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Targeting the PI3K/AKT/mTOR Pathway in Cancer Cells


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1. Introduction

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway is a critical regulator of many essential physiological processes, but it also plays a key role in the malignant transformation of human tumors and their subsequent growth, metabolism, proliferation, and metastasis [1]. Previous studies have demonstrated that the PI3K/AKT/mTOR pathway is frequently activated in human cancers due to the somatic mutation and amplification of genes encoding key components [2,3]. In addition, aberrant PI3K/AKT/mTOR signaling activation also confers resistance to conventional therapies and is a poor prognostic factor for many types of cancers [4,5]. Several agents that target the PI3K/AKT/mTOR cascade elements are undergoing evaluation in preclinical and clinical studies. These include PI3K inhibitors, AKT inhibitors, mTOR catalytic site inhibitors, and dual PI3K-mTOR inhibitors. This chapter focuses on recent preclinical and clinical data on the efficacy of PI3K/AKT/mTOR pathway inhibitors either as monotherapy or in combination with conventional chemotherapy or others target drugs. Herein, we review four different classes of PI3K pathway inhibitors: PI3K inhibitors, AKT inhibitors, mTOR catalytic site inhibitors, and dual PI3K-mTOR inhibitors.

2. The PI3K/AKT/mTOR pathway

The PI3K/AKT/mTOR constitutes an important pathway downstream of growth factor tyrosine kinase receptors, thus regulating a plethora of biological processes as angiogenesis, proliferation, metabolism, survival, and differentiation [3]. Accumulating evidences indicate,
therefore, that alterations in the PI3K/AKT/mTOR axis play critical and multifaceted role in
cancer pathogenesis and progression. Indeed, systematic analysis performed in 3,281 tumors
from 12 cancer types of the Cancer Genome Atlas Pan-Cancer effort has revealed that elements
of the PI3K/AKT/mTOR signaling pathway are among the highest frequently mutated genes
in cancer, such as uterine corpus endometrioid, breast, colon, lung, head and neck, and ovarian
carcinomas [4,5].

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Table 1. The PI3K proteins family

PI3K is a heterodimer of its catalytic and regulatory subunits and has been classified as class
I, II, and III. Class I PI3K is constituted by four 110-kDa catalytic subunits and two main
regulatory domains, which is subdivide in class IA and IB. Class IA PI3K (PI3K α, β, and δ) is
activated by receptors with tyrosine kinase activity, and class IB PI3K (PI3K γ) is activated by
G protein-coupled receptors. The class IA enzymes are dimers of p110α, p110β, or p110δ
catalytic subunits and the regulatory subunits p85α (or its splice variants p55a and p50a),
p85β, p55γ, p101, or p84 [6,7]. In turn, class IB enzymes are dimers of p110γ catalytic subunit
and either p101 or p84 (also known as p87PIKAP) regulatory subunits [8]. The four class I
catalytic isoforms share overlapping but distinct functions. Although the expression of p110c and p110d isoforms seems to be confined to immune cells, p110a and p110b are ubiquitously expressed but exhibit isoform-specific cell-type- and context-dependent requirements, thus being involved in a wide range of cellular effects [9–13]. Class II PI3K (PI3KC2) subfamily has additional domains in both N- and C-terminal extensions and exists as 3 isoforms, PI3K-C2α, PI3K-C2β, and PI3K-C2γ [14]. On the other hand, class III PI3K occurs as a single isoform constituted by the catalytic subunit Vps34p and regulatory subunit Vps15 [14] (Table 1).

The PI3K family recruits effector proteins, altering their localization, activity, and conformation. There are some binding proteins domains that mediate such events [14]. The best-characterized domains among them are FYVE (Fab 1, YOTB, Vac 1, EEA1) [15–17], PH (pleckstrin homology) [18], and PX (Phox) [19-23]. Nonetheless, the peculiar composition of the three PI3K subfamilies results in the activation of distinct cellular functions.

In brief, after activation by receptor tyrosine kinases, including members of platelet-derived growth factor receptor, the insulin and insulin-like growth factor 1 (IGF-1) receptors and human epidermal growth factor receptor family (EGFR and HER2), PI3K phosphorylates phosphatidylinositol 4,5-trisphosphate (PIP₂) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP₃) [24]. In physiological conditions, the level of PIP3 is strictly regulated by PTEN (phosphatase and tensin homolog), a phosphatase that specifically catalyzes the dephosphorylation of PIP3, converting PIP3 back to PIP2, thus constituting an important endogenous-negative feedback loop of the PI3K signaling pathway [25,26]. The lipid product of PI3K, PIP₃, recruits a subset of signaling proteins with PH domains to the membrane, including 3-phosphoinositide-dependent protein kinase (PDK1) and AKT, resulting in its phosphorylation at threonine-308 and activation [24].

In both physiological and pathological conditions, AKT exists in three isoforms in mammals: AKT1, AKT 2, and AKT 3 [27,28]. AKT phosphorylates tuberous sclerosis complex 2 (TSC2), thereby inhibiting the GTPase activity of the TSC1/TSC2 complex and enabling mTOR activation by RAS homologue enriched in brain (RHEB), thus allowing signal propagation [26,29]. mTOR exists in two different structural protein complex: mTORC1 and mTORC2, each of which is expressed in different subcellular compartments, therefore affecting their activation and function. mTORC1 complex is composed of a catalytic subunit mTOR, regulatory-associated protein of mTOR (RAPTOR), mammalian lethal with SEC13 protein 8 (MLST8), and the noncore components PRAS40 and DEP domain-containing mTOR-interacting protein (DEPTOR). Once activated, mTORC1 leads to increased protein synthesis via its effectors, named translation-regulating factors ribosomal S6 kinase 1 (S6K-1) and eukaryote translation initiation factor 4E binding protein-1 (4EBP-1). S6K-1 and 4EBP1 are major regulators of protein translation [30]. On the other hand, mTORC2 is composed by rapamycin-insensitive companion of mTOR (RICTOR), MLST8, and mammalian stress-activated protein kinase interacting protein 1 (SIN1). The function of mTORC2 remains not fully understood, but it is required to phosphorylate AKT at serine-473, thus resulting in its maximal activation [31]. Of clinical relevance, differently from mTORC1, mTORC2 is insensitive to rapamycin inhibition, opening an avenue for drug discovery in face of the development of resistance by cancer cells against first-generation mTOR inhibitors (rapalogs) that particularly target mTORC1 [32] (Figure 1).
Figure 1. Overview of PI3K/AKT/mTOR signaling pathway and some inhibitors of this pathway in clinical studies. The activation of the PI3K by receptor tyrosine kinases promotes conversion of PIP$_2$ to PIP$_3$. PTEN dephosphorylates PIP$_3$, negatively regulating the PI3K signaling. The phosphorylation and activation of AKT impacts many downstream effectors, such as mTORC1, and finally leads to multiple cellular processes.

