Review

PI3 Kinase Inhibitors in the Clinic: An Update

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Abstract. *The phosphoinositide-3 kinase/protein kinase-B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway has been identified as a key signaling pathway for important cellular functions such as growth control, metabolism and translation initiation. Several proteins within this pathway are valuable anticancer drug targets, among which several inhibitors of mTOR are now administered in routine practice. A better understanding of the structure and functions of PI3K has led to the development of novel inhibitors that have a more favorable toxicity profile as compared to the first generation of anti-PI3K drugs. In this article, we review the basics of PI3K biology and focus on its inhibitors, currently under investigation in clinical trials. The perspective for future directions in the setting of PI3K inhibition and novel trials is also discussed.*

Structure and Functions of the Phosphoinositide 3 Kinases

The phosphoinositide-3 kinases (PI3Ks) catalyze the production of lipid second-messengers from phosphoinositide-2 phosphate into phosphoinositide triphosphate in cellular membranes (1). There are eight classes of phosphoinositide kinase in mammals, among which only class I products are involved in second-messenger signaling with phosphoinositide triphosphate (2). Apart from being activated by tyrosine kinase receptors (RTKs), class IA PI3Ks are activated by G-protein-coupled receptors (GPCR) and oncoproteins, whereas class IB products are only regulated by GPCRs (3). The enzyme consists of the association of two subunits, p85 and p110, harboring regulatory and catalytic properties, respectively. There are three different isoforms of p110: p110α, β, or δ, that are encoded by *PIK3CA*, *PIK3CB* and *PIK3CD*, respectively. All p110 isoforms have a similar structure, with well-identified domains: an amino-terminal adaptor-binding domain (ABD) interacting with p85, a rat sarcoma (RAS)-binding domain (RBD), a C2 (protein kinase-C homology-2) domain with affinity for lipid membranes, a helical domain, and a carboxyl-terminal kinase domain (4). The p85 regulatory subunit is encoded by three genes: *PIK3R1*, *PIK3R2* and *PIK3R3* (5). Among the four regions of p85, the nSH2 domain is mostly involved in p110 regulation, and inhibits its kinase activity, unless p110 is activated from an upstream signal, leading to the removal of the nSH2 inhibition (6). Besides the regulation of p110, p85 is also involved in a number of cellular functions, such as endocytosis, cytoskeleton organization, receptors trafficking, *etc*.. [reviewed in (5)]. There are four isoforms for the catalytic subunit, α, β, γ, δ, respectively. In class I PI3Ks, either p110α, β, or δ form a heterodimer with one of five regulatory proteins p85α, p85β, p85γ, p50α, and p55α out of which the two smaller proteins are splicing variants of p85α (7). Interestingly, only *PIK3CA*, encoding p110α is linked to a number of types of cancer, whereas *PIK3CB* has oncogenic properties only in cultured cell models (3, 8).

Activation of PI3K comes from an upstream signal [*e.g.* receptor tyrosine kinase (RTK) dimerization and activation through ligand binding], leading to i) the direct binding of p85 to the RTK and the subsequent p110 activation; or ii) the binding of growth factor receptor-bound protein 2 (GRB2) to the RTK, followed by GRB2-associated-binding (GAB) protein recruitment and further p85 activation; or iii) from RAS-mediated p110 activation through the recruitment of GRB2 and son of sevenless (SOS) to the receptor (9). A wide number of transmembrane receptors have been identified as PI3K activators.

