



## Review Article

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# Targeting the Phosphatidylinositol-3-kinase Pathway in Gastric Cancer: Can Omics Improve Outcomes?

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Phosphatidylinositol-3-kinase (PI3K) pathway signaling is an established oncogenic signal transduction pathway implicated in multiple malignancies. Therapeutic targeting of PI3K pathway components has improved outcomes in chronic lymphocytic leukemia, kidney cancer, breast cancer, and neuroendocrine tumors. Gastric cancers harbor some of the highest rates of oncogenic alterations in PI3K but attempts to translate this genomic observation have met with limited clinical success and novel approaches are needed. In the following review we discuss PI3K signaling, previous preclinical and clinical investigations in gastric cancer, and discuss future strategies aimed at overcoming resistance and improving efficacy. Identification and refinement of molecular tumor subtypes, development of predictive biomarkers along, and rational drug combination strategies are key to capitalizing on the therapeutic potential of PI3K pathway directed therapies in gastric cancers.

**Keywords:** PIK3CA portein; Stomach Neoplasms; Molecular Targeted Therapies; AKT oncogene protein; mTOR protein; Clinical Trial


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## INTRODUCTION

Gastric adenocarcinoma (GC) is the fifth most common cancer in the world, with approximately one million new cases and 730,000 deaths occurring annually [1]. In the United States, approximately 21,600 new cases occurred in 2015 [2]. Therapeutic advances in gastric cancer have been slow and 5-year survival is less than 10% with a median overall survival of 1 year for advanced disease [3,4]. Surgery with or without chemotherapy and/or radiation is potentially curative in resectable disease although metastatic recurrence rates remain high [5-7]. Systemic multiagent chemotherapy remains the mainstay of treatment

for advanced disease [8,9]. The phase III ToGA trial (Trastuzumab for Gastric Cancer) was the first study to demonstrate success for a targeted therapy in *ERBB2*-amplified gastric cancer, but this is only relevant for the 12%–20% of advanced gastric cancer patients who harbor *ERBB2* (Her2) amplification, and new therapies are needed [10].

Geographic differences in gastric cancer incidence are well described, and gastric cancers are the second most commonly diagnosed cancer and a leading cause of cancer-related death in Korea [11]. Risk is partly related to geographic and ethnic origins and observations that migration and associated change in environmental risk factors affects gastric cancer risk has led to

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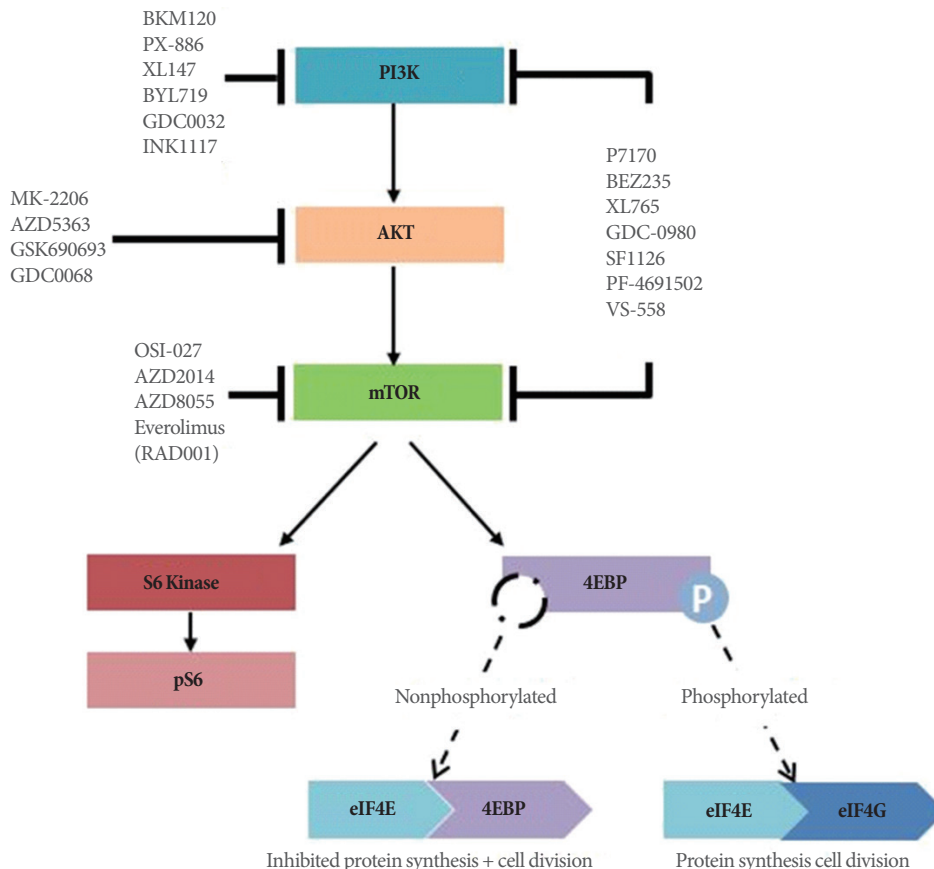
some questions about underlying biologic differences [12,13]. The incidence of gastric cancer in Asian American populations has remained stable or slightly decreased over time, largely mirroring the larger United States trend [14]. Although data is limited it appears PIK3CA mutations may be less common in east Asian populations whereas phosphatase and tensin homolog (PTEN) deletion more frequent when compared to Caucasian gastric cancer patients [15]. Despite the lack of well characterized genomic differences, large phases II and III trials continue to report outcome differences in Asian and non-Asian populations [16-19].