3. The role of PI3K/AKT/mTOR in cancer

Somatic mutations and/or gains and losses of genes are possible genetic alterations affecting the PI3K/AKT/mTOR pathway in different solid and hematological tumors [33,34]. Indeed, PI3K pathway can be activated by direct upstream signs and can be intrinsically activated due to gain of functional mutations or amplifications in PIK3CA (p110 subunit), mutations in PIK3R (p85 subunit), and mutations or amplifications in one of the AKT isoforms or loss of PTEN [35]. Loss of PTEN via inactivating mutations, due to either copy number loss or homozygous deletions, is associated with both resistance to chemotherapy and reduced survival of human patients [3].

PIK3CA mutations in primary breast tumors have been associated with lymph node metastases and overexpression of ER, PR, and HER2 [36]. Furthermore, the presence of activating
PI3KCA mutations and loss of PTEN in HER2-overexpressing cancers is correlated with a lower response to trastuzumab and lapatinib [37]. In non-small cell lung cancer, the downregulation of PTEN is also related with poor prognosis [38,39]. In ovarian cancer, PI3K/akt/mTOR molecular alteration appears to be histological subtype specific. Studies have described amplifications in PIK3CA, amplifications of one of the AKT isoforms, and PTEN deletions in 20%, 15%, and 5% of the high grade serous ovarian cancer (HGSOC) cases, respectively [40,41]. The individual mutations, rare events in HGSOC, are prevalent in low grade serous, mucinous, endometrioid, and clear cell ovarian cancer; 20% of endometrioid and 35% of clear cell ovarian tumors display these PIK3CA mutations [42,43]. Besides, copy number changes in the genes encoding PIK3CA and PIK3CB subunits have been associated with a poor prognosis, and the inhibition of PI3K/mTOR was found to delay tumor growth and prolong survival [44,45].

Moreover, mutations of mTOR itself and/or in components of mTOR-related signaling pathways have frequently been described in human malignant diseases [46-48]. Different genetic lesions that mediate mTORC1 activation have diverse consequences: PTEN loss uncouples mTORC1 activation from growth factor signaling; liver kinase B1/serine/threonine kinase 11 (LKB1/STK11) mutations allow mTORC1 activation despite nutrient deprivation in poorly vascularized tumors; P53 mutations uncouple DNA damage from the inhibition of bioenergetic processes and cell cycle arrest [49]; and hyperactivation of S6K-1, 4E-BP1 and eIF4E, and cancer growth by activating the lipid and protein biosynthesis. Furthermore, the increased phosphorylation of mTOR is associated with acquired cisplatin resistance, and AKT signaling has been implicated in primary platinum resistance [50]. In fact, AKT or mTOR inhibitors likely restore chemosensitivity to platinum derivates in vitro and in xenograft models [51,52].

These molecular alterations, in addition to the druggability of the components of the PI3K/akt/mTOR signaling cascade, suggest that targeting the pathway might represent a useful treatment strategy in the fight against cancer.

4. PI3K inhibitors in cancer therapy

As aforementioned, PI3K/akt/mTOR pathway has been implicated in tumorigenesis, promotion of cell survival, angiogenesis, cellular invasion, tumor growth, and the acquisition of chemoresistant phenotype by cancer cells [1]. Currently, more than fifty PI3K/akt/mTOR axis inhibitors are in different stages of development, with a great number of such inhibitors reaching clinical trials [53]. Analogs of rapamycin (inhibitors of mTORC1), temsirolimus and everolimus, are currently in the lead, having already been approved by the Food and Drug Administration (FDA) as anticancer agents [54-56]. The PI3K/akt/mTOR pathway inhibitors are summarized in Table 2.

4.1. PI3K inhibitors

PI3K inhibitors can be divided in isoform-specific inhibitors or pan-PI3K inhibitors. pan-PI3K inhibitors target all class IA PI3Ks in tumor cells, whereas isoform-specific inhibitors were
developed to decrease toxicity and might be particularly effective in cancers with PIK3CA
mutations, for example.

The first-generation of PI3K inhibitors include wortmannin, a fungal metabolite isolated from
*Penicillium wortmannin* that irreversibly inhibits p110 by reacting covalently with the catalytic
site [57], and LY294002, a synthetic, competitive, and reversible inhibitor of the ATP binding
site of PI3K [58]. Both agents achieve significant antiproliferative and pro-apoptotic effects in
preclinical *in vitro* and *in vivo* studies. However, unfavorable pharmacokinetic properties,
insolubility in water, high levels of toxicity, and lack of selectivity for oncogenic isoforms of
Class I PI3K limit its use in clinical trials [59,60]. Although this limiting features for their clinical
use, wortmannin and LY294002 have served as important research tool for elucidating diverse
signal transduction processes involving PI3K pathway and has spawned a new generation of
PI3K inhibitors [61] (Table 2).

