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Inhibition of the PI3K/AKT/mTOR Pathway in Solid Tumors

Patricia Mucci LoRusso

Yale Cancer Center, New Haven, CT.

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Corresponding author: Patricia Mucci LoRusso, DO, Yale Cancer Center, Yale School of Medicine, 333 Cedar St, www205, New Haven, CT 06510; e-mail: patricia.lorusso@yale.edu.

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ABSTRACT

The phosphoinositide 3-kinase (PI3K) pathway plays an integral role in many cellular processes and is frequently altered in cancer, contributing to tumor growth and survival. Small molecule inhibitors have been developed that target the three major nodes of this pathway: PI3K, AKT, and mammalian target of rapamycin. However, because oncogenic PI3K pathway activation is achieved in diverse, potentially redundant ways, the clinical efficacy of these inhibitors as monotherapies has, so far, been limited, despite demonstrating promising preclinical activity. Moreover, pathway activation is associated with resistance to other therapies; thus, in combination, PI3K pathway inhibitors could restore therapeutic sensitivity to these agents. To maximize therapeutic benefit, drug combinations and schedules must be explored to identify those with the highest efficacy and lowest toxicity overlap. In addition, defining appropriate patient subpopulations, for both monotherapy and drug combinations, will be important. However, identifying predictive biomarkers remains a challenge.

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INTRODUCTION

The phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway is frequently altered in cancer,[1] promoting growth, proliferation, and survival.[1,2] Targeting its three major nodes (PI3K, AKT, and mTOR), therefore, represents a key therapeutic opportunity.[1]

Class IA PI3Ks are heterodimers composing a regulatory (p85) and catalytic (p110) subunit, and exist in four isoforms (α, β, γ, and δ) with differential tissue expression.[1] Growth factor stimulation of receptor tyrosine kinases triggers PI3K activation, downstream activation of phosphoinositide-dependent kinase 1 (PDK1) and AKT, and, subsequently, mTOR complex 1 (mTORC1), which promotes cell growth and protein synthesis.[2] The mTORC1 substrate ribosomal S6 protein kinase (p70S6K) phosphorylates ribosomal protein S6, stimulating protein synthesis, and feeds back to insulin receptor substrate 1 to downregulate insulin-mediated PI3K pathway activation. The pathway can be activated by G protein-coupled receptors or by oncogenic proteins such as RAS.[1]

The tumor suppressor phosphatase and tensin homolog (PTEN) is a key negative regulator of the PI3K pathway.[2] Others include inositol polyphosphate 4-phosphatase type II (INPP4B)[3] and the protein tyrosine phosphatase nonreceptor 12 (PTPN12/PTP-PEST).[4] This review summarizes PI3K pathway alterations found in solid tumors and discusses pathway inhibitors, their class-specific toxicities, and the possible challenges underpinning patient selection and drug resistance.

THE PI3K PATHWAY IS FREQUENTLY ALTERED IN SOLID TUMORS

PI3K pathway alterations include somatic amplification, mutation, loss of heterozygosity, or changes in DNA methylation, often in multiple genes (Fig 1).[5]

Breast Cancer

In breast cancer, most mutations occur in *PIK3CA*. Three frequent "hotspot" mutations within the helical (E545K and E542K in exon 9) and kinase domains (H1047R in exon 20) result in constitutive p110α activity.[6] Approximately 20% to 50% of breast cancers exhibit *PIK3CA* mutations, including approximately 35% of hormone receptor (HR)–positive and approximately 23% of human epidermal growth factor receptor 2 (HER2)–positive breast cancers.[7] *PIK3CA* mutations occur less frequently (<10%) in triple-negative breast cancer (TNBC), although pathway activation may be driven instead by *PIK3CA* amplification or genomic loss of *PTEN* or *INPP4B*.[7,8] In particular, *INPP4B* is lost in 30% to 56% of TNBC.[8,9]