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The PI3K/AKT/mTOR Cascade and its Relevancy to Cancer

Signaling through PI3K drives a number of cell functions that are linked to cell growth, apoptosis regulation, cell adhesion, transformation, survival, and motility through the activation of the downstream AKT protein (10, 11). Importantly this pathway activation is regulated through the PI3K antagonistic phosphatase and tensin homolog (PTEN) that is deleted or inactivated in a wide range of malignancies (12). The downstream effector AKT phosphorylates a number of proteins, among which is mTOR. mTOR acts as the catalytic subunit in the protein complexes mTORC1 and mTORC2, in which the former regulates S6 kinase and 4E binding protein 1 (4EBP1), leading to translation initiation and protein synthesis, and the latter is involved in a feedback activation of the cascade through the phosphorylation of AKT on the Ser^{473} residue (13). Inhibition of mTOR has proven efficacious in numerous solid tumors, such as breast and kidney cancer, well-differentiated endocrine tumors and sarcomas. Hence, finding other targets within the PI3K/AKT/mTOR pathway has a high relevance to developing innovative compounds. Indeed, inhibition of mTORC1 has the caveat of a feedback activation of PI3K that might be responsible for rapamycin analogs (rapalogs) resistance, providing a strong rationale for combining mTOR and PI3K inhibition (14).

Oncogenic Mutations of PI3K

The *PI3KCA* gene is mutated in a wide range of cancer types, including those of breast, colon, prostate, endometrium, and of the ovary (7). Although mutations in the PI3K pathway seem to occur in a mutually exclusive manner, coexistence of *PTEN* and *PI3KCA* mutations have been reported in endometrial cancers (7, 15). About 80% of *PI3KCA* mutations occur within three hot spots, two of them mapping to the helical domain of PI3KCA and one in the kinase domain, with distinct mechanisms of protein activation (16). These mutations induce a gain of function in p110α, with increased and detectable levels of downstream effectors that can be surrogate markers of *PI3KCA* mutations (reviewed in 17). Mutations in the helical domain, such as *E542K* and *E545K* result in the lack of p110α regulation by the regulatory subunit, whereas H1047R in the kinase domain induces a conformational change in the activation loop, thus mimicking RAS-mediated activation (16, 18). This conformational change increases the protein interaction with the lipid membrane, thus making phosphoinositide diphosphate more accessible to the enzyme (19). Indeed, having identified such mutations, and having established their frequency among carcinomas provides a strong rationale for the development of anti-PI3K drugs, targeting the kinase domain through the inhibition of ATP binding. Mutations in the *p85* regulatory subunit have also been identified and consist of truncations or deletions, resulting in the disruption of the interaction of nSH2 and iSH2 domains with the C2 domain of p110α, thus abolishing the kinase domain inhibition by p85 (19).

Targeting PI3K in Anticancer Therapy: From the Bench to Phase II Trials

Given the elucidation of the PI3K structure, the identification of mutation hot spots, and the understanding of the related structure/function changes, efforts towards innovative drugs design should now focus on the design of isoform-specific, mutant-specific inhibitors (19). Although such a personalized approach is not yet feasible in routine practice, several PI3K inhibitors have been evaluated, both pre-clinically and in the clinic, with phase I and phase II trials for the latter. Initial data were obtained with two compounds, wortmannin and LY294002, which served as a proof of concept in preclinical models, though suffering from unfavorable pharmaceutical and toxicity profiles and yielding more in-depth research for better drugs (20, 21). In this section we focus on the clinical data that are available for these compounds, as well as on ongoing trials and future perspectives.

NVP-BEZ235

NVP-BEZ235 was synthesized by Novartis Pharma, (Novartis Institute for Biomedical Research Oncology, Basel, Switzerland) as a potent p110α inhibitor, with a dual mTOR inhibition capacity. NVP-BEZ235 has activity against p110α, p110α-H1047R and p110α-E545K, with a half maximal inhibitory concentration (IC_{50}) in the low nanomolar range (22). NVP-BEZ235 inhibits PI3K by blocking the ATP-binding site, a common mechanism of other tyrosine kinase inhibitors and possesses strong antiproliferative activity towards several cell lines and against tumor xenografts (22-24). Phase I data with NVP-BEZ235 showed an acceptable toxicity profile, with mild or moderate, and manageable nausea, and vomiting, diarrhea, fatigue, anemia, and anorexia. Two patients out of 59 had partial response (PR), whereas 16 experienced minor responses. Interestingly, in 14 patients with stable disease ≥4 months, 6 had deregulated PI3K pathway (25). Another phase I study of BEZ235, with a different formulation (SDS sachet) has been reported showing a maximal tolerated dose of 1600 mg/d, and a similar toxicity profile. The dose-limiting toxicities were grade 3 thrombopenia and fatigue (26). Clinical studies are ongoing with the drug in several malignancies, with an emphasis on breast cancer (Table I). Most of the trials focus on single-agent activity of NVP-BEZ235, despite a few trials investigating combinations with chemotherapy (capecitabine,