Currently, water-soluble wortmannin conjugates are being developed to overcome this issue.
PX-866 is a semisynthetic analog of wortmannin with potent, irreversible, pan-class I PI3K
inhibitory property against p110-α, p110-δ, and p110-γ enzymes in biochemical assays [62]. In
preclinical studies, the compound alone or in combination with chemotherapy (cisplatin),
radiotherapy, and targeted cancer drugs (gefitinib) exhibited *in vivo* antitumor activity against
numerous mouse xenograft models of human cancers [62,63]. In addition, a phase I study in
eighty-four patients with advanced solid tumors showed that PX-866 is well tolerated. The
most frequent study drug-related adverse events were gastrointestinal disorders, with
diarrhea being the most common [64]. PX-866 is being currently tested in a combination phase
I/II studies with cetuximab (NCT01252628) in squamous cell carcinoma of the head and neck
(SCCHN) and in metastatic colorectal carcinoma. Furthermore, more two phase I/II studies
with PX866 are ongoing: with docetaxel (NCT01204099) in non-small cell lung cancer and
SCCHN and in combination with vemurafenib in patients with advanced melanoma
(NCT01616199).

Buparlisib (NVP-BKM120) is an oral highly specific pan-class I PI3K inhibitor with inhibitory
property against p110-α, p110-β, p110-δ, and p110-γ enzymes [65]. The compound is also active
against activating p110α somatic mutations but does not significantly inhibit the related class
III and class IV PI3K kinases. In preclinical cancer studies, buparlisib has shown antiprolifer‐
vative and proapoptotic activity against a panel of 353 cell lines that display different genetic
abnormalities that promote PI3K pathway activation [66]. *In vivo* studies have also shown that
buparlisib potently inhibits the growth of human xenografts models and behaves synergisti‐
cally when combined with cytotoxic agents such as temozolomide, alkylating agent, and
docetaxel, antimitic drug, or with targeted agents such as HER2 and mitogen-activated
protein kinase kinase (MEK) inhibitors [66].

A phase I dose-escalation study in thirty-five patients with advanced-stage solid tumors
showed that buparlisib is a safe and well-tolerated drug with favorable pharmacokinetic
properties. The major treatment-related adverse events included rash, hyperglycemia,
diarrhea, anorexia, mood alteration, nausea, fatigue, pruritus, and mucositis [67]. Importantly,
hyperglycemia was more common at higher doses and represents a class effect of the inhibition
of PI3K signaling, commonly observed with other PI3K/AKT/mTOR pathway inhibitors [67].
Later, phase I dose-escalation and expansion study of buparlisib was performed in eighty-three patients with advanced solid tumors demonstrating that buparlisib was well tolerated up to 100 mg/day and showed preliminary activity in patients with advanced cancers [68]. This subsequently led to the initiation of several clinical trials in multiple cancer types, such as non-small cell lung cancer, prostate cancer, breast cancer, colon cancer, and glioblastoma multiform (GBM).

BASALT-1, an ongoing phase II trial (NCT01297491), is investigating the efficacy of single-agent buparlisib in patients with metastatic non-small cell lung cancer with PI3K pathway activation. Furthermore, phase Ib/II is under evaluation in patients with advanced non-small cell lung cancer of different histotype, testing buparlisib in combination with other targeted agents such as everolimus (NCT01470209), erlotinib (NCT01487265), MEK inhibitor (NCT01363232), or in combination with standard chemotherapeutic drugs, such as docetaxel (NCT01911325), gemcitabine, and cisplatin (NCT01971489) and carboplatin and paclitaxel (NCT01820325).

At present, several active, not recruiting, and recruiting clinical trials are being conducted in all the biological subsets of breast cancer, including combinations with endocrine therapy, anti-HER2 agents, poly (ADP-ribose) polymerase (PARP) inhibitors, and chemotherapy with buparlisib. Two large phase III studies (BELLE-2 and BELLE-3) (NCT01610284, NCT01633060) are investigating the combination of buparlisib plus fulvestrant in postmenopausal women with hormone receptor-positive/HER2-negative breast cancer after failure of aromatase inhibitor alone or aromatase inhibitor plus mTOR inhibitor treatment, respectively. Another ongoing clinical study is BELLE-4, a placebo-controlled phase II trial of buparlisib with paclitaxel in the first-line treatment of HER2-negative metastatic breast cancer (NCT01572727).

Buparlisib has also been evaluated in a phase II study of paclitaxel plus trastuzumab in HER2-overexpressing breast cancer (NCT01816594).

Pilaralisib (XL147) is an oral pan-class I PI3K inhibitor (α, β, γ, and δ) through reversible, competitive inhibition with ATP for p110-α, -δ, -γ, and -β enzymes [69]. In vitro tests revealed that pilaralisib inhibits the formation of PIP3 in the membrane and phosphorylation of AKT and S6K-1 in multiple tumor cell lines with diverse genetic alterations in PI3K pathway [70]. Moreover, in mouse xenograft models, oral administration of pilaralisib results in significant tumor growth inhibition and combination with chemotherapeutic agents improved the growth-inhibitory effect observed with the single agents [71]. Based on this preclinical rationale, pilaralisib has been evaluated in phase I/II clinical trials.

In a phase I dose-escalation trial of sixty-nine patients with advanced solid tumors, pilaralisib was tolerable at doses associated with PI3K pathway inhibition, and the most frequent drug-related adverse events included dermatologic toxicities, diarrhea, nausea, and decreased appetite [72]. However, a phase I dose-escalation study of pilaralisib with erlotinib in patients with solid tumors showed that combination had limited antitumor activity with moderate inhibition of PI3K, MAPK and EGFR pathways [73]. Moreover, phase I/II study of pilaralisib in combination with trastuzumab or trastuzumab plus paclitaxel in trastuzumab-refractory HER2-positive metastatic breast cancer related that no responses were observed in patients treated with pilaralisib plus trastuzumab while clinical activity was observed in paclitaxel arm...
Additional clinical evaluation of this PI3K inhibitor is ongoing in phase I/II studies (NCT01587040).