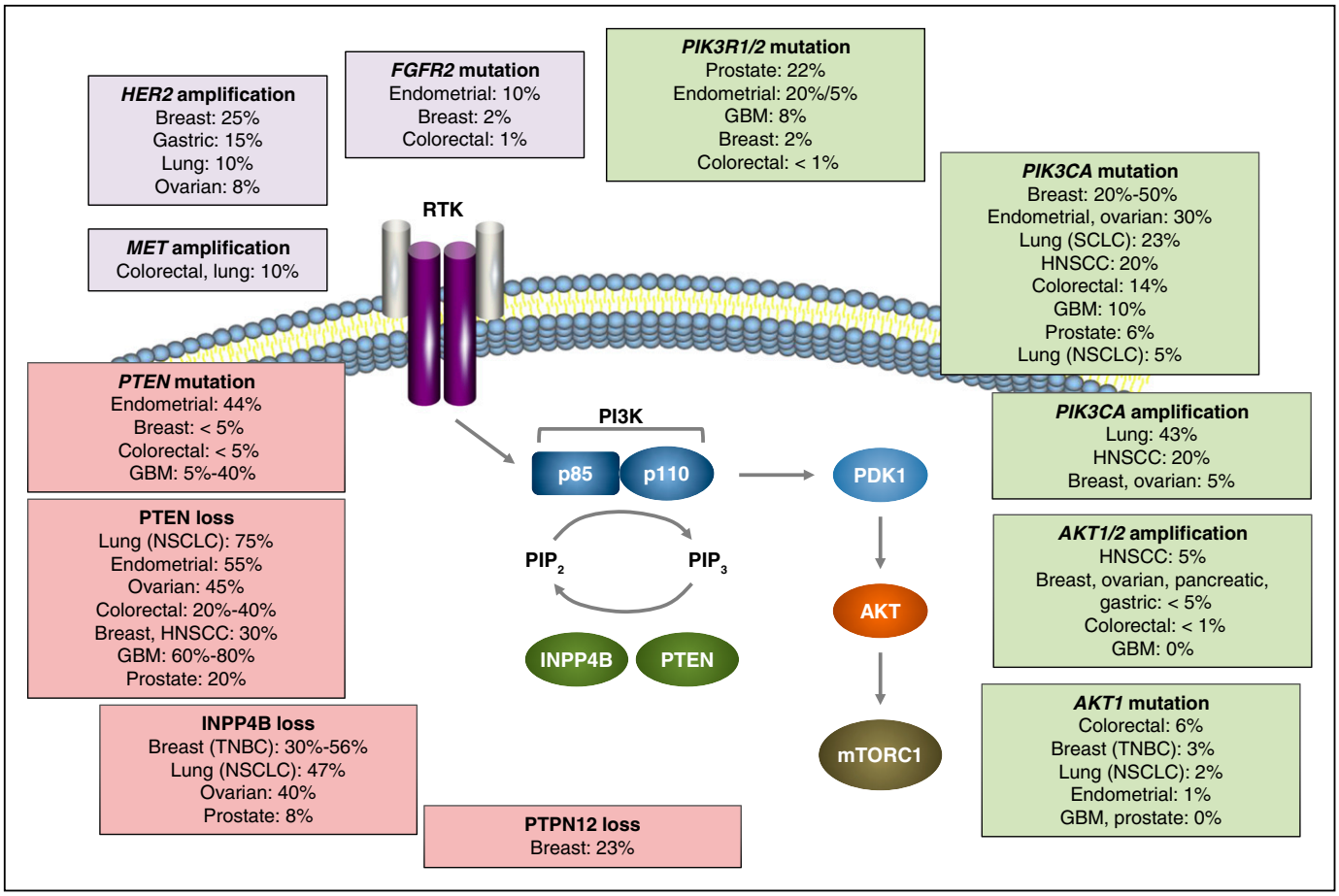

Fig 1. Common PI3K pathway aberrations found in a variety of solid tumor types. Activation of the PI3K pathway contributes to tumor growth, survival, and resistance to anticancer therapies. FGFR2, fibroblast growth factor receptor 2; GBM, glioblastoma multiforme; HER2, human epidermal growth factor receptor 2; HNSCC, head and neck squamous cell carcinoma; INPP4B, inositol polyphosphate 4-phosphatase type II; MET, hepatocyte growth factor receptor; mTORC, mammalian target of rapamycin complex; NSCLC, non–small-cell lung cancer; PI3K, phosphoinositide 3-kinase; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog; PTPN12, protein tyrosine phosphatase nonreceptor 12; RTK, receptor tyrosine kinase; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer. Adapted from a figure provided by Ana Maria Gonzalez-Angulo.

PTEN mutations occur in < 3% of breast cancers; however, loss of PTEN protein occurs in approximately 30% of cases.[5,7] PTEN protein loss and *PIK3CA* mutations appear to have different functional effects: PTEN protein loss is associated with elevated AKT phosphorylation, whereas *PIK3CA* mutations have not been associated with significant differences in the levels of PTEN protein or of phosphorylated downstream substrates compared with wild-type *PIK3CA* breast tumors.[7]

Activating mutations in the catalytic domain of AKT have not been observed. However, approximately 3% of HR-positive breast cancers exhibit an E17K substitution in the pleckstrin homology domain, resulting in constitutive activation.[7,10]

In breast tumors, PTPN12 downregulates growth factor receptor signaling to suppress the transformation of human mammary epithelial cells.[4] PTPN12 protein expression is lost in approximately 23% of breast tumors, especially TNBC,[4] and is associated with poor patient outcome.[11]

Lung Cancer

PI3K pathway activation, as demonstrated by AKT phosphorylation, occurs in 50% to 70% of non-small cell lung cancers (NSCLCs).[12] This pathway is altered in 47% of squamous cell carcinomas.[13] PI3K pathway activation can occur through activating mutations in *EGFR*, *KRAS*, *PI3K*, or *AKT*, as well as *PIK3CA* amplification or loss of PTEN expression.[12] Somatic mutations in *PIK3CA* are relatively infrequent,[14] whereas genomic amplification is more common, occurring in 43% of lung cancers.[15] Mutations in *AKT* itself are rare; the *AKT* E17K mutation has been reported in approximately 2% of NSCLCs, restricted to the squamous histotype[16]; however, the importance of oncogenic AKT activity is underlined by the high incidence of loss of PTEN and INPP4B protein expression (75% and 47% of NSCLCs, respectively).[17,18]

Head and Neck Cancer

PI3K pathway alterations occur in 30% to 66% of head and neck squamous cell carcinomas (HNSCCs); this rate increases to 90% if changes in mRNA levels are also considered.[19,20] Common alterations include reduced PTEN expression (30% of patients) and *AKT* amplification (5%).[20] *PIK3CA* is the most frequently altered gene (36%); mutation and amplification are mutually exclusive and equally prevalent.[20] Human papillomavirus-positive tumors are associated with *PIK3CA* hotspot mutations.[19,20]

HNSCC tumors harboring multiple aberrations in the PI3K pathway are linked to advanced disease, suggesting genomic instability contributions to disease progression.[19]

Gynecologic Cancers

PI3K pathway activation occurs in up to 30% of ovarian cancers, mainly due to *PIK3CA* or *AKT* mutation or amplification.[21,22] Although it is less common in ovarian cancers, *PTEN* loss of heterozygosity occurs in up to 45% of the endometrioid subgroup.[22] *INPP4B* has been identified as a tumor suppressor in ovarian cancers, and loss of INPP4B protein correlates with reduced patient survival.[3]

In endometrial cancers, *PIK3CA* mutations and PTEN loss (through mutations or reduction of protein expression) occur in up to 30% and 55% of tumors, respectively.[23] Endometrial cancers are highly complex, often exhibiting coexistent alterations in *PTEN*, *PIK3CA*, *PIK3R1*, and *KRAS*.[24] Although this may contribute to the difficulty of treatment, PI3K pathway reliance may sensitize tumors to PI3K pathway inhibition.[20]

Colorectal Cancers

PI3K pathway alterations in colorectal cancers (CRCs) are dominated by *PIK3CA* and *PTEN*. Approximately 14% exhibit *PIK3CA* catalytic domain hotspot mutations and are associated with invasive, progressive disease.[25] Amplification and overexpression of *PIK3CB* (p110β), and mutations in *PIK3R1* (p85α) have been observed.[25] Loss of PTEN protein occurs in 20% to 40% of cases.[25] The *AKT* E17K mutation has only been observed in 6% of CRCs, and the functional consequences of *AKT* kinase domain mutations are poorly understood.[25] Mutations in *INPP4B* have been identified.[26]

