on the tumor genotype, with imatinib-sensitive KIT exon 11 mutant tumors being the most responsive. A dose-escalation and dose-expansion, multinational, phase 1/2 clinical trial is currently underway for the combination treatment of alpelisib and imatinib as third-line...
treatment for patients with GIST. A phase 1 trial including patients with solid malignancies bearing PIK3CA mutations showed an acceptable side effect profile and efficacy that justified its further development in phase 2 trials. Also, a phase I study of isoform specific PI3K inhibitor (p110α) BYL719 and HSP90 inhibitor AUY922 in patients with gastric cancer is ongoing. Given the preclinical data suggesting the activation of PI3K as a mechanism of primary resistance to drugs acting on the MAPK pathway, a phase 1 trial of BYL719 in combination with cetuximab and LGX818, a selective protein kinase B-Raf inhibitor, is underway in patients with BRAF mutant metastatic colorectal cancer. A phase Ib study of safety and efficacy alpelisib with everolimus in patients with pancreatic tumors is ongoing.

b- INK1117 (serabelisib, MLN-1117 or TAK-117): INK1117 is another novel, selective p110α inhibitor. It is particularly more effective and sensitive to tumors bearing PIK3CA mutations. With good oral bioavailability in preclinical xenograft studies, it has entered a phase I study for advanced solid tumors including gastric cancer to evaluate its safety, tolerability, pharmacokinetic, and pharmacodynamic properties.

c- WX-037: A study evaluated the novel PI3K inhibitor WX-037 and the MEK inhibitor WX-554, as single agents and in combination, in colorectal carcinoma (HCT116 and HT29) cell lines and tumor xenograft-bearing mice. Pharmacokinetic analyses indicated that there was no interaction between the two drugs at low doses, but at higher doses, WX-037 might delay tumor uptake of WX-554. These studies showed that combined treatment with novel MEK inhibitor WX-554 and novel PI3K inhibitor WX-037 could induce synergistic growth inhibition in vitro, which translates into enhanced anti-tumor efficacy in vivo.

d- XL147 (pilaralisib): Pilaralisib (XL147) is a selective and reversible class I PI3K inhibi-

tor for PI3Kα/δ/γ in cell-free assays, less potent than PI3Kβ. In phase 1 trial, combination XL147 with primasertib (MEK inhibitor) and erlotinib (EGFR inhibitor) in patients with advanced solid tumors. In phase 1 trial, XL147 broadly active class I PI3K inhibitor that lack anti-mTOR activity, was tolerable at doses shown to inhibit enzyme activity in blood, skin, or tumor cells.