Pictilisib (GDC-0941) is another potent, selective, and orally bioavailable inhibitor of pan-class I PI3K. In biochemical assays, pictilisib demonstrates selectivity over a large panel of protein kinases and PI3K family kinases, including mTOR and DNA-dependent protein kinase (DNA-PK) [75]. Interestingly, pictilisib induces apoptosis in a subset of human tumor cell lines and potently inhibited tumor growth in xenograft models, including those with mutations in PI3K, PTEN, and K-Ras [76]. Significant in vivo antitumor activity has also been observed when administered orally in combination with other anticancer drugs, for example, docetaxel and MEK inhibitor U0126 [77-80].

In a first-in-human phase I study of pictilisib in sixty patients with advanced solid tumors, the most frequently reported drug-related adverse events were nausea, fatigue, and rash [81]. Importantly, one patient with V600E BRAF-mutant melanoma and another with platinum-refractory ovarian cancer exhibiting PTEN loss and PIK3CA amplification demonstrated partial response [81]. Pictilisib is currently under evaluation in several phase I/II clinical trials, mainly in non-small cell lung cancer and breast cancer (NCT01918306, NCT01740336, NCT01493843, and NCT00974584).

One strategy to achieve significant pathway inhibition clinically with tolerable adverse effect profile is the use of isoform-specific PI3K inhibitors. As aforementioned, each isoform has distinct role in normal physiological processes and disease (Table 1). PI3K catalytic subunit p110α is predominantly responsible for mediating growth factor signaling from receptor tyrosine kinases and is a frequent genetic driver (PIK3CA mutations) in several cancers [82]. However, p110α is dispensable for PI3K pathway activation in tumors lacking PTEN. Thus, these cells depend largely on p110β to activate the pathway [82,83]. Preclinical tests showed that p110β-selective inhibitors had a significantly greater activity in cell lines with PTEN null than in those with PTEN intact, although, some PTEN-intact cell lines were sensitive and a number of cells lines lacking PTEN were resistant [84]. GSK-2636771 is a PI3K p110β-selective inhibitor currently in phase I studies in subjects with advanced solid tumors with PTEN deficiency (NCT01458067). Moreover, PI3Kδ is predominantly expressed in leukocytes and control immune responses [85]. Idelalisib (CAL-101), a highly specific PI3Kδ inhibitor, was the first isoform-specific PI3K inhibitors approved for cancer treatment [86].

Alpelisib (NVP-BYL719) is an oral inhibitor that selectively targets PI3K p110α equipotent against the wild type and the most common somatic mutations of p110α [87]. NVP-BYL719 has been the first PI3Kα-selective inhibitor to enter in clinical trials after positive preclinical investigations. In vivo studies have demonstrated dose-dependent antitumor activity of NVP-BYL719 in PIK3CA-mutant or PIK3CA-amplified tumor xenograft models, such as ovarian, breast, and head and neck cancers [88, 89]. Preliminary results of phase I study performed in patients with advanced solid tumors carrying PIK3CA gene alterations demonstrated that NVP-BYL719 has a favorable safety profile with manageable toxicities, as hyperglycemia, nausea, diarrhea, decreased appetite, vomiting, and fatigue [90]. To date, more than fifteen clinical trial is ongoing in order to evaluate the combination of NVP-BYL719 with several agents, such conventional cytotoxic drugs (paclitaxel, cisplatin, and irinotecan) and target
drugs (cetuximab, olaparib, and trastuzumab) in a subset of cancers (NCT02051751, NCT01822613, NCT01602315, NCT01623349, and NCT02167854).

Taselisib (GDC-0032) is a PI3K inhibitor with higher affinity for mutated PI3Kα with reduced inhibitory activity against PI3Kβ [91]. Preclinical studies show that taselisib has enhanced activity against PI3Kα isoform mutant cancer cell lines [92]. In an ongoing phase I study, taselisib has been well tolerated with hyperglycemia and fatigue being the dose-limiting toxicities [93]. This selectivity profile and excellent pharmacokinetic properties allowed fewer clinical studies with GDC-0032. Currently, several clinical studies are ongoing to evaluate the combination of taselisib with endocrine therapy, trastuzumab, and conventional chemotherapy in breast cancer (NCT02285179, NCT02390427, and NCT01862081). In addition, a phase I study is currently ongoing in taselisib with CDK4/6 inhibitor, palbociclib, in advanced solid tumors and breast cancer (NCT02389842).

Idelalisib was approved in 2014 in the United States and European Union for the treatment of three indolent B-cell neoplasms: relapsed chronic lymphocytic leukemia, in combination with rituximab, relapsed follicular B-cell non-Hodgkin’s lymphoma, and relapsed small lymphocytic lymphoma (as monotherapy) [94]. In lymphoid cell lines and primary patient samples, idelalisib abrogates PI3K/AKT/mTOR signaling and promotes apoptosis [95,96]. The first phase I trial in healthy volunteers established the bioavailability and safety of idelalisib [97]. Another phase I study in patients with relapsed/refractory mantle cell lymphoma reported the most common adverse events, which includes diarrhea, nausea, pyrexia, fatigue, rash, upper respiratory infection, pneumonia and alanine transaminase, or aspartate transaminase elevations [98]. To date, about twenty-five clinical trials are ongoing with idelalisib. A phase I/II trial studies aimed evaluated idelalisib in combination with lenalidomide and rituximab in patients with relapsed or refractory mantle cell lymphoma (NCT01838434). In addition, idelalisib is being evaluated in combination with rituximab in adults with previously treated indolent non-Hodgkin lymphoma (NCT01732913).

5. AKT inhibitors in cancer therapy

AKT inhibitors constitute another class of drugs that has gained recent interest. As discussed previously, AKT is involved in the regulation of various signaling downstream pathways involved in cell survival, growth, proliferation, metabolism, and angiogenesis. AKT inhibition promotes decreasing cancer cell survival by preventing signal transduction through its downstream effectors. In addition, targeting AKT is an interesting pharmacological approach due to the AKT activation in consequence of the feedback loop release when mTOR is inhibited.