Molecular characterization of gastric cancers has revealed high rates of recurrent somatic alterations in members of the PI3K/AKT/mTOR pathway, suggesting potential therapeutic targets [20]. The PI3K/AKT/mTOR pathway is an important promoter of cell growth, metabolism, survival, metastasis, and resistance to chemotherapy. Despite the appreciation of frequent PI3K pathway alterations in GC, the ability to translate

this genomic observation to improved outcomes has been limited. In the following review we discuss PI3K signaling, preclinical rationale, current clinical data, and future directions.

### CANONICAL PI3K SIGNALING

Phosphatidylinositol-3-kinase (PI3K) is a lipid kinase existing as a heterodimer consisting of a regulatory subunit p85 (p85 $\alpha$ , p85 $\beta$ , and p55 $\gamma$ ) and a catalytic subunit p110 (p110 $\alpha$ , p110 $\beta$ , p110 $\gamma$ , and p110 $\delta$ ). Although there are 3 classes of PI3K based on the structure, distribution, and mechanism of activation, class IA PI3K is mostly associated with malignancy [21,22]. Under physiologic conditions PI3K is activated by multiple receptor tyrosine kinases (RTKs) and/or G-protein-coupled receptors located at the cell surface (Fig. 1). Upon RTK activation PI3K phosphorylates phosphatidylinositol 4,5 biphosphate (PI(4,5)P2) at the 3' OH position to become phosphatidylinositol 3,4,5 trisphosphate (PI(3,4,5)P3), which in turn directly binds to the

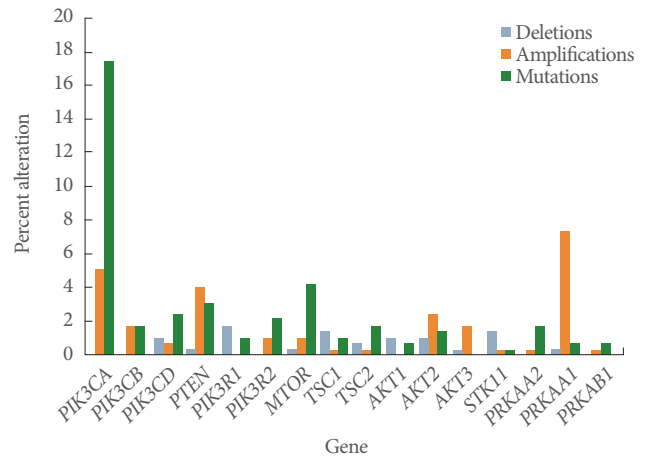


**Fig. 1.** Canonical phosphatidylinositol-3-kinase (PI3K) signaling. Key nodes are represented and examples of small molecule inhibitors acting on key components are shown. mTOR, mammalian target of rapamycin; 4EBP1, eukaryotic initiation factor 4E.