Table I. *Ongoing clinical trials with NVP-BEZ235 (http://clinicaltrials.gov/ct2/results?term=bez235, accessed April 17, 2012).*

Condition	Study title	Companion drug	Clinicaltrials.gov identifier
Kidney cancer	BEZ235 in Patients with Advanced Renal Cell Carcinoma (RCC)	Not applicable (N/A)	NCT01453595
Solid tumors/breast and kidney	Dose Finding Study of RAD001 (Everolimus, Afinitor®) in Combination with BEZ235 in Patients with Advanced Solid Tumors	Everolimus	NCT01482156
Breast	Phase Ib/II Trial of BEZ235 with Paclitaxel in Patients with HER2 Negative, Locally Advanced or Metastatic Breast Cancer	Paclitaxel	NCT01495247
Breast	A Phase Ib/II Study of BEZ235 and Trastuzumab in Patients with HER2-positive Breast Cancer Who Failed Prior to Trastuzumab	Trastuzumab	NCT01471847
Breast	A Trial of Oral BEZ235 and BKM120 in Combination with Paclitaxel with or without Trastuzumab	BKM120/trastuzumab	NCT01285466
Breast	PhIb BKM120 or BEZ235+Endocrine Treatment in Post-menopausal Patients with Hormone Receptor + Metastatic Breast Cancer	BKM120/endocrine therapy	NCT01248494
Breast	Study of BKM120 or BEZ235 and Capecitabine in Patients with Metastatic Breast Cancer	BKM120/capecitabine	NCT01300962
Breast	Pharmacodynamic Study of BKM120 and BEZ235 in Breast Cancer	BKM120	NCT01513356
Solid tumors/breast	A Phase I/II Study of BEZ235 in Patients with Advanced Solid Malignancies Enriched by Patients with Advanced Breast Cancer	N/A	NCT00620594
Solid tumors	Study of PI3 Kinase/mTOR Inhibitor BEZ235 Twice Daily for Advanced Solid Tumors	N/A	NCT01343498
Solid tumors	Safety, Pharmacokinetics and Pharmacodynamics of BEZ235 Plus MEK162 in Selected Advanced Solid Tumor Patients	MEK162	NCT01337765
Solid tumors	Safety Study of BEZ235 with Everolimus in Subjects with Advanced Solid Tumors	Everolimus	NCT01508104
Solid tumors	A Study of BEZ235 in Adult Japanese Patients with Advanced Solid Tumor	N/A	NCT01195376

paclitaxel) or targeted therapies (trastuzumab, everolimus and other PI3K inibitors such as BKM120). Genotype indicators for the NVP-BEZ235 efficacy have been found, at least in endometrial cancer, such as the presence of *PTEN* mutations without *KRAS* alterations, which might be strong predictive factors for NVP-BEZ235 efficacy in this condition (27). Unexpectedly, with regard to molecular abnormalities that were evidenced in endometrial cancer, NVP-BEZ2345 study has been stopped in this condition and endometrial cancer clinical trials were withdrawn.