Glioblastoma Multiforme

PI3K pathway alterations occur in 50% of glioblastoma multiforme (GBM) tumors and are associated with poor survival.[27] Mutations in *PTEN* occur in 5% to 40% of GBM tumors, whereas loss of heterozygosity occurs in 60% to 80% of all cases.[28] *PIK3CA* and *PIK3R1* are mutated in approximately 10% and approximately 8% of tumors, respectively,[27] contributing to tumor invasion and migration.[29] *AKT* mutations have not been observed, and there is limited evidence that other PI3K pathway nodes play significant roles.[30,31]

Prostate Cancers

PI3K pathway activation is associated with metastasis, resistance to therapy, and poor outcome in patients with prostate cancer.[32] In one study, 49% of patients with metastatic, castration-resistant prostate cancer harbored somatic alterations in the PI3K pathway, including biallelic loss of *PTEN*, hotspot mutations, amplifications and activating fusions in *PIK3CA*, and E17K-activating mutations in *AKT1*.[33] *PTEN* alterations include deletions and inactivating mutations in approximately 15% of primary tumors and in 50% in hormone-refractory disease.[34] Loss of PTEN protein occurs in approximately 20% of localized tumors and is correlated with advanced stage and high Gleason score.[34] In contrast, *PIK3CA* alterations occur in only 6% of primary tumors and in 16% of metastases, although the regulatory subunit *PIK3R1* is mutated in 22% of primary and 58% of secondary tumors, providing an alternative route to pathway activation.[35] *PIK3CB* mutations have been observed in *PTEN*-deficient metastatic cases.[33] Tumor suppressor *INPP4B* has been shown to be altered or downregulated in primary and metastatic disease.[35,36] The net result of these diverse alterations is activation of the PI3K/AKT/mTOR pathway, leading to increased tumor growth, survival, and resistance to targeted therapies.

THE ROLE OF PI3K PATHWAY ACTIVATION IN TREATMENT RESISTANCE

PI3K pathway activation is implicated in de novo and acquired treatment resistance in various tumor types treated with targeted therapies (Fig 2).[37] Genetic resistance mechanisms can arise through genomic instability.[38] Resistance of tumor-initiating cells to apoptosis and epigenetic mechanisms may also contribute to relapse after therapy.[39,40] Genetic and epigenetic mechanisms are associated with PI3K pathway activation.[37] A large-scale RNA interference screen in HER2-positive breast cancer found that loss of the *PTEN* transcript conferred trastuzumab resistance.[41] Oncogenic mutations in *PIK3CA* also conferred trastuzumab resistance in vitro, and activation of the PI3K pathway predicted poor trastuzumab response.[41] In addition, patients with HER2-positive breast cancer whose tumors harbor *PIK3CA*-activating mutations derive less benefit from neoadjuvant HER2-targeted therapies than patients without a *PIK3CA*-activating mutation.[42] In *KRAS*-mutant CRC cell lines, *PIK3CA* and *PTEN* mutations were associated with resistance to MEK inhibition.[43] Moreover, PI3K pathway activation promotes resistance to BRAF inhibitors in *BRAF*-mutant melanoma, with 22% of progressive tumors harboring mutations that upregulate PI3K pathway activity.[44] Loss of PTEN expression has been associated with reduced number and function of tumor-infiltrating T cells and resistance to anti-PD-1 immunotherapy in patients with melanoma.[45] These findings have raised the possibility that targeted PI3K pathway inhibitors could potentially restore sensitivity to existing treatments.

INHIBITORS OF THE PI3K PATHWAY

The PI3K pathway is dysregulated in many solid tumors, supporting the use of PI3K pathway inhibitors in the clinic. Oncogenic PI3K pathway activation is achieved in different (and potentially redundant) ways, requiring rational, tailored strategies to inhibit appropriate pathway nodes in each tumor type. Recently developed small-molecule inhibitors are presented in Tables 1 and 2, and Figure 3.

Pan-Class I PI3K Inhibitors

Pan-class I PI3K inhibitors target all four isoforms of p110. Buparlisib (BKM120), the most advanced agent in this class, inhibits all class I PI3K isoforms, with little activity toward other classes of PI3K or mTOR, and has demonstrated strong antiproliferative activity in more than 400 cancer cell lines (data on file; Novartis, Basel, Switzerland).[46] Given its ability to penetrate the