pleckstrin homology (PH) domains of various signaling proteins, including phosphoinositide-dependent kinase 1 (PDK1) [23]. PDK1 phosphorylates AKT in the kinase domain at threonine 308 while PDK2 phosphorylates AKT at serine 473 domain, leading to full AKT activation [24]. Once activated, AKT phosphorylates multiple downstream targets in the cytoplasm and nucleus to promote cell growth and survival [25]. For instance, AKT inhibits proapoptotic Bcl-2 proteins such as BAX and BAD and antagonizes p-53 mediated apoptosis by phosphorylating Mdm2 [26-28]. AKT also phosphorylates TSC2, which prevents the TSC1/TSC2 complex from inhibiting Rheb. Activated Rheb stimulates the mammalian target of rapamycin (mTOR) complex 1 (mTORC1), resulting in increased activity of eukaryotic initiation factor 4E (4EBP1) and the ribosomal S6 protein (S6K1), leading downstream to cell proliferation [27]. mTORC1 also upregulates other genes involved in cell division and angiogenesis, such as cyclin D and hypoxia-inducible factor-1a (HIF-1a), respectively [29,30]. The major negative regulator of the PI3K pathway is the lipid PTEN, a tumor suppressor gene that encodes a lipid phosphatase that converts PIP3 back to PIP2 [31]. Loss of PTEN results in constitutive activation of Akt and alteration of downstream factors in Akt signaling in multiple preclinical models (Fig. 1).

## PI3K PATHWAY ALTERATIONS IN GASTRIC CANCER

The PI3K/AKT/mTOR pathway is the second most commonly altered pathway in human cancer after the p53 pathway with the observed frequency of 30%–60% across tumor types [32]. Pathologic PI3K pathway activation is mediated by several mechanisms ranging from upstream RTKs, decreased expression of PTEN, genetic alteration in PIK3CA and AKT and other less frequent events [33]. Within GC PIK3CA is the most commonly mutated PI3K isoform with a mutation and amplification frequency of 18% and 5% respectively (Fig. 2). This finding is consistent with previous studies that reported PIK3CA mutation rates of 4%–25% [34-37]. Approximately 80% of PIK3CA mutations occur at three recurrent hotspots; E545K and E542K in the helical domain (exon 9) and H1047R in the kinase domain (exon 20) [33]. PIK3CA mutation frequency in GC correlates with stage, seen in 21.4% of pT4 tumors compared to 6.4% in pT2 lesions [37]. In addition to stage there is a strong predilection for PIK3CA mutation in Epstein-Barr virus (EBV) positive gastric cancer with a nonsilent mutation rate up



**Fig. 2.** Frequency of alterations in key PI3K-pathway genes in gastric adenocarcinoma. Data derived from TCGA via MSKCC cbio portal ([www.cbioportal.org](http://www.cbioportal.org), accessed 2016 Aug). PI3K, phosphatidylinositol-3-kinase.

to 80% [20]. In contrast the activating alterations in other p110 isoforms (delta and beta) are rare (Fig. 2).

PTEN is a tumor suppressor gene on chromosome 10q23.3 and the major negative regulator of PI3K activity under physiologic conditions. Within the cancer genome atlas (TCGA) database, the frequency of deletion, mutation and amplification of PTEN in gastric cancer is 0.3%, 3.1%, and 4%, respectively (Fig. 2). There is significant difference in the rate of *PIK3CA* and *PTEN* mutations between Asian and Caucasian GC patients. A meta-analysis found that East Asian and Caucasian GC patients differ significantly among the frequencies of *PIK3CA* Exon 9 and 20 mutations (7% vs. 15%, respectively), *PTEN* deletion (21% vs. 4%) and *PTEN* loss (47% vs. 78%) [15]. Another study identified 19% *PTEN* mutation rate in a Chinese population [38]. The genetic alterations in the study included missense (55.6%), nonsense (33.3%), deletion (7.4%), and a mutation within *PTEN* intron 6 (3.7%). *PTEN* missense mutations abrogated or attenuated phosphatase activity up to 90% of the time suggesting functional relevance [39]. *PTEN* mutation rate is higher in advanced stage and poorly differentiated gastric cancer [40]. *PTEN* status did not predict response to PI3K/mTOR inhibitors reliably, perhaps because patients with negative and reduced *PTEN* expression had a higher incidence of simultaneous MAPK (*KRAS*, *NRAS*, *BRAF*) mutations.