BKM120

BKM120 has been developed by Novartis Pharma (Novartis Institute for Biomedical Research Oncology, Basel, Switzerland) and is a selective pan-PI3K inhibitor, with an IC_{50} towards p110α, p110α-H1047R and p110α-E545K in the nanomolar range, and no activity towards mTOR and other kinases (14). BKM120 binds to the ATP-binding site of the lipid kinase in a mixed competitive and non-competitive manner. Preclinical data showed activity toward different cell lines, including glioma and myeloma (14, 28, 29). Interestingly, cell lines harboring *PI3KCA* oncogenic mutations had a greater sensitivity to BKM120 as compared to those with wild-type *PIK3CA* (14). Moreover, the presence of a concomitant *KRAS* activating mutation was found to reduce sensitivity to BKM120, a finding that has been previously observed in the clinic with mTOR inhibitors, such as everolimus (30). Interestingly, preclinical data combining BKM120 with a signal transducer and activator of transcription 3 (STAT3) inhibitor showed that the combination was synergistic in gastric cells harboring *KRAS* mutations as opposed to those with wild-type *KRAS* (31). A phase I study of BKM120 in patients with advanced solid tumors has recently been reported, showing an acceptable toxicity profile, with expected side-effects for PI3K/AKT/mTOR pathway inhibition (diarrhea, mucositis, hyperglycemia and anorexia). Importantly, mood disorders were observed both at the maximal tolerated dose (MTD; 100 mg daily) and the lower dose level (80 mg daily) (32). Particular attention should therefore be paid to a medical history of depression in patients likely to receive BKM120. Of note, among the 35 enrolled patients, one experienced a confirmed PR (triple-negative breast cancer) and seven had disease control for at least eight months. Many trials with BKM120 are currently recruiting patients (Table II) with various malignancies including, as opposed to NVP-BEZ235, endometrial cancer, notably the phase II GINECO ENDOPIK trial that has recently started enrolment (Clinicaltrials.gov identifier: NCT01397877). A number of other trials are not yet recruiting patients, but are scheduled to open rapidly worldwide.

Table II. *Ongoing clinical trials with BKM120 (http://clinicaltrials.gov/ct2/results?term=bkm120, Accessed April 17, 2012).*

Condition	Study title	Companion drug	Clinicaltrials.gov identifier
Colorectal	A Trial of Irinotecan and BKM120 in Previously Treated Advanced Colorectal Cancer	Irinotecan	NCT01304602
Breast	Safety and Efficacy of BKM120 in Combination with Trastuzumab in Patients with Relapsing HER2 Overexpressing Breast Cancer Who Have Previously Failed Trastuzumab	Trastuzumab	NCT01132664
Breast	Study of BKM120 or BEZ235 and Capecitabine in Patients with Metastatic Breast Cancer	Capecitabine	NCT01300962
Breast	PhIb BKM120 or BEZ235+Endocrine Treatment in Post-menopausal Patients with Hormone Receptor + Metastatic Breast Cancer	Endocrine therapy	NCT01248494
Solid tumors/breast	A Study to Investigate Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of BKM120 Plus GSK1120212 in Selected Advanced Solid Tumor Patients	GSK1120212 (MEK inhibitor)	NCT01155453
Solid tumors	Trial of Oral BEZ235 and BKM120 in Combination with Paclitaxel with or without Trastuzumab	BEZ235, paclitaxel, trastuzumab	NCT01285466
Solid tumors	BKM120 + Carboplatin + Paclitaxel for Patients with Advanced Solid Tumors	Carboplatin, paclitaxel	NCT01297452
Solid tumors	Safety, Pharmacokinetics and Pharmacodynamics of BKM120 Plus MEK162 in Selected Advanced Solid Tumor Patients	MEK162	NCT01363232
Solid tumors/ glioblastoma	Combination of BKM120 and Bevacizumab in Refractory Solid Tumors and Relapsed/Refractory Glioblastoma Multiforme	Bevacizumab	NCT01349660
Glioblastoma	A Phase I Dose Escalation Study of BKM120 with Radiation Therapy and Temozolomide in Patients with Newly Diagnosed Glioblastoma	Temozolomide	NCT01473901
Glioblastoma	Phase II Study of BKM120 for Subjects with Recurrent Glioblastoma	Not applicable (N/A)	NCT01339052
Urothelial cancers	BKM120 in Metastatic Transitional Cell Carcinoma of the Urothelium	N/A	NCT01551030
Prostate	BKM120 in Metastatic Castration-resistant Prostate Cancer	N/A	NCT01385293
Kidney	Bevacizumab and BKM-120 in Patients with Metastatic Renal Cell Carcinoma	Bevacizumab	NCT01283048
Lung	A Trial of Gefitinib in Combination with BKM120 in Patients with Advanced Non-small Cell Lung Cancer, with Enrichment for Patients Whose Tumours Harbour Molecular Alterations of PI3K Pathway and Known to Overexpress EGFR	Gefitinib	NCT01570296
Lung (NSCLC)	Safety and Efficacy of BKM120 in Patients with Metastatic Non-small Cell Lung Cancer	N/A	NCT01297491
Solid tumors	A Phase I Study of BKM120 and Everolimus in Advanced Solid Malignancies	Everolimus	NCT01470209
Uterus	BKM120 as Second-line Therapy for Advanced Endometrial Cancer	N/A	NCT01289041
Uterus	GINECO-EN102b - BKM120 as Monotherapy in the Treatment of Initial or Recurrent Metastatic Endometrial Cancer (ENDOPIK)	N/A	NCT01397877