AKT inhibitors can be grouped into three classes, including lipid-based phosphatidylinositol (PI) analogs, ATP-competitive inhibitors (catalytic inhibitors), and allosteric inhibitors. To date, the most developed inhibitor of AKT is perifosine (KRX-0401), a lipid-based inhibitor. Perifosine is an allosteric inhibitor that targets the PH domain of AKT, thereby preventing its translocation to the plasma membrane required for pathway activation [99]. Perifosine has demonstrated great efficacy in vitro and in vivo against several human cancers such as breast,
osteosarcoma, ovarian, multiple myeloma, leukemia, and glioma [100,101]. Additional in vitro data demonstrate synergistic effects of perifosine and traditional chemotherapeutic agents such as paclitaxel and cisplatin in ovarian cancer [102,103], etoposide in leukemia cells [104], doxorubicin in multiple myeloma cells [105], and gemcitabine in pancreatic cells [106].

Despite these encouraging preclinical studies, results from phase I/II clinical trials of perifosine as single agent in a various tumor types (metastatic breast cancer, metastatic head and neck cancer, locally advanced soft tissue sarcoma, prostate cancer, and metastatic In behalf of the poor efficacy of perifosine as a single agent observed in most tumor types evaluated thus far, efforts have been made to combine this drug with target agents and chemotherapy. Phase I studies have now confirmed the safety of these combinations with different agents, including sorafenib in patients with Hodgkin lymphoma and taxanes in high-grade epithelial ovarian cancer [112,113]. Currently, one clinical trial with perifosine is recruiting patients, a phase II study with perifosine and temsirolimus in patients with malignant gliomas (NCT02238496).

GSK-690693 is a potent ATP-competitive AKT inhibitor selective for all three AKT isoforms versus the majority of kinases assessed by biochemical tests [114]. GSK690693 displayed antiproliferative activity in vitro and in vivo models of ovarian, breast, and prostate cancer [114]. The compound has entered phase I trials for refractory hematologic malignancies but was withdrawn prior to enrolment (NCT00666081).

6. mTOR inhibitors in cancer therapy

6.1. Rapamycin and its derivatives

As discussed previously, mTOR is involved in many cell signaling pathways, and clinical trials for cancer treatment showed that tumor cells with mutations in p53 or PTEN are susceptible to mTOR inhibitors [115]. mTOR inhibitors are categorized in first- and second-generation presenting a wide variety of target and mechanism. The first-generation mTOR inhibitors include rapamycin and its analogs that employ allosteric mechanism to block, whereas the second-generation mTOR inhibitors (AZD8055, Torin1, PP242, and PP30) have as target ATP binding site to impede kinase activity of both mTORC1 and mTORC2 [116].

Rapamycin, discovered in 1975, is a macrocyclic lactone isolated from the soil bacterium Streptomyces hygroscopicus, and it has clinical applications including antifungal, immunosuppressant, and anticancer proprieties [117,118]. FDA approved this drug in 1997 for prevention of host-rejection during kidney transplants [119]. Preclinical studies have shown that rapamycin presents strong antiangiogenic and antiproliferative properties against a variety of human cancers such as the phase II study, which showed rapamycin potentiates the effect of paclitaxel in endometrial cancer cell lines [120].

Three different mechanisms of action have been proposed: first, the binding of the FKBP-12–rapamycin complex to mTOR that could lead dephosphorylation of downstream effector
molecules such as S6K-1 and 4EBP1 [121]; second, the FKBP-12–rapamycin complex competes with phosphatidic acid to bind to the FRB domain of mTOR, blocking mTOR kinase function [122]; and third, the FKBP-12–rapamycin complex bounds to mTOR and destabilizes the mTOR–raptor–4EBP1/S6K-1 scaffold complex, leading to dephosphorylation of S6K-1 and 4EBP1 [123,124].

This inhibitor has limited bioavailability due to its poor aqueous solubility. In an effort to improve its pharmacokinetics, several rapamycin analogs, named rapalogs, have been developed, such as temsirolimus (CCI-779), everolimus (RAD001), and ridaforolimus (MK-8669/AP23573) [125-127].

Some studies have shown that these compounds are able to disrupt the mTORC2 complex in a dose-, time-, and cell type-dependent manner [24,128,129]. A possible mechanism by which rapamycin and rapalogs could inhibit mTORC2 relies on the interaction of newly synthesized mTOR molecules and rapamycin/rapalogs-FKBP12 complexes. In turn, this interaction would prevent mTOR from the interaction with RICTOR, thus inhibiting mTORC2. Indeed, it has been shown that prolonged exposure of cancer cells to rapamycin can promote its binding to mTOR before the assembly of the mTORC2 complex, with subsequent inhibition of the AKT-mediated signaling [24].

Rapamycin and its derivates exhibit a safe toxicity profile, being the side effects of skin rashes and mucositis dose dependent [130]. Other symptoms commonly described are fatigue, nausea, anemia, hypertriglyceridemia, hypercholesterolemia, and neutropenia [131]. Furthermore, temsirolimus and sirolimus are associated with significant rate of pulmonary toxicity [130,131]. Rare side effects of the aforesaid drugs include interstitial lung disease, risk of secondary lymphoma, and reactivation of latent infections [35].

Everolimus (Afinitor®), the oral mTOR inhibitor, has been approved by the FDA in 2009 for advanced renal cell cancer. Everolimus exhibit strong antiangiogenic and antiproliferative activity against various human cancer such as metastatic or unresectable pancreatic neuroendocrine tumors, subependymal giant cell astrocytoma [132], metastatic renal cell carcinoma, and advanced estrogen receptor (ER)-positive [133] and human epidermal growth factor receptor-2 (HER2)-negative breast cancer [134].