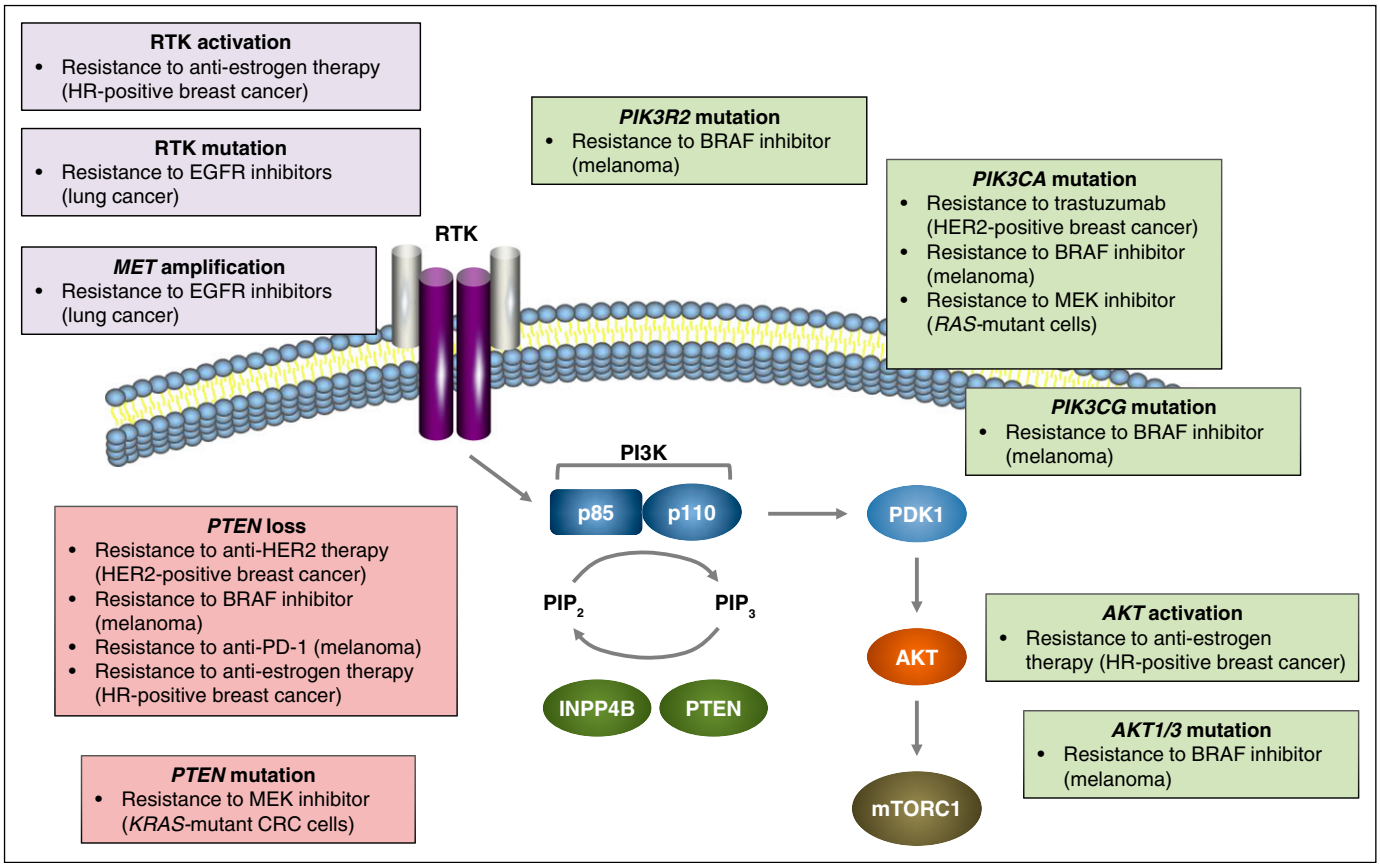

Fig 2. Common nodes of resistance to targeted therapies within the PI3K pathway. PI3K pathway alterations that confer resistance to targeted therapies across various tumor types are shown. CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; INPP4B, inositol polyphosphate 4-phosphatase type II; MET, hepatocyte growth factor receptor; mTORC, mammalian target of rapamycin complex; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha; PIK3CG, phosphatidylinositol 3-kinase catalytic subunit gamma; PIK3R2, phosphatidylinositol 3-kinase regulatory subunit beta; PIP_2, phosphatidylinositol 4,5- bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase.

blood-brain barrier, it may represent a therapeutic option for GBM tumors or brain metastases, as shown in early-phase trials in refractory GBM[84,85] and breast cancer-derived brain metastases.[86] Buparlisib and letrozole have demonstrated antitumor activity in HR-positive breast cancer.[87]

Pictilisib (GDC-0941) is being investigated in HER2-positive metastatic breast cancer and advanced NSCLC. It has equipotent activity in vitro against p110α and -δ isoforms, and also inhibits p110β and -γ.[47] Phase I studies demonstrated signs of clinical activity in advanced solid tumors.[88,89]

Copanlisib (BAY 80-6946) is an intravenously administered pan-class I PI3K inhibitor.[48] It inhibits p110α and -δ, and, therefore, may suit T-cell malignancies; although, interestingly, concomitant p110δ inhibition in solid tumors may contribute to an immune environment that facilitates cytotoxic T-cell responses in addition to the cell-intrinsic antiproliferative effects of p110α inhibition.[90]

Isoform-Specific PI3K Inhibitors

The rationale for PI3K isoform-specific inhibition was validated in p110δ-driven hematologic malignancies by combined idelalisib and rituximab treatment.[91] In solid tumors, isoform-specific PI3K inhibitors might have fewer toxicities compared with pan-PI3K inhibitors, allowing higher doses and resulting in more complete inhibition.[1] Alpelisib (BYL719) was the first potent, p110α-selective inhibitor. A first-in-human phase I study in patients with advanced solid tumors demonstrated a manageable safety profile and antitumor activity, notably in patients with *PIK3CA*-mutant HR-positive breast cancer.[92] Alpelisib has shown preliminary efficacy in combination with cetuximab in patients with recurrent or metastatic HNSCC.[93]

Taselisib (GDC-0032) inhibits p110α, -γ, and -δ equally, and p110β with 30-fold lower potency.[51] Greater isoform selectivity is predicted to translate into improved efficacy in *PIK3CA*-mutant-driven tumors compared with pan-PI3K inhibitors. Preliminary results have shown activity in a *PIK3CA*-mutant xenograft model,[94] as well as in *PIK3CA*-mutant HER2-positive and HR-positive breast tumors.[95-97] Taselisib combined with letrozole has shown activity in *PIK3CA*-mutant breast cancers.[98]

The rationale for p110β inhibition is less straightforward than p110α. Although p110β might be a valid target in some tumors exhibiting PTEN loss, preclinical studies suggest that p110α and p110β have overlapping roles. The success of p110β inhibition may depend on the absence of concomitant