BAY 80-6946

BAY80-6946 (Bayer Healthcare Pharmaceuticals, Berlin, Germany) is a potent and highly selective pan-class I PI3K inhibitor with antitumor activity described in preclinical models. A phase I trial of BAY 80-6946 administered weekly for three out of four weeks, has been reported in solid tumors, with an MTD of 0.8 mg/kg. Dose-limiting toxicities included grade 4 hyperglycemia and acute left ventricular dysfunction, other toxicities being mild (fatigue, nausea, diarrhea, mucositis, anemia and dysgeusia). Two patients experienced stable disease for six and eight months, with endometrial and oesophageal cancer, respectively (33). Four trials exploring BAY 80-6946 are currently recruiting patients (Table III).

GDC-0941

GDC-0941 (Genentech, CA, USA) is a potent, selective, orally bioavailable inhibitor of PI3K that has shown efficacy in various preclinical models (34-36). Moreover synergy with Map-Erk Kinase (MEK) inhibitors was observed with enhanced tumor cell apoptosis in preclinical models, including gefitinib-resistant lung cancer cell lines (37, 38). Phase I data showed that GDC-0941 has an acceptable toxicity profile, without observed dose-limiting toxicities, and with moderate side-effects, including diarrhea, nausea, dysgeusia, peripheral sensory neuropathy, dry mouth, thrombocytopenia, and increased aspartate aminotransferase (39). Similar results were obtained in another phase I study,

Table III. *Ongoing clinical trials with BAY80-6946 (http://clinicaltrials.gov/ct2/results?term=BAY+80-6946, Accessed April 17, 2012).*

Condition	Study title	Companion drug	Clinicaltrials.gov identifier
Solid tumors	Phase 1 Study of PI3 (Phosphatidylinositol-3)-Kinase Inhibitor BAY80-6946 with Gemcitabine or Cisplatin Plus Gemcitabine in Patients with Advanced Cancer	Gemcitabine Cisplatin	NCT01460537
Solid tumors	Phase Ib Study of PI3 (Phosphoinositol 3)-Kinase Inhibitor BAY80-6946 with MEK (Mitogen-activated Protein Kinase) Inhibitor BAY86-9766 in Patients with Advanced Cancer	BAY86-9766	NCT01392521
Solid tumors	BAY80-6946 Open Label, Phase I Study in Patients with Advanced Cancer	N/A	NCT00962611
Solid tumors	Phase I Study of PI3 (Phosphoinositol 3)-Kinase Inhibitor BAY80-6946 with Paclitaxel in Patients with Advanced Cancer	Paclitaxel	NCT01411410