Several studies have been conducted to analyze the effectiveness of rapamycin and rapalogs alone and in combination with standard chemotherapy, hormonal therapy such as anti-VEGF inhibitors in the treatment of several types of cancers such breast, ovarian, cervical, and endometrial. Phase II studies are ongoing in order to test everolimus in combination with chemotherapy (cisplatin and gemcitabine) in patients with metastatic triple negative breast cancer (NCT01939418 and NCT01931163). In addition, a recent study of breast cancer (BOLERO-3) demonstrated that the combination of everolimus with trastuzumab and vinorelbine significantly prolonged progression-free survival (PFS) in patients with trastuzumab-refractory and taxane-pretreated, HER2-positive advanced breast cancer [135]. Moreover, another breast cancer study, BOLERO-1, evaluated patients treated with paclitaxel and trastuzumab with or without everolimus as first-line therapy [136]. Furthermore, clinical studies have
evaluated the aromatase inhibitor letrozole in combination with everolimus in patients with metastatic endometrial carcinoma (NCT01068249) and breast cancer (NCT00107016).

Temsirolimus (Torisel®), the first rapamycin analog to be FDA approved as an anticancer drug, is an intravenous injection drug and gets converted into rapamycin in vivo [137]. This drug was valued with bevacizumab or in combination with chemotherapeutic agents in endometrial cancer cell lines, and results showed the increase progesterone mRNA expression and inhibition of ER mRNA expression [138,139]. Also, preliminary phase II study using temsirolimus in patients with metastatic cervical cancer showed positives results [140]. Another phase II clinical study (NCT01196429) evaluates additional effects of the temsirolimus combined with paclitaxel/carboplatin therapy have been conducted in patients with stages III/IV clear cell adenocarcinoma [141]. However, some studies failed to show the efficiency of temsirolimus in patients with persistent/recurrent epithelial ovarian cancer/primary peritoneal cancer showing a modest activity of this mTOR inhibitor, and the results were insufficient to justify further study in a phase III [142].

Ridaforolimus (MK-8869/AP23573), a non-rapamycin prodrug, is available in both oral and intravenous formulations. This mTOR inhibitor is actively being evaluated as either monotherapy or in combination with other therapies for treatment of various cancers, including sarcomas, endometrial, prostate, breast, and non-small cell lung cancer [143]. Studies had been conducted in patients with advanced endometrial cancer and clinical benefit response was reported in 33% of the patients [144]. Another phase II study using oral ridaforolimus in patients with advanced or recurrent endometrial cancer also showed partial response in 7.7% patients [145].

Although clinically promising, the efficacy of rapalogs is partially limited by the negative feedback loops in the mTOR pathway. With this regard, the exclusive inhibition of the mTORC1 complex by the rapalogs compromises the S6K-1-mediated feedback loop towards IRS-1, resulting in the activation of both the PI3K/AKT and the mitogen-activated protein kinase/extracellular signal-regulated kinases (MAPK/ERK) pathways, hence promoting compensatory cell survival, and the acquisition of chemoresistant phenotype [127,146,147]. Efforts have been made to overcome the previously mentioned clinical limitation by means of developing new generation mTOR inhibitors, which inhibit the catalytic activity of both mTORC1 and mTORC2 complexes.

7. ATP-competitive inhibitors

Although rapamycin is a potent allosteric mTORC1 inhibitor with clinical applications, a second-generation ATP-competitive inhibitor have been developed, including Torin1, Torin2, PP242, PP30, KU0063794, WAY-600, WYE-687, WYE-354, XL-388, INK-128, AZD-2014, AZD8055, and OSI-027 [148-153]. The ATP-competitive inhibitors of mTOR directly inhibit the mTOR kinase activity, affecting both mTORC1 and mTORC2 complexes simultaneously and suppress AKT activity.
ATP-competitive mTOR inhibitors represent a promising new approach to target the pathway with potentially greater tolerability and efficacy than rapamycin. It has been shown that ATP inhibitors displayed dramatic antiproliferative activity across a range of cancer cell lines [151,154,155].

Studies have been conducted with PP242 in colon cancer cells in vitro and in vivo showed decrease cell growth alone or in combination with MEK inhibitors [156]. Another ATP competitive inhibitor, Torin2, was developed to overcome the pharmacological limitations of Torin1 and it is a potent inhibitor of ATR, ATM, and DNA-PK [157,158]. Lung cancer cell treatment with Torin2 resulted in a prolonged block in negative feedback and consequent threonine-308 phosphorylation on AKT. These effects were associated with strong growth inhibition in vitro [159].

Studies conducted by Rodrik-Outmezguine and colleagues [160], comparing mTORC1 inhibition with rapamycin and AZD8055, revealed that rapamycin treatment led to an almost complete loss in the mTORC1 phosphorylation of S6K-1 (threonine-389) and increased phospho-AKT (serine-473). In contrast, AZD8055 treatment led to reductions in phospho-S6K-1 (threonine-389), phospho-4EBP1 (threonine-37/40, threonine-65, and threonine-70), and phospho-AKT (serine-473). Thereby, AZD8055 was a better inhibitor of mTORC1 in comparison to rapamycin. In vivo studies indicated that AZD8055 can inhibit tumor growth and AZD8055 showed promise as a therapeutic agent.

At present, there are several clinical trials focused on the examination of new agents, such as AZD-8055 (NCT00731263), OSI-027 (NCT00698243), and INK128 (NCT02142803), in a variety of human hematological malignancies and solid tumors, including breast cancer. Also some studies were conducted using GSK795 in patients with advanced platinum-resistant ovarian and showed interesting results as tumor regressions and CA125 decreases [161]. Phase I study are ongoing to evaluate the safety and toxicity profile of AZD2014 in combination with paclitaxel in patients with ovarian cancer (NCT02193633).

Despite the clinical improvements observed with the ATP-competitive inhibitor when compared to the rapalogs, the literature still acknowledges significant limitations that outcome from compensatory cellular events. With this regard, it has been found that loss of the feedback on PI3K results in compensatory activation of the MAPK/ERK cascade by mTOR downstream effectors, such as 4EBP1/elf4E, maintaining cell proliferation [162]. Furthermore, it has been shown that chronic inhibition of mTORC2 induces the activation of AKT by its phosphorylation mediated by PDK-1, even in the absence of the priming serine-473 phosphorylation. Altogether, the referred mechanisms ultimately drive the acquisition of the resistant phenotype by the cancer cells [154,163].