The Akt family of genes consists of Akt1, Akt2, and Akt3 genes. Akt1 and 2 are normally expressed in all tissues while Akt 3 is mainly restricted to brain and testes. Although the overex-

pression of AKT by immunohistochemistry is up to 74% in gastric cancer, genomic alterations are relatively rare at 1%–3% in gastric cancer (Fig. 2) [41]. Differential isoform expression has functional implications and may be relevant for future isoform-specific therapeutic approaches. For example, AKT1 promotes cellular survival and proliferation while AKT2 stimulates cellular invasiveness and mesenchymal transformation [42,43]. Loss of AKT2 expression may decrease metastatic potential while loss of AKT1 paradoxically can increase invasiveness, presumably due to a shunt to AKT2 isoform production [44]. The functional implications of genomic aberrations in downstream signaling nodes *MTOR* are less well studied although effective inhibitor of mTOR signaling appears important for optimal efficacy. Preclinical studies have demonstrated activity with AKT selective inhibitors in gastric cancer [45].

### PI3K-PATHWAY INHIBITORS

There are 4 major classes of drugs that target the PI3K-AKT pathway: PI3K inhibitors, dual PI3K-mTOR inhibitors, mTOR inhibitors, and AKT inhibitors (Table 1). PI3K inhibitors have been developed as either isoform-specific or pan-PI3K inhibitors. Theoretically, isoform-specific inhibitors should have an inherent specificity thereby minimizing on-target side effects results from inhibition of all isoforms. However, potential disadvantage of selective PI3K inhibition is an incomplete blockade of AKT activation in conditions where multiple p110 isoforms exist.

Compounds inhibiting the mTOR catalytic site block both mTOR1 and mTOR2, a critical node mediating downstream function. Catalytic site inhibitors largely overcome the insulin receptor substrate 1 (IRS-1)-mediated feedback thought to limit the efficacy of earlier mTOR inhibitors like sirolimus (rapamycin) [46-48]. Patients with AKT1 and AKT2 amplifications may be theoretically more sensitive to AKT inhibitors. Most of these drugs are either ATP mimetics or noncatalytic site allosteric inhibitors. Allosteric inhibitors block the PH domain from binding phosphoinositides at the plasma membrane, preventing Akt phosphorylation [44]. Similar to the theory of PI3K inhibitors, it is possible that AKT inhibitors may eventually be isoform specific for AKT1 or AKT2, to deliver lower effective doses with less side effects. A phase II S1005 study evaluated MK-2206, an allosteric inhibitor of AKT, as second-line therapy for 66 patients with advanced gastric cancer [49]. There were two treatment related deaths (cardiac arrest and respiratory failure).

**Table 1.** Summary of clinical investigations targeting the PI3K/AKT/mTOR pathway in gastric cancer

Compound	Target	Study design	Result
Everolimus	mTOR	Phase III	No OS benefit
BKM120	Pan-PI3K	Phase II	N/A
PX-886	Pan-PI3K	Phase I	No DLT SD in 2 of 6 patients
XL147	Pan-PI3K	Phase I	DLT = grade 3 rash SD in 6 of 39 patients
WX-037	Pan-PI3K	Phase I	N/A
BYL719	p110α PI3K	Phase I	N/A
GDC0032	p110α PI3K	Phase I	DLTs = diarrhea and hyperglycemia
INK1117	p110α PI3K	Phase I	N/A
P7170	PI3K/mTOR	Phase I	N/A
BEZ235	PI3K/mTOR	Phase I/II	DLT = diarrhea
XL765	PI3K/mTOR	Phase I	DLTs = nausea/ vomiting, diarrhea, elevated liver enzymes SD in five of 36 patients
GDC-0980	PI3K/mTOR	Phase I	DLTs = hyperglycemia and mucositis
SF1126	PI3K/mTOR	Phase I	N/A
PF-05212384	PI3K/mTOR	Phase I	N/A
PF-4691502	PI3K/mTOR	Phase I	DLTs = fatigue and rash SD in 12 of 36 patients
VS-558	PI3K/mTOR	Phase I	N/A
OSI-027	mTOR 1/2	Phase I	N/A
AZD2014	mTOR 1/2	Phase I	N/A
AZD8055	mTOR 1/2	Phase I	N/A
Temsirolimus	mTOR	Phase I	N/A
MK-2206	Allosteric AKT	Phase I	DLT = rash and mucositis SD in 6 of 19 pts
AZD5363	Catalytic AKT	Phase II	N/A
AZD5363	Catalytic AKT	Phase II	N/A
GSK690693	Catalytic AKT	Phase I	DLTs = hyperglycemia and hyperlipidemia
GDC0068	Catalytic AKT	Phase II	N/A