Dual PI3K/mTOR inhibitors
PI3K/mTOR dual inhibitors inhibit PI3K and downstream mTOR kinase activity by binding to ATP binding cleft of these enzymes. Regarding the single inhibitors, these drugs have the benefit of inhibiting mTORC1 and mTOCR2, as well as all the isoforms of PI3K. Evidence has suggested that mTORC1/S6K axis has a “twoedged sword”like function in activation of PI3K/mTOR pathway by promoting growth signals downstream of Akt serine/threonine kinase, as well as mediating a potent negative feedback loop that restrains signaling via insulin/IGFR and other RTKs. Dysregulation of this negative feedback loop has been reported to contribute towards resistance in cancers subjected to single inhibitors. As a result, the concern for the clinical application of dual inhibition is that it may result in unacceptable toxicity when utilizing doses needed for desirable target inhibition. The theoretical advantage of dual PI3K/m-TOR inhibitors is that they attempt to fully shut down the PI3K pathway, thereby preventing AKT activation, which is the result of the negative feedback of allosteric mTORC1 inhibitors, including everolimus. The structures of the catalytic domains of p110 subunits and mTOR are similar. Therefore, numerous PI3K inhibitors currently under development also inhibit mTOR complexes. These inhibitors were among the first to be developed, and it is anticipated that they will block PI3K-AKT-mTOR signaling in tumors having RTK activation, PIK3R1 mutations, PIK3CA mutations, or PTEN loss. Preclinical studies mentioned below have widely evaluated dual PI3K-mTOR inhibitors, including NVP-BEZ235, XL765, and LY3023414.
NVP-BEZ235 (dactolisib or BEZ235): NVP-BEZ235 is a novel dual ATP-competitive PI3K and mTOR inhibitor for p110α/β/γ/δ and mTOR kinase, with inhibitory doses at nano-molar ranges. It first entered phase trials for breast cancer. The effectiveness of BEZ235 has been investigated in both PIK3CA mutated and wild type cell lines in vitro and in xenograft models in vivo. The first group reporting an effect of BEZ235 on gastric xenografts showed reduced tumor growth for NCI N87 but not MKN45 or MKN28 xenografts. Interestingly, the reduction in tumor growth correlated with thymidine kinase expression and not PI3K/mTOR pathway inhibition. Another group demonstrated in vitro increased sensitivity of AGS, PIK3CA mutated cells than for NCI N87 and MKN45, wild type PIK3CA GC cells. Clinically, the response rate for BEZ235 was the highest for patients with PIK3CA mutations compared with those without this mutation. Zhang and colleagues investigated the effects of NVP-BEZ235, a novel dual PI3K/mTOR inhibitor, alone and in combination with nanoparticle albumin-bound (nab)-paclitaxel in experimental gastric cancer. BEZ235 effectively inhibited cell proliferation in vitro and provided additive effects in combination with nab-paclitaxel. Net local tumor growth inhibition for the BEZ235, nab-paclitaxel and BEZ235 + nab-paclitaxel groups was 45.1, 77.9, and 97% compared with controls. The effects of treatment on intra tumoral proliferation and apoptosis corresponded with tumor growth inhibition data. Median animal survival was 26.5 days after BEZ235, 90.5 days after nab-paclitaxel and 97 days in the BEZ235+nab-paclitaxel combination treatment group. The findings suggested that BEZ235 exerted some antitumor effects against gastric cancer and enhanced the effects of nab-paclitaxel through inhibition of cell proliferation and modulation of PI3K/mTOR pathway. The study investigated in vitro and in vivo efficacy of NVP-BEZ235 in PIK3CA mutant and wild-type colorectal cancer (CRC). In vitro treatment of CRC cell lines with NVP-BEZ235 decreased cell viability. In vivo treatment of colonic tumor-bearing mice with NVP-BEZ235 resulted in transient PI3K inhibition. Longitudinal tumor surveillance by optical colonoscopy demonstrated a 97% increase in tumor size in control mice vs. a 43% decrease in treated mice. These studies provide the rationale for examining the efficacy of dual PI3K/mTOR inhibitor NVP-BEZ235 in treatment of PIK3CA wild-type CRC. In mice with xenograft tumors, NVP-BEZ235 inhibited the development of tumor vasculature by inhibiting PI3K and Akt but not mTORC1. In a study, it has been demonstrated that paclitaxel (PTX) together with BEZ235 exhibited a synergetic inhibitory effect on colon cancer cell growth. Furthermore, nano-emulsion (NE)-loaded PTX and BEZ235 were more effective than the free drug, and a combination treatment of both NE drugs increased the efficiency of the treatments. Combined treatment with NE-BEZ235 and NE-PTX could kill 50% of HCT-116 and HT-29 cells. The data indicated that the combination therapy of PTX with BEZ235 using NE delivery might hold promise for a more effective approach for colon cancer treatment. Yu and co-workers showed that NVP-BEZ235 and cis-diammine dichloroplatinum (DDP) had synergistic effects in inhibiting cell proliferation and migration of HT-29 human colorectal adenocarcinoma cells. The expression of protein involved in apoptosis (cleaved caspase-3) was higher in drug combination group compared with NVP-BEZ235 single treatment group. In patients with RAS-mutant colorectal carcinoma, the combination of BEZ235 with selumetinib, a MEK inhibitor, produced disease stabilization in 70% of the cases. This is in concordance with the data suggesting that these drugs are cytostatic and highlights the prospect of being tested in combination with chemotherapy drugs. BEZ235 is currently being assessed in early clinical trials for safety, pharmacokinetics, and pharmacodynamics in solid tumors.

a- XL765 (voxtalisib or SAR245409): XL765, a dual-target PI3K/mTOR inhibitor, inhibits cell growth and apoptosis in many more cell lines and at lower concentrations as compared with PI3K-selective inhibitors XL147 and PIK90. The effect can be recapitulated by using combinations of single-
targeted compounds. XL765 significantly reduces phosphorylation of the mTOR targets S6, S6K, and 4EBP1, which is associated with greater apoptosis induction rather than to PI3K inhibition alone.\textsuperscript{89} In a phase 1 trial of XL765, disease stabilization was reported in seven (46%) patients with CRC. This high stabilization rate is difficult to interpret outside a randomized trial as it might represent patients with slow growing tumors. Further trials are needed to assess the activity of XL765 in patients with CRC.\textsuperscript{89}

\textbf{b- LY3023414 (prexasertib):} LY3023414 is an oral ATP competitive inhibitor of the class I PI3K isoforms and mTOR. In a study done by Zaidi and colleagues, LY3023414 was used intraperitoneally for rats with esophageal adenocarcinoma (EAC) during 40 weeks. Magnetic resonance imaging (MRI), histology, immunohistochemistry, immunofluorescence, and western blot were used to determine clinical response, apoptosis, and proliferation, respectively. Results showed that LY3023414 was downregulated PI3K-α in the treatment group compared with the controls and this established the rational for clinical testing.\textsuperscript{90,91}

\textbf{Concluding Remarks}

PI3K pathway is significantly implicated in GC carcinogenesis and is currently one of the most important areas in anticancer drug development. Figure 1 summarizes PI3K inhibitors in clinical trials for GC treatment. We suggest key issues for successful development of PI3K inhibitors in patients with GC: 1) Increasing the use of tumor genotype analysis in clinics, which helps to identify patients most likely to respond to drugs targeting PI3K pathway, 2) Development of rational combinations of PI3K inhibitor drugs in order to whether inhibitors of this pathway will be more effective than single agents, 3) Development of new PI3K inhibitor drugs and also more understanding of their pharmacodynamic to evaluate the magnitude of target inhibition required for efficacy, and 4) Further clinical trials on compounds acting on PI3K axis to evaluated optimal results in patients with heterogenous malignancy of gastrointestinal tract.

\textbf{ETHICAL APPROVAL}

There is nothing to be declared.

\textbf{CONFLICT OF INTEREST}

The author declares no conflict of interest related to this work.

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