Table 1. PI3K Pathway Inhibitor Potencies

Drug	Target	IC_{50} (nM) p110α	p110β	p110δ	p110γ	mTOR
Pan-class I PI3K inhibitors						
Buparlisib (BKM120)[46]	Pan-PI3K	52	166	116	262	2,866
Pictilisib (GDC-0941)[47]	Pan-PI3K	3	33	3	75	580
Copanlisib (BAY 80-6946)[48]	Pan-PI3K	0.5	3.7	0.7	6.4	45
SAR245408 (XL147)[49]	Pan-PI3K	39	383	36	23	> 15,000
PX-866[50]	Pan-PI3K	5.5	> 300	2.7	9.0	—
Isoform-specific PI3K inhibitors						
Taselisib (GDC-0032)[51]	p110α	0.29	9.1	0.12	0.97	1,200
Alpelisib (BYL719)[52]	p110α	4.6	1,156	290	250	> 9,100
MLN1117[53,54]	p110α	15	4,500	13,900	1,900	1,670
BAY 1082439[55]	p110α/β	4.9	15.0	—	—	> 5,000
CH5132799[56]	PI3Kα/γ	14	120	500	36	—
GSK2636771[57]	p110β	—	5.2	58	—	—
AZD8186[58]	p110β	> 1,000	5	15	—	—
SAR260301[59]	p110β	—	52	—	—	—
Idelalisib (CAL-101)[60]	p110δ*	820	565	2.5	89	> 1,000
IPI-145[61]	p110δ*	1,602	85	2.5	27	–
AMG319[62]	p110δ*	—	—	< 10	—	—
Dual-specificity PI3K/mTOR inhibitors						
BEZ235[63]	PI3K/mTOR	4	75	7	5	20.7
GDC-0980[64]	PI3K/mTOR	5	27	7	14	17
PF-05212384[65]	PI3K/mTOR	0.4	6	8	6	1
PF-04691502[66]†	PI3K/mTOR	1.8	2.1	1.6	1.9	16
GSK-2126458[67]†	PI3K/mTOR	0.019	0.13	0.024	0.06	0.18/0.3‡
SAR245409 (XL765)[68]	PI3K/mTOR	39	113	43	9	190/908‡
mTOR inhibitors, rapalogs						
Sirolimus (rapamycin)[69]	mTOR	—	—	—	—	0.1
Nab-rapamycin[70]	mTOR	—	—	—	—	—
Temsirolimus[71]	mTOR	—	—	—	—	1,760
Everolimus[72]	mTOR	—	—	—	—	1.6-2.4
Ridaforolimus[73]	mTOR	—	—	—	—	0.2-5.6
mTOR inhibitors, catalytic						
OSI-027[74]	mTOR	1,300	> 30,000	—	420	22/65‡
AZD2014[75]	mTOR	3,800	> 30,000	> 29,000	> 30,000	2.8
MLN0128[76]	mTOR	219	5,293	230	221	1
PP242[77]	mTOR	2,000	2,200	100	1,300	8
ML-223[78]	mTOR	—	—	—	—	—

NOTE. Dashes indicate data not available.
Abbreviations: IC_{50}, concentration for 50% of maximal inhibition of cell proliferation; mTOR, mammalian target of rapamycin; mTORC, mTOR complex; PI3K, phosphoinositide 3-kinase.
*p110δ-selective inhibitors are under investigation for hematologic malignancies.
†K_i binding affinity.
‡IC_{50} for mTORC1/mTORC2.

p110α-activating mutations.[90,99] Selective inhibitors of p110β that have undergone phase I investigation include GSK2636771 and SAR260301.[59,100]

Table 2. AKT Inhibitor Potencies

Drug	Target	IC_{50} (nM) AKT1	AKT2	AKT3
Ipatasertib (GDC-0068)[79]	AKT1/2/3	5	18	8
MK-2206[80]	AKT1/2/3	8	12	65
AZD5363[81]	AKT1/2/3	3	7	7
Perifosine (KRX-0401)[82]	AKT1/2/3	—	—	—
GSK2141795	AKT1/2/3	—	—	—
ALM301	AKT1/2	—	—	—
Archexin (RX-0201)[83]	AKT1	—	—	—

NOTE. Dashes indicate data not available.
Abbreviations: IC_{50}, concentration for 50% of maximal inhibition of cell proliferation.

DUAL-SPECIFICITY PI3K/mTOR INHIBITORS

Dual-specificity inhibitors were designed to inhibit the structurally similar PI3K and mTOR kinase domains simultaneously and have the benefit of interrupting the feedback loop that activates AKT when mTORC1 is inhibited in isolation (Fig 3).[101] Compounds in this class include BEZ235, GDC-0980, and SAR245409 (XL765).

Although phase I studies initially reported clinical activity,[102,103] subsequent studies revealed that controlling bioavailability and limiting toxicities are challenging. For example, issues with dosing and bioavailability of BEZ235 led to the development of different oral formulations,[102] and the phase II FERGI trial (GDC-0980 with fulvestrant in breast cancer) was stopped because of toxicity concerns.

mTOR Inhibitors: Rapalogs

mTOR inhibitors were the first agents developed to target the PI3K pathway. The earliest compound in this class, rapamycin