PI3K, phosphatidylinositol-3-kinase; mTOR, mammalian target of rapamycin; OS, overall survival; N/A, not available; SD, stable disease; DLT, dose limiting toxicity.

Common toxicities included anemia 15%, anorexia 27%, diarrhea 24%, fatigue 48%, hyperglycemia 29%, nausea 40%, vomiting 20%, maculopapular rash 30%, and acneiform rash 8%. The response rate (RR), progression free survival (PFS), and overall survival (OS) were 2%, 1.8 month, and 5 months, re-

spectively. The study did not meet primary endpoint of OS 6.5 months. A multinational phase II JAGUAR trial comparing the efficacy of mFOLFOX6 plus ipatasertib, an oral AKT inhibitor, versus mFOLFOX6 plus placebo in 120 patients with advanced untreated gastric cancer is currently undergoing [50].

Though PI3K signaling inhibitors are promising, there are some theoretical shortcomings which raise concern for their clinical efficacy. Preclinical studies in breast cancer cells with PI3KCA mutations show *in vivo* efficacy of PI3K-mTOR inhibitors or Akt inhibitors. However, treatment leads to cytostatic rather than cytotoxic effects when given as monotherapies [51,52]. It remains to be seen whether inhibitors of the PI3K signaling pathway will be efficacious in single-agent therapy, though unlikely. A potential reason for limited efficacy of single-agent therapy is positive feedback loops and activation of coinciding proliferative signaling pathways. The most common alternate pathway involves nodes in the Ras-Raf-MEK-ERK signal transduction pathway. Logically, this observation has led to the development of combination strategies. Murine models of lung cancer with KRAS overexpression showed no efficacy of either a PI3K or MEK inhibitor alone, however, the combination was highly effective [53]. KRAS mutant colorectal cancer mouse model cells that demonstrated resistance to PI3K/mTOR inhibitor had restored sensitivity to dual PI3K/mTOR inhibitor in combination with a pan-ERBB inhibitor [54]. Similarly, the combination of PI3K/mTOR and RAS/ERK pathway inhibitors shows synergy in treating ovarian cancer [55]. Studies such as these suggest that combination therapy may delay resistance and be used in cancers which were initially responsive [56].

## EARLY CLINICAL EXPERIENCE

Preclinical studies demonstrated that treatment of gastric cancer cell lines with everolimus and sirolimus lead to G1 cell cycle arrest and growth inhibition [57,58]. In 5-FU-resistant gastric cancer cells, the addition of everolimus to chemotherapy demonstrated synergistic growth inhibition [59]. Administration of rapamycin to mouse xenograft models decreased tumor volume and microvessel density, as well as downstream factors such as S6K1, 4EBP1, HIF-1 $\alpha$  and vascular endothelial growth factor [60]. In a phase 2 multicenter trial in 53 advanced heavily pretreated gastric cancer patients who was treated with everolimus, the disease control rate (DCR), PFS, and OS were 56%, 2.7 months, and 10.1 months, respectively [61]. There was no ob-