Table IV. *Ongoing clinical trials with GDC-0941 (http://clinicaltrials.gov/ct2/results?term=gdc-0941, Accessed April 17, 2012).*

Condition	Study title	Companion drug	Clinicaltrials.gov identifier
Solid tumors	A Study Evaluating the Safety, Tolerability and Pharmacokinetics of GDC-0973 in Combination with GDC-0941 When Administered in Patients with Locally Advanced or Metastatic Solid Tumors	GDC-0973	NCT00996892
Solid tumors	A Study of GDC-0941 in Patients with Locally Advanced or Metastatic Solid Tumors for Which Standard Therapy Either Does Not Exist or Has Proven Ineffective or Intolerable	Not applicable (N/A)	NCT00876109
Solid tumors	A Study of GDC-0941 in Patients with Locally Advanced or Metastatic Solid Tumors or Non-Hodgkin's Lymphoma for Which Standard Therapy Either Does Not Exist or Has Proven Ineffective or Intolerable	N/A	NCT00876122
Solid tumors	A Study of the Safety and Pharmacology of GDC-0941 in Combination with Erlotinib in Patients with Advanced Solid Tumors	Erlotinib	NCT00975182
Breast	Trastuzumab and Trastuzumab-MCC-DM1 Administered Intravenously and GDC-0941 Administered Orally to Patients with HER2-Positive Metastatic Breast Cancer Who Have Progressed on Previous Trastuzumab-Based Therapy	Trastuzumab Trastuzumab-MCC-DM1	NCT00928330
Breast	A Study of PI3-Kinase Inhibitor GDC-0941 in Combination with Paclitaxel and Bevacizumab in Patients with Locally Recurrent or Metastatic Breast Cancer	Paclitaxel Bevacizumab	NCT00960960
Breast	Study of GDC-0941 or GDC-0980 with Fulvestrant *versus* Fulvestrant in Advanced or Metastatic Breast Cancer in Patients Resistant to Aromatase Inhibitor Therapy	Fulvestrant GDC-0980	NCT01437566
Lung (NSCLC)	A Study of the Safety and Pharmacology Of PI3-Kinase Inhibitor GDC-0941 In Combination with Either Paclitaxel And Carboplatin (with or without Bevacizumab) or Pemetrexed, Cisplatin, And Bevacizumab in Patients with Advanced Non-small Cell Lung Cancer	Paclitaxel Carboplatin Pemetrexed Cisplatin Bevacizumab	NCT00974584
Lung (NSCLC)	Study Evaluating the Safety and Efficacy Of Carboplatin/Paclitaxel And Carboplatin/Paclitaxel/Bevacizumab with and without GDC-0941 in Patients with Previously Untreated Advanced or Recurrent Non-small Cell Lung Cancer	Carboplatin Paclitaxel Bevacizumab	NCT01493843

where the MTD was exceeded at 450 mg daily, and responses were observed in melanoma, gastro-intestinal stromal tumors (GIST) and ovarian cancer patients (40). Trials investigating GDC-0941, currently recruiting patients are shown in Table IV.

GDC-0980

GDC-0980 (Genentech, CA, USA) is a novel, dual PI3K/mTORC inhibitor that targets all PI3K class I isoforms and mTORC at low nanomolar concentrations, which is

Table V. *Ongoing clinical trials with GDC-0980 http://clinicaltrials.gov/ct2/results?term=GDC-0980 Accessed April, 17 2012).*