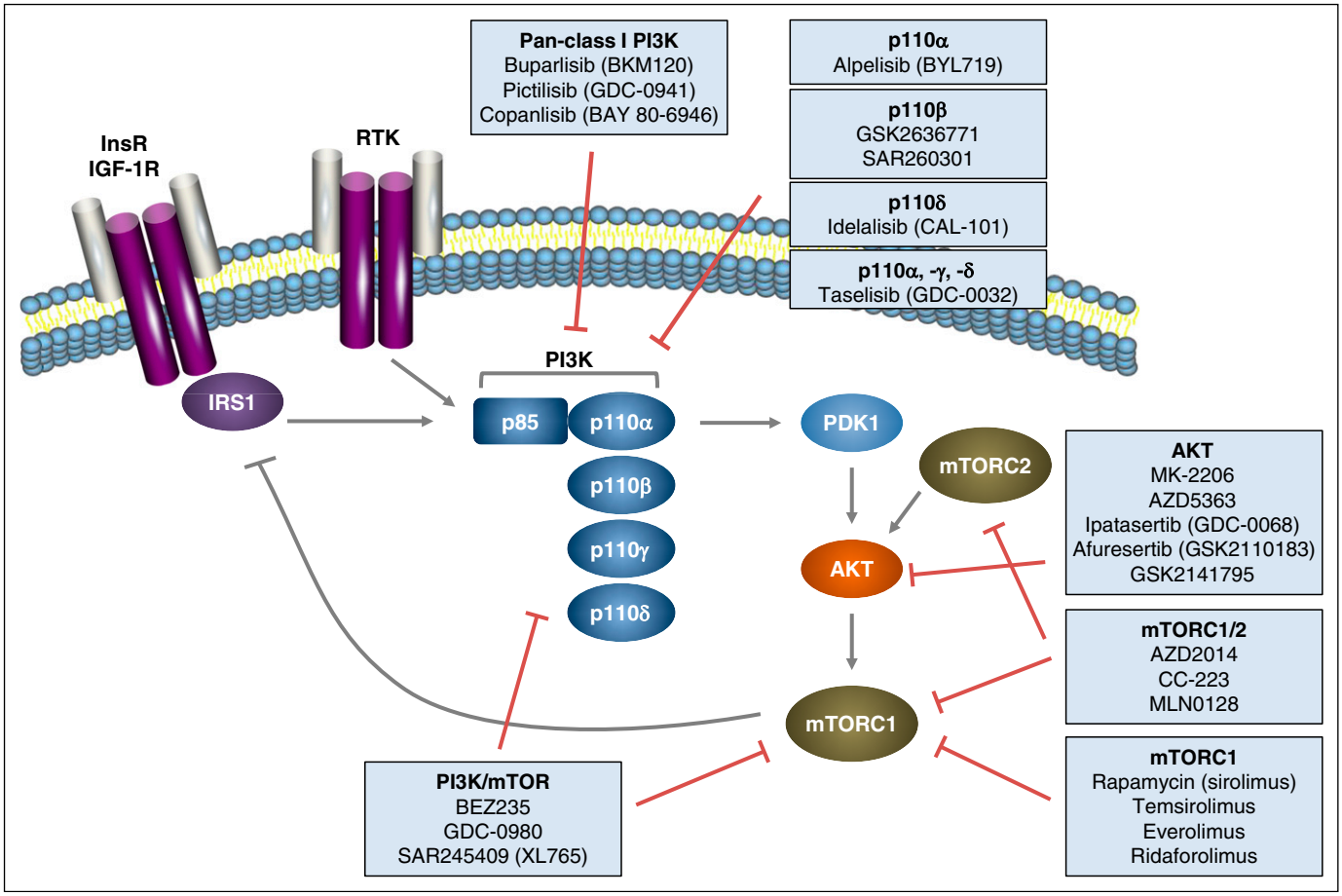

Fig 3. Targeting the PI3K pathway in cancer with small-molecule inhibitors. Inhibitors discussed in the text are included in the figure. IGF-1R, insulin-like growth factor 1 receptor; InsR, insulin receptor; IRS1, insulin receptor substrate 1; mTORC, mammalian target of rapamycin complex; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphoinositide 3-kinase; RTK, receptor tyrosine kinase.

(sirolimus), inhibits the activity of mTORC1 but not mTORC2.[104] Limitations in the pharmacokinetic (PK) properties of sirolimus led to the development of analogs (called "rapalogs") with improved characteristics, including temsirolimus, everolimus, and ridaforolimus.[104] Both temsirolimus and everolimus were approved for use in renal cell carcinoma, highlighting PI3K pathway activation importance in this setting.[104] Improvements in sirolimus PK continue to be investigated, with a nanoparticle albumin-bound formulation in development.[70]

mTOR Inhibitors: Catalytic

Catalytic mTOR inhibitors improve on rapalogs by inhibiting both mTORC1 and mTORC2, thus suppressing the feedback-mediated activation of AKT by mTORC2.[105] In a phase I trial, AZD2014 shows signs of clinical activity in advanced solid tumors,[106] and CC-223 shows indications of activity in patients with neuroendocrine tumors, NSCLC, GBM, and hepatocellular carcinoma.[107,108] Trials of MLN0128 in advanced prostate cancer and GBM are ongoing.[109,110]

AKT Inhibitors

As one of the key effector nodes in the PI3K pathway, AKT could be a promising target in PI3K pathway-activated tumors. Pan-AKT inhibitors under development are either allosteric (MK-2206) or adenosine triphosphate (ATP)-competitive (AZD5363, ipatasertib [GDC-0068]). MK-2206, AZD5363, and ipatasertib have shown preliminary activity in phase I trials, and are being tested in a range of solid tumors.[111-114] Two more ATP-competitive AKT inhibitors, afuresertib (GSK2110183) and GSK2141795, have undergone clinical investigation.[115,116]

p70S6 Kinase Inhibitors

p70S6K is activated downstream of AKT and regulates translation by phosphorylating ribosomal protein S6. *p70S6K* amplification confers a proliferative advantage on tumor cells, is correlated with poor prognosis and reduced survival,[117] and is, therefore, under investigation as a drug target in several phase I clinical trials.[118,119]

CHALLENGES FOR PI3K INHIBITOR DEVELOPMENT

Recognition of the PI3K pathway's contributions to tumorigenesis has stimulated the development of numerous targeted agents (Table 1); however, the efficacy of monotherapy inhibition has been disappointing.[90] Insufficient target inhibition, due to toxicity or suboptimal dosing schedules, represents one potential

explanation.[1] Evaluating alternative dosing schedules may help overcome toxicities and enable maximal target inhibition.[90] Incorporation of pharmacodynamic assessments of validated, robust biomarkers into clinical trials is needed to identify patients who may derive therapeutic benefit.[90,120,121]

The limited clinical efficacy with these agents may also result from a feedback response whereby PI3K pathway inhibition stimulates compensatory activation of a complementary pathway such as growth factor receptor signaling, bypassing the effects of targeted blockade.[90] Data suggest that PTEN loss represents a convergent evolutionary mechanism of treatment resistance.[122] Schwartz et al showed that p110α activity was suppressed in *PTEN*-mutant tumors, and that PI3K signaling was instead driven by p110β.[123] However, p110β inhibition only transiently inhibited AKT/mTOR signaling due to feedback inhibition of insulin-like growth factor 1 receptor and other receptors, resulting in p110α activation and rebound downstream signaling.[123] Combined p110α and p110β inhibition suppressed this rebound effect.[123] In *PTEN* knockdown models, PTEN loss contributed to alpelisib resistance, an effect that was reversed by concurrent p110α and p110β inhibition.[122] Similarly, prolonged treatment with pictilisib resulted in PTEN loss, leading to the development of pictilisib resistance in CRC cell lines, which was overcome by concurrent PI3K and MAPK inhibition.[124]

Another explanation for the lack of pan-PI3K inhibitor single-agent activity stems from the relative lack of p110β inhibition in vitro.[1] Residual p110β activity during pan-PI3K inhibitor treatment may provide sufficient downstream PI3K signaling for continued growth, particularly in PTEN-deficient tumors where p110β is the major isoform mediating tumorigenesis.[1]

Similarly, isoform-selective inhibitors may not achieve sustained benefit due to rebound activation of the uninhibited isoforms, which has been observed in luminal breast cancer cell lines harboring *PIK3CA* or *HER2* amplifications treated with alpelisib,[125] and in *PTEN*-mutated breast and prostate tumors treated with AZD8186. In these models, concomitant p110α and p110β inhibition had a synergistic antitumor effect, similar to that reported by Schwartz et al.[123,125] Interestingly, p110β-mediated PI3K pathway reactivation in *PIK3CA*-mutated breast cancer cells occurred independently of AKT activation, indicating that other signals downstream of PI3K might contribute to lack of efficacy in these cells.[125] Indeed, many *PIK3CA*-mutant cancer cell lines and human breast tumors appear to rely on activation of PDK1 and its substrate, serum/glucocorticoid regulated kinase 3 (SGK3), rather than AKT, for growth and tumorigenicity.[126] These findings demonstrate that a variety of feedback mechanisms can reactivate the PI3K pathway in response to PI3K inhibitor treatment.