8. Dual mTOR/PI3K inhibitors

Scientist have explored to shed light on strategies to overcome the limitations by concomitantly targeting two molecules in the PI3K/AKT/mTOR pathway, PI3K and mTOR, whereas the
resistance mTOR inhibitors cloud arise via feedback PI3K activation. This molecular knowledge has stimulated the development of new inhibitors termed dual PI3K-mTOR inhibitors that include NVP-BEZ235, XL765, BGT226, PI-103, PF-04691502, PKI-587, and GDC-0980 [164-170]. Comparing with the other types of PI3K pathway inhibitors, dual PI3K-mTOR inhibitors have the possible advantage of inhibiting all PI3K catalytic isoforms, mTORC1 and mTORC2 [171]. Therefore, these inhibitors may effectively turn off this pathway completely and display best efficacy in feedback inhibition normally observed with mTORC1 inhibitors [172]. However, it is not clear that dual PI3K-mTOR inhibitors will be tolerable at doses that effectively inhibit all p110 isoforms and mTOR [171].

The potential clinical value of the dual PI3K/mTOR inhibitors has been demonstrated by their significant inhibition of cell growth, the induction of apoptosis and/or autophagy [173] in a variety of tumor cancer cells [174-176]. In addition, these inhibitors have shown powerful effects in xenograft models of breast cancer [177], pancreatic cancer [178], melanoma [179], multiple myeloma [180], and RCC [181].

In agreement, dual PI3K/mTOR inhibitors have entered clinical trials either monotherapy or polytherapy. A single agent includes BEZ235/NVP-BEZ235 (NCT00620594) and BGT226 (NCT00600275 and NCT00742105) in advanced solid tumors and breast cancer, GDC-0980 (NCT00854126, NCT00854152, and NCT01455493) in non-Hodgkin lymphoma and endometrial carcinoma, and PF-04691502 (NCT00927823) and GSK2126458 (NCT00972868 and NCT01248858) in solid tumors. In combination with others agents, the treatment includes XL765 (Exelixis) with erlotinib (NCT00777699), letrozole (NCT01082068), and temozolomide (NCT00704080) in non–small cell lung cancer, breast cancer, and gliomas, respectively.

Both BEZ235 and XL765 have shown good tolerability, with adverse effects including diarrhea, anorexia, and nausea [49]. Furthermore, the combined therapy using rapamycin and dual PI3K/mTOR kinase inhibitor (PI-103) has been shown to be efficacious against human ovarian cells in vivo [183].