served partial response (PR) or complete response, and common side effects included stomatitis (73.6%), anorexia (52.8%), fatigue (50.9%), rash (45.3%), nausea (32.1%), peripheral edema (22.6%), diarrhea (20.8%), and pruritus (18.9%). Based on these results, the phase III GRANITE 1 trial evaluated the safety and efficacy of everolimus versus placebo in 656 patients who progressed after the first or second line chemotherapy, randomized to a 2:1 schedule [62]. Although PFS was modestly improved (median: 1.7 months vs. 1.4 months,  $P < 0.001$ ), overall survival, the primary endpoint, was not (median: 5.4 months vs. 4.3 months,  $P = 0.124$ ). However, there were patients who derived durable stable disease and the modest PFS improvement suggested potential benefit in selected patients. Multiple potential predictive biomarkers have been explored, including PIK3CA/PTEN mutation status, AKT activation, pS6<sub>Ser240/4</sub> and other members of the AKT/mTOR pathway. One preclinical study demonstrated that tumor cells harboring PIK3CA and/or PTEN mutations were more likely to be rapamycin responsive ( $P = 0.0123$ ) [63]. Additionally, Akt phosphorylation (S473 and T308) was significantly higher in rapamycin sensitive cells ( $P < 0.0001$ ) in this study. Another study demonstrated significant correlations between everolimus sensitivity and a battery of markers consisting of total S6 levels, p235-S6, p240-S6, pEIF4, Rictor, Raptor, total AKT, and pAKT [64]. However, the authors noted that such approach would be infeasible in real clinical practice. The ratio of p235-S6/total-S6 and pAKT alone are able to provide adequate predictive power. The potential role of pS6<sub>Ser240/4</sub> as predictive marker was shown in an Asian phase II study evaluating PFS rate at 4 months in 54 advanced gastric cancer pts receiving everolimus [65]. The DCR was 38.9% with 3.7% PR (2 patients). The 4-month PFS rate was 18.4% (less than the hypothesized PFS of 30%) and the median PFS and OS were 1.7 and 8.3 months, respectively. However, high baseline expression of pS6<sub>Ser240/4</sub>, defined as immunohistochemistry (IHC) staining  $> 2$ , was significantly associated with higher disease control rate (DCR) ( $P < 0.043$ ) and prolonged PFS ( $P < 0.001$ ). The US study showed numerically inferior outcomes compared to the Asian study with median OS 3.4 months and PFS 1.8 months. However, this study reaffirmed a strong correlation between  $\geq 2$ +IHC staining for p-S6 in tumor samples with better PFS ( $P < 0.0001$ ) and DCR ( $P = 0.0001$ ) [66]. Anecdotal evidence seems to validate the p-S6 overexpression and concurrent *PIK3CA* mutation may identify a group of patient able to derive prolonged benefit from PI3K-directed therapy [67]. Further studies are required to validate these bio-

markers not only for mTOR inhibitors but also other PI3K pathway inhibitors.

## FUTURE DIRECTIONS

The disappointing activity of everolimus in advanced GC highlighted the need for a more biologically informed development process for PI3K pathway inhibitors in gastric cancer. Recently Lei et al. [68] proposed a new gastric cancer classification that was distinct from the well-known Lauren classification. This classification included mesenchymal, proliferative and metabolic as the 3 distinct histologic subtypes based on the differentially expressed genes. For instance, the gene clusters in the mesenchymal tumors are mostly involved in the epithelial mesenchymal transition pathway with high mTOR pathway activity. The mesenchymal subtype was found to be sensitive to PI3K inhibitors while the proliferative subtype was more sensitive to 5-FU *in vitro*. Another subgroup that may benefit from PI3K inhibitors are those who carry EBV positive tumors which was shown to harbor PI3KCA mutation up to 80% according to the TCGA study [20].

We believe that -omics platforms characterizing gastric cancer and other tumors are a critical step toward refining the role of PI3K compounds. While hotspot mutational analysis is readily available we feel that the genomic context of a PI3K/AKT/mTOR alterations will be important in guiding outcomes. The relatively low response rate even for PI3KCA mutated tumors may be due to intrinsic resistance, acquired resistance mechanism and crosstalk between different pathways. One preclinical study demonstrated that HNSCC cell lines with *PIK3CA* mutations were universally sensitive to PI3K, mTOR inhibitors, or both. However, *PIK3CA* amplification, PTEN loss, and basal PI3KCA/AKT/mTOR pathway activity did not predict response [69]. As more clinical experience with PI3K inhibitors becomes available, we will be able to predict which specific PI3K pathway gene dysregulation would be sensitive to specific combination of inhibitors. Whole genome sequencing will also identify genetic alteration in other pathways such as RAS or BRAF, which are known to negate the effect of PI3K inhibitor. One study using the *PIK3CA*/PTEN/Ras testing protocol prior to PI3K pathway inhibition found that treated patients with wild-type *KRAS* had a higher PR rate of 31% compared to 6% in patients with simultaneous *KRAS* mutations ( $P=0.05$ ) [70]. The PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways are known to interact at multiple points, resulting in cross-activa-

tion, cross-inhibition, and pathway convergence. Examples include activation of PI3K directly by RAS, suppression of TSC2 by phosphorylated ERK or AKT, initiating mTORC1 complex formation [71].