Additional mechanisms of resistance have been investigated. Cell lines sensitive to alpelisib treatment were associated with complete inhibition of TORC1 pathway signaling, while resistant cell lines had persistently active mTORC1; combining alpelisib with everolimus overcame resistance in vitro and in vivo.[127] In the clinic, pS6 (a biomarker of mTORC1 signaling) was expressed in tumors that initially responded and subsequently progressed.[127] A combinatorial screen demonstrated the efficacy of the cyclin-dependent kinase (CDK) 4/6 inhibitor ribociclib (LEE011) combined with alpelisib, particularly in tumors with phosphorylated retinoblastoma protein (pRB).[128] Notably, CDK4/6 inhibition emerged as the strongest sensitizer for PI3K inhibition, exerting its activity by binding and activating cyclin D1, whose expression is often regulated by TORC1.[128-130] Other resistance mechanisms include *MYC* overexpression or amplification, matrix-associated resistance, and activity of ribosomal S6 kinase 3/4.[48,128,131-133] CDK4/6 and mTOR inhibitors should be tested in the clinic to understand feedback alteration of various pathways and provide novel strategies in response to treatment resistance. Improved clinical responses might be achieved by combining PI3K inhibitors with other agents targeting known resistance pathways that interact with PI3K, such as the estrogen receptor pathway.[134]

Table 3. Common Toxicities Associated With PI3K Pathway Inhibitors*

PI3K Pathway Inhibitors	Toxicities
Pan-PI3K class I inhibitors[88,89,135–138]	Hyperglycemia, fatigue, nausea/vomiting, diarrhea, decreased appetite, rash, liver dysfunction, mood alterations†
Isoform-specific inhibitors[92,95,139–143]	α: Hyperglycemia, fatigue, nausea/vomiting, diarrhea, decreased appetite β: Fatigue, nausea/vomiting, diarrhea, decreased appetite, anemia δ: Fatigue, nausea/vomiting, diarrhea, rash, liver dysfunction, pneumonia, pyrexia, hematologic toxicities
Dual-specificity PI3K/mTOR inhibitors[103,144–149]	Hyperglycemia, fatigue, nausea/vomiting, diarrhea, decreased appetite, rash, mucositis
mTOR inhibitors, rapalogs[70,150–152]	Hyperglycemia, fatigue, nausea/vomiting, anemia, stomatitis, mucositis, pulmonary and metabolic toxicities, mood alterations‡
mTOR inhibitors, catalytic[106,153,154]	Hyperglycemia, fatigue, nausea/vomiting, diarrhea, decreased appetite, liver dysfunction, pneumonia, stomatitis, mucositis
AKT inhibitors[111,113,115,116,155,156]	Hyperglycemia, fatigue, nausea/vomiting, diarrhea, decreased appetite, rash
p70S6 kinase inhibitors[118,119]	Fatigue, nausea/vomiting, pancreatitis, increased lipase, hyperphosphatemia

Abbreviations: mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase.
*Toxicities were derived from phase I, single-agent safety/efficacy studies of drugs listed in Table 1.
†Buparlisib only.
‡Nab-rapamycin only.

MANAGEMENT OF CLASS-SPECIFIC TOXICITIES

Toxicity profiles of PI3K pathway inhibitors are related to their mechanism of action and have become more favorable with the advent of second-generation agents (Table 3).[157] Managing and minimizing toxicity risks, particularly in susceptible patients (eg, hyperglycemia in diabetic patients), are important considerations when designing treatment strategies. Several management guidelines for commonly encountered toxicities have been published and may be helpful to clinicians using this class of agent, namely those for hyperlipidemia, hyperglycemia, rash, stomatitis, and noninfectious pneumonitis.[158-161]

BIOMARKERS FOR THERAPY SELECTION

The promise of personalized therapy depends on the availability of predictive biomarkers for treatment response. Despite preclinical evidence that *PIK3CA*-mutant cell lines and tumors are sensitive to

PI3K inhibition,[121] correlations between molecular status and clinical efficacy are less clear. Retrospective analyses of patients suggest that *PIK3CA* H1047R correlates with response,[162,163] although in the phase I trial of alpelisib with letrozole in HR-positive breast cancer, clinical responses were also seen in *PIK3CA* wild-type patients.[121,164] Although this pathway is important, other factors are probably involved in determining sensitivity to PI3K pathway inhibition.

Work must continue to validate biomarkers to inform clinical treatment decisions, including factors predictive of treatment response or resistance. As an example, a phase II trial of alpelisib or buparlisib with letrozole is ongoing in patients with confirmed *PIK3CA* mutation status.[165] Strategies to monitor the status of other biomarkers, such as pRB, will be important for combination regimens.[128]

COMBINATION THERAPY STRATEGIES

Single-agent activity of pan-PI3K inhibitors has been limited. Isoform-specific p110δ (idelalisib) and p110α inhibitors (alpelisib, taselisib) have had greater success, and will be important as combination partners to maximize therapeutic benefit. A key challenge is developing effective drug combinations with complementary modes of action, targeting the most relevant pathways in each tumor type (Table 4).

Combinations With Growth Factor Receptor Inhibitors

Growth factor receptors are common nodes of oncogenic alteration; for example, *HER2* amplification is frequently observed in breast cancer.[183] Inhibition of the growth factor receptor has several advantages: By blocking initiation of signaling and cross-talk with complementary pathways, tumor cells are sensitized to treatment with chemotherapy and radiotherapy.[183] As examples, combinations of buparlisib with paclitaxel and trastuzumab in HER2-positive breast cancer[184] and alpelisib with cetuximab in HNSCC[93] have shown early indications of antitumor activity, supporting the rationale for this combination approach.