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Trade name (company)</th>
<th>Drug target</th>
<th>Development stage</th>
<th>Tumor types</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>LY294002</td>
<td>-</td>
<td>Pan-PI3K</td>
<td>Preclinical</td>
<td>-</td>
<td>[57,58]</td>
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<tr>
<td>Wortmannin</td>
<td>-</td>
<td>Pan-PI3K</td>
<td>Preclinical</td>
<td>-</td>
<td>[57,59,60]</td>
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<td>PX-866</td>
<td>(Oncothyreon)</td>
<td>Pan-PI3K</td>
<td>Phase II</td>
<td>Solid cancers, prostate, colorectal, glioblastoma, SCCHN,[62,64] non-small cell lung cancer</td>
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<tr>
<td>NVP-BKM120</td>
<td>Buparlisib (Novartis)</td>
<td>Pan-PI3K</td>
<td>Phase III</td>
<td>Non-small cell lung cancer, prostate, breast, GBM, colon</td>
<td>[65,66]</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>Trade name (company)</td>
<td>Drug target</td>
<td>Development stage</td>
<td>Tumor types</td>
<td>Reference</td>
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<tr>
<td>XL147</td>
<td>Pilaralisib (Sanofi-Exelixis)</td>
<td>Pan-PI3K inhibitor</td>
<td>Phase II</td>
<td>Solid cancers, breast, breast, endometrial, ovarian, non-small cell lung cancer, glioblastoma, lymphoma</td>
<td>[69,72]</td>
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<td>GDC-0941</td>
<td>Pictilisib (Genentech-Roche)</td>
<td>Pan-PI3K inhibitor</td>
<td>Phase II</td>
<td>Solid cancers, breast, non-small cell lung cancer, glioblastoma, non-Hodgkin's lymphoma</td>
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<tr>
<td>GSK-2636771</td>
<td>(GlaxoSmithKline)</td>
<td>PI3Kβ inhibitor</td>
<td>Phase I</td>
<td>Solid cancers (PTEN deficient), prostate</td>
<td>[84]</td>
</tr>
<tr>
<td>NVP-BYL719</td>
<td>Alpelisib (Novartis)</td>
<td>PI3Kα inhibitor</td>
<td>Phase II</td>
<td>Advanced solid tumors, SCCHN, breast, ovarian</td>
<td>[87,90]</td>
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<tr>
<td>GDC-0032</td>
<td>Taselisib (Genentech)</td>
<td>PI3Kα inhibitor</td>
<td>Phase III</td>
<td>Solid cancers, breast, non-small cell lung cancer</td>
<td>[91,93]</td>
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<tr>
<td>CAL-101</td>
<td>Idelalisib (Gilead Sciences)</td>
<td>PI3Kδ inhibitor</td>
<td>Phase III</td>
<td>Lymphomas, multiple myelomas, chronic lymphocytic leukemia,[94,97,98] acute myeloid leukemia</td>
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<tr>
<td>KRX-0401</td>
<td>Perifosine (Pfizer)</td>
<td>AKT inhibitors</td>
<td>Phase II</td>
<td>Solid tumors, non-small cell lung cancer, colon, kidney, breast, gliomas, multiple myeloma, leukemia, lymphomas</td>
<td>[107,111,112,113]</td>
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<tr>
<td>GSK-690693</td>
<td>(GlaxoSmithKline)</td>
<td>ATP-competitive AKT inhibitor</td>
<td>Phase I</td>
<td>Hematologic malignancies</td>
<td>[114]</td>
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<tr>
<td>Rapamycin</td>
<td>Sirolimus (Wyeth)</td>
<td>Inhibits mTOR kinase by binding to FKBP12</td>
<td>Phase I</td>
<td>Glioblastoma, non-small cell lung cancer</td>
<td>[182]</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>Trade name (company)</td>
<td>Drug target</td>
<td>Development stage</td>
<td>Tumor types</td>
<td>Reference</td>
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<tr>
<td>RAD001</td>
<td>Everolimus (Novartis)</td>
<td>Inhibits mTOR kinase by binding to FKBP12</td>
<td>Phase I/II/III (FDA has approved for RCC, 2009)</td>
<td>Metastatic renal cell carcinoma, breast cancer, melanoma, ovarian cancer, neuroendocrine tumors of the pancreatic origin (PNET), endometrial carcinoma</td>
<td>[56,133,134,135,136], NCT01939418, NCT01931163</td>
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<tr>
<td>CCI-779</td>
<td>Temsirolimus (Wyeth/Pfizer)</td>
<td>Inhibits mTOR kinase by binding to FKBP12</td>
<td>Phase I/II/III (FDA and European Medicine Agency have approved for RCC, 2007)</td>
<td>Non-small cell lung cancer; advanced solid tumors, metastatic renal cell carcinoma, hepatocellular carcinoma, cervical cancer, clear cell adenocarcinoma</td>
<td>[138,139,141]</td>
</tr>
<tr>
<td>MK-8669/AP23573</td>
<td>Ridaforolimus</td>
<td>Inhibits mTOR kinase by binding to FKBP12</td>
<td>Phase I/II/III</td>
<td>Sarcoma, bone, endometrial cancer</td>
<td>[144,145]</td>
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<tr>
<td>PP242</td>
<td>ATP competitive inhibitor of mTOR and in vitro Studies</td>
<td>Colon cancer, acute myeloid leukemia</td>
<td>[156]</td>
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<tr>
<td>Torin2</td>
<td>ATP competitive inhibitor of mTOR and in vitro Studies</td>
<td>Lung cancer</td>
<td>[159]</td>
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<tr>
<td>AZD8055</td>
<td>ATP competitive inhibitor of mTOR</td>
<td>Advanced solid tumors, lymphoma</td>
<td>[183,184]</td>
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<td>OSI-027</td>
<td>ATP competitive inhibitor of mTOR</td>
<td>Advanced solid tumors, lymphoma</td>
<td>[185]</td>
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<td>INK128</td>
<td>ATP competitive inhibitor of mTOR</td>
<td>Glioblastoma, advanced solid tumors</td>
<td>NCT02142803</td>
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<td>GSK795</td>
<td>ATP competitive inhibitor of mTOR</td>
<td>Advanced solid tumors</td>
<td>[134]</td>
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<td>NVP-BEZ235</td>
<td>(Novartis) Dual mTOR/PI3K</td>
<td>Phase I/II</td>
<td>Advanced solid tumors, breast cancer, prostate cancer</td>
<td>[94], NCT00620594</td>
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<td>Inhibitor</td>
<td>Trade name (company)</td>
<td>Drug target</td>
<td>Development stage</td>
<td>Tumor types</td>
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<tr>
<td>BGT226</td>
<td>(Novartis)</td>
<td>Dual mTOR/PI3K</td>
<td>Phase I</td>
<td>Advanced solid tumors, breast cancer</td>
<td>[169], NCT00600275, NCT00742105</td>
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<tr>
<td>GDC-0980</td>
<td>(Genentech)</td>
<td>Dual mTOR/PI3K</td>
<td>Phase I/II</td>
<td>Non-Hodgkin lymphoma, endometriose</td>
<td>NCT00854126, NCT00854152, NCT01455493</td>
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<tr>
<td>PF-04691502</td>
<td>(Pfizer)</td>
<td>Dual mTOR/PI3K</td>
<td>Phase I</td>
<td>Advanced solid tumors</td>
<td>NCT00927823</td>
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<td>GSK2126458</td>
<td>(GlaxoSmithKline)</td>
<td>Dual mTOR/PI3K</td>
<td>Phase I</td>
<td>Advanced solid tumors</td>
<td>NCT00972686, NCT01248858</td>
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<tr>
<td>XL765</td>
<td>(Exelixis)</td>
<td>Dual mTOR/PI3K</td>
<td>Phase I/II</td>
<td>Non-small cell lung cancer, breast cancer, gliomas</td>
<td>NCT00777699, NCT1082068, NCT00704080</td>
</tr>
</tbody>
</table>

Table 2. Overview of PI3K/AKT/mTOR pathway inhibitors.

9. Conclusions/future perspectives

Advances in molecular research have resulted in an improved understanding of cancer biology. There is strong preclinical rationale to support the continued development of PI3K/AKT/mTOR inhibitors, especially in some genetically defined cancer subtypes that may be the most sensitive to single-agent PI3K pathway inhibitors. These include cancers with PIK3CA activating mutations, mutations in PIK3R (p85 subunit), mutations or amplifications in one of the AKT isoforms or loss of PTEN. However, rational clinical trials design with a focus in identifying a patient population most likely to benefit from this strategy is imperative to the success of single-agent therapeutics.

The combination of PI3K/AKT/mTOR inhibitors with cytotoxic chemotherapy and other biological agents such as anti-HER2 compounds, EGFR inhibitors, and antiangiogenic agents may optimize the action of those agents in different pathways that control protein translation, cell growth, migration, metastasis, and angiogenesis. The successful development of the combinations will require determining the duration, doses, and schedules of targeted therapy and how to best incorporate it into standard treatment protocols. Several clinical trials are underway to prove the clinical use of the PI3K/AKT/mTOR inhibitors. The druggability of the components of the PI3K/AKT/mTOR signaling cascade, in addition to the enlightenment of the mutational landscape of human cancers, which points to the high frequency of genetic alterations and anomalous activation of the pathway, strongly suggests that targeting its elements might represent a useful treatment strategy in the fight against cancer.
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