Condition	Study title	Companion drug	Clinicaltrials.gov identifier
Solid tumors Non-Hodgin's lymphoma	A Study Evaluating GDC-0980 Administered Once Weekly in Patients with Refractory Solid Tumors or Non-Hodgkin's Lymphoma	N/A	NCT00854126
Uterus	A Study of GDC-0980 in the Treatment of Recurrent or Persistent Endometrial Carcinoma	N/A	NCT01455493
Breast	A Study of the Safety and Pharmacology of GDC-0980 in Combination with Paclitaxel, Bevacizumab, and Trastuzumab in Patients with Locally Recurrent or Metastatic Breast Cancer	N/A	NCT01254526
Breast	Study of GDC-0941 or GDC-0980 with Fulvestrant *versus* Fulvestrant in Advanced or Metastatic Breast Cancer in Patients Resistant to Aromatase Inhibitor Therapy	Fulvestrant GDC-0941	NCT01437566
Prostate	Study of GDC-0068 Or GDC-0980 with Abiraterone Acetate *versus* Abiraterone Acetate in Patients with Castration-Resistant Prostate Cancer Previously Treated with Docetaxel Chemotherapy	Abiraterone Prednisone	NCT01485861
Solid tumors	GDC-0980 in Combination with a Fluoropyrimidine, Oxaliplatin, and Bevacizumab in Patients with Advanced Solid Tumors	Fluoropyrimidine Oxaliplatin Bevacizumab	NCT01332604
Solid tumors	A Study of the Safety and Pharmacology of GDC-0980 in Combination with Paclitaxel and Carboplatin with or without Bevacizumab in Patients with Solid Tumor	Paclitaxel Carboplatin Bevacizumab	NCT01301716

active in several cancer cell lines of breast, prostate and lung cancer, including those with activated PI3K or *PTEN* loss (41, 42). A phase I study of GDC-0980 in patients with advanced solid tumors recommended a daily dosing <70 mg, on a 21/28 day schedule. Toxicity consisted of rash, hyperglycemia, mucositis and pneumonitis, which resolved with drug cessation. Antitumor effects were observed in 3/33 patients with mesothelioma. Fluorodeoxyglucose positon emiting tomography (PET-FDG) responses were also observed in GIST and adrenal gland cancer (43). A prior phase I study was also reported, at a daily dosing of 16 mg, again on the 21/28 day schedule, showing consistent results (44). Studies currently recruiting patients in GDC-0980-based therapies are shown in Table V.

Future Perspectives for Targeting the PI3 Kinase

Since the mTOR inhibitors have demonstrated that inhibiting the PI3K/AKT/mTOR pathway is a relevant goal for improving the outcome in several types of cancers (kidney, breast, endocrine tumors and sarcomas), this pathway has been extensively studied. Indeed, as modern chemistry and molecular biology offer the opportunity to decipher in detail the molecular mechanisms of protein activation though the kinase family, there is a continuously growing number of novel compounds that are being designed and evaluated. There is now a solid body of evidence suggesting that selective inhibition of the PI3K isoforms that are involved in carcinogenesis and the mechanisms of cancer progression is a relevant approach. Indeed, this review identified a large number of phase I studies, contrasting with a much lower number of phase II trials. Hence, more data are awaited from single-agent phase II studies to ascertain the actual antitumor properties of PI3K inhibitors, in terms of indicators that are more relevant to the patients and the physicians, such as survival. Moreover, it is so far uncertain whether transient responses observed in early trials, as well as surrogate markers of efficacy such as TEP-FDG standard uptake value (SUV) responses in heavily pretreated patients are actually meaningful. A more problematic issue arises from resistance to the inhibition of PI3K. Indeed, as evidenced upon mTOR inhibition, activating feedbacks may quickly jeopardize the benefits of the targeted therapy. Hence, future directions should focus on concomitant inhibition of pathways that are involved in the feedback activation loops, with obvious tolerance issues. Trials are ongoing for this purpose, as well as those combining PI3K inhibitors with cytotoxic drugs. Finally, much is awaited from the identification of tumor biomarkers associated with the efficacy of PI3K inhibitors, such as concomitant *KRAS* mutation, or *PI3K*-activating mutations. Tumor genotyping in patients receiving such drugs is not only mandatory in early phase trials, but will certainly be part of routine practice in the near future. Hence, we will be able to identify patients which are most likely to benefit from these new targeted therapies.

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