Table 4. PI3K Inhibitor Combination Partners Under Investigation in Clinical Trials

Therapy	PI3K Inhibitor Combinations
Growth factor receptor RTK inhibitors	Buparlisib with capecitabine and trastuzumab or lapatinib[166]
	Alpelisib with trastuzumab emtansine[167]
MAPK pathway inhibitors	Buparlisib with trametinib[168]
	Alpelisib with MEK162[169]
	GSK2141795 with trametinib[170]
	MK-2206 with AZD6244[171]
Endocrine therapy	Alpelisib with letrozole[165]
	Buparlisib with fulvestrant[172]
	Taselisib with fulvestrant and/or letrozole[173]
	Buparlisib with abiraterone acetate[174]
	Everolimus with radiation therapy[175]
	Ipatasertib or GDC-0980 with abiraterone acetate and prednisone[176]
	MK-2206 with bicalutamide[177]
Chemotherapy	Buparlisib with cisplatin/radiotherapy in HNSCC[178]
	Alpelisib with paclitaxel in breast cancer and HNSCC[179]
	Pictilisib with cisplatin in breast cancer[180]
	Copanlisib with gemcitabine/cisplatin in advanced solid tumors[135]
	Copanlisib with paclitaxel in breast cancer[181]
PARP inhibitors	Buparlisib with olaparib in TNBC or high-grade serous ovarian cancer[182]

Abbreviations: HNSCC, head and neck squamous cell carcinoma; MAPK, mitogen-activated protein kinase; PARP, poly(ADP-ribose) polymerase; PI3K, phosphoinositide 3-kinase; RTK, receptor tyrosine kinase; TNBC, triple-negative breast cancer.

Combinations With Mitogen-Activated Protein Kinase Inhibitors

The PI3K and mitogen-activated protein kinase (MAPK) pathways interact at multiple levels, providing a potential escape mechanism for tumors treated with single-agent PI3K or MAPK pathway inhibitors, suggesting that simultaneous inhibition may be required to achieve adequate tumor control.[185] In support of this, a retrospective analysis of patients receiving PI3K and MAPK pathway inhibitors in phase I trials showed combination treatment can improve efficacy relative to single-pathway inhibition, albeit with increased toxicity that can limit treatment exposure.[186] Examples include combinations of copanlisib and refametinib, buparlisib and vemurafenib, or pictilisib and GDC-0973.[187-189]

In phase I trials, promising efficacy signals have been observed in *KRAS*- or *BRAF*-mutant tumors treated with combinations of pictilisib and GDC-0973,[187] SAR245409 and pimasertib,[190] and buparlisib and trametinib.[191] Likely indications for PI3K and MAPK inhibitor combinations will include solid tumors reliant on MAPK pathway activation, such as *BRAF*- and *KRAS*-mutant melanoma, CRC, and ovarian cancer. Continued investigation of combinations of agents from both of these pathways will be necessary, because toxicity has delayed the development of these regimens.

Combinations With Endocrine Therapy

Aberrant hormone receptor signaling plays an important role in HR-positive breast and prostate cancers. Patients who initially respond to endocrine therapy often develop resistance and progress. The PI3K pathway is activated in approximately 35% of HR-positive breast cancers,[7] and PI3K pathway blockade can restore sensitivity to endocrine therapy in breast cancer cell lines.[192] Findings that estrogen deprivation triggers apoptosis in PI3K pathway-inhibited cells provide further rationale for combination therapy, perhaps even as a first-line option.[193] Final results of the BOLERO-2 (Breast Cancer Trials of Oral Everolimus-2) phase III trial of everolimus in HR-positive breast cancer showed the everolimus combination was more effective than exemestane alone.[194]

Likewise, PI3K pathway alterations are prevalent in prostate cancer, contributing to the development of castration-resistant prostate cancer.[32] Cross-talk between PI3K and androgen receptor pathways suggests combined inhibition may provide improved benefit over hormone therapy alone,[195] and preclinical studies show p110β inhibition and hormone therapy have synergistic antitumor activity.[196]

COMBINATIONS WITH CHEMOTHERAPY

Preclinical studies suggest that PI3K pathway inhibitors might sensitize tumors to chemotherapy by altering surrounding

vasculature and tumor perfusion,[197] thereby increasing exposure to systemic therapies and synergistically inducing apoptosis.[198-200] Early clinical studies showed PI3K pathway inhibitors were well tolerated with chemotherapy: Antitumor activity was observed in patients with NSCLC treated with pictilisib, carboplatin, and paclitaxel, with or without bevacizumab.[201] Preliminary positive results of ipatasertib with chemotherapy have supported the initiation of a phase II trial in gastric cancers.[202]

Combination With Poly(ADP-Ribose) Polymerase Inhibitors

Targeting the connection between the PI3K pathway and DNA repair is emerging as a therapeutic strategy in BRCA1-deficient tumors, based on findings that PI3K pathway inhibitors increase DNA damage and sensitize cell lines to poly(ADP-ribose) polymerase inhibitors.[203,204] A phase I study of buparlisib with olaparib is ongoing in patients with TNBC or high-grade serous ovarian cancer.[182,205] Results from these trials will lead to a better understanding of this combination, potentially lending insight into strategies to overcome resistance.

CHALLENGES FOR COMBINATION THERAPY

Overlapping toxicity profiles with many PI3K inhibitor-containing combinations is challenging, often preventing sufficient dose administration to achieve the necessary exposure of each drug.[187] A notable exception is the reduction in hyperproliferative cutaneous events for combined MEK and BRAF inhibition, which is a mechanistic effect of suppressing paradoxical MAPK pathway activation.[206] However, PI3K inhibitor combinations generally result in cumulative, nonspecific toxicities, and the most tolerable dose ratios and drug sequences will have to be found empirically.

Toxicities need to be closely monitored, adjusting drug doses appropriately to prolong treatment of as long as possible. Compared with monotherapy, toxicity management for combination regimens could be increasingly complex.

In conclusion, the importance of the PI3K pathway in solid tumors is well established; however, treatments with single-agent PI3K inhibitors have been disappointing. Several questions must be investigated to guide the design of effective treatment regimens. First, which PI3K pathway components contribute the most to particular tumor types? Second, how do different pathways interact to support tumor growth, and how should they be targeted (individually or in tandem, and at what potencies)?

Finally, can treatment strategies be designed to respond to the emergence of drug resistance? These questions will be addressed by continued investigation through intelligently designed, biomarker-driven clinical trials, using treatment combinations tailored toward defined molecular alterations.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Inhibition of the PI3K/AKT/mTOR Pathway in Solid Tumors

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