Multiple resistance mechanisms to PI3KCA inhibitors have been identified and they likely contribute to poor efficacy. The most well-known mechanism is the activation of multiple RTK pathways after PI3KCA inhibition. Inhibition of mTORC1 with rapamycin and catalytic mTOR inhibitors increase insulin receptor substrate 1 (IRS-1) levels and induce AKT phosphorylation and downstream signaling [52,72]. AKT inhibition leads to loss of transcription factor FOXO3 regulation and subsequent increased expression of multiple RTKs [73,74]. Moreover, simultaneous Wnt- $\beta$ -catenin pathway hyperactivation and PI3K-AKT signaling inhibition promote nuclear accumulation of  $\beta$ -catenin and FOXO3a, and eventual metastasis [75]. Additionally, enhanced HER2 signaling following PI3K inhibition has been reported to lead to ERK activation [76]. Dual blockade with either MEK and PI3K or ERK and PI3K inhibitors lead to higher rate of apoptosis in numerous preclinical studies, prompting the rationale for combination therapy [32,76].

The clinical experience with dual MEK and PI3K inhibitors in treating solid tumors are limited as most trials are still in early phases. The preliminary results from these studies implicate potential efficacy in the combination therapy. There are no known published gastric cancer cases that are sensitivity to dual pathway blockade. In a phase I trial where 49 patients with RAS or BRAF mutant advanced solid tumors were treated with trametinib and BKM120, 3 patients with RAS ovarian cancers achieved PR, 2 with BRAF mutant melanoma achieved stable disease (SD) [77]. The combination was well tolerated with common adverse events including rash, nausea, fatigue, vomiting, decreased appetite, and elevated CPK. Grade 3 DLTs included stomatitis, dysphagia, decreased ejection fraction, CPK elevation, nausea and anorexia. The combination of GDC-0973 and GDC-0941 was evaluated in 78 patients with solid tumors yielded 3 PRs (1 BRAF mutant melanoma, 1 BRAF mutant pancreatic, and 1 KRAS mutant endometrial cancer) and 5 SD [78]. This combination therapy was well tolerated, with comparable toxicities to monotherapy. In a retrospective study, 5 patients with coactivation of PI3K/AKT and RAS/RAF/MEK pathways who received dual inhibition had tumor regression/stabilization from 2%–64% (3 colon, 2 melanoma). Conversely, all 4 colon cancer patients in the single pathway inhibition group developed progressive disease. This finding is consistent

with other studies that PI3K inhibition alone is insufficient for tumors with concurrent Ras/BRAF activation. For the unselected population, there was no significant difference in both tumor control rate for single or dual inhibition (52.7% and 64.6%, respectively,  $P=0.16$ ) [79]. There were more grade III/IV adverse events observed in the dual pathway inhibition group. However, this study was limited by its retrospective nature. The data were derived from different phase I trials that are heterogeneous. The response rates are low and appear mainly restricted to RAS and RAF mutated cancers. The most responsive tumors included BRAF positive melanoma, KRAS positive ovarian cancer, and KRAS positive colon cancer.

## CONCLUSIONS

Gastric cancer is a heterogeneous disease and recent genomic characterization has refined our understanding of molecular subtypes [80]. Alterations in the PI3K/AKT/mTOR pathway occur across gastric cancer types but have yet to translate to improved outcomes in prospective trials. Anecdotal reports provide preliminary support for a possible rare subset with multiple PI3K pathway activating alterations and the absence of MAPK alterations which may provide ready resistance. The need to assess multiple genomic alterations in order to identify a narrow subset makes large prospective trials more difficult, however, is likely a key need to maximize the potential to exploit oncogenic PI3K pathway alterations in gastric and other tumors. We will eagerly await additional information from some of the aforementioned ongoing clinical trials.

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