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Alterations and Molecular Targeting of the GSK-3 Regulator, PI3K, in Head and Neck Cancer

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Abstract

Head and neck squamous cell carcinoma (HNSCC) is a highly morbid, genetically unstable disease derived from the mucoepithelium of the upper aerodigestive tract. Recent characterization of this disease has implicated the PI3K-Akt-mTOR pathway as one of the most frequently dysregulated pathways. As such, there are several classes of PI3K inhibitors currently undergoing clinical trials. In this article, we review the PI3K pathway, mutations of this pathway in HNSCC, drugs that target PI3K, the impact of these agents on the PI3K and GSK-3 signaling axes, ongoing clinical trials evaluating PI3K inhibitors, and the challenges of using these drugs in the clinic.

Keywords

GSK-3; PI3K; PIK3CA; head and neck squamous cell carcinoma; HNSCC

1 Introduction

Glycogen synthase kinase-3 (GSK-3) is a ubiquitous kinase with pleiotropic roles. It is constitutively expressed in all mammalian tissues and over 100 distinct substrates have been elucidated [1,2]. First identified in 1980 in the context of insulin signaling, GSK-3 has since been shown to be involved in numerous signaling pathways, such as those mediated by Notch, Wnt, and phosphinositide 3-kinase (PI3K) [3-6]. Of particular interest is the interaction of GSK-3 with the PI3K signaling pathway, a well-characterized and often implicated oncogenic pathway in nearly all solid cancers [7].

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Competing interests

JRG and DEJ are co-inventors of cyclic STAT3 decoy and have financial interests in STAT3 Therapeutics, Inc. STAT3 Therapeutics, Inc. holds an interest in a cyclic STAT3 decoy oligonucleotide. The remaining authors declare no conflicts.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Signaling via the PI3K pathway is initiated by the activation of plasma membrane receptor tyrosine kinases (RTKs) following binding of growth factor or cytokine ligands such as epidermal growth factor (EGF) or insulin (Figure 1) [8,9]. Ligand binding induces autophosphorylation of tyrosine residues in the receptor cytoplasmic domain, which then serve as binding sites for PI3K, leading to activation of the PI3K enzyme. Activation of PI3K eventually leads to phosphorylation and activation of the serine/threonine kinase Akt [10]. Akt can phosphorylate a variety of proteins, including the amino-terminal serine residue in the autoinhibitory domain of GSK-3 [11]. Phosphorylation at this site leads to inhibition of GSK-3 activity. Normally, GSK-3 acts to maintain the inactive states of key cell cycle regulators, such as cyclin D and c-Myc [1,12]. Hence, Akt-mediated phosphorylation of GSK-3 serves to activate proteins that are normally inhibited by GSK-3 (Figure 1) [11]. Given this close interaction between the PI3K and GSK-3 pathways, a thorough understanding of the regulation of GSK-3-mediated signaling requires knowledge of the PI3K signaling pathway and the impact of PI3K genetic alterations that commonly occur in human cancers. This review will focus on alterations in the PI3K pathway in the setting of HNSCC.

2 Head and Neck Squamous Cell Carcinoma

HNSCC is the sixth most common type of cancer in the world with over 650,000 new cases diagnosed every year [13,14]. Known risk factors include tobacco or alcohol consumption, and human papilloma virus (HPV) infection [15]. Though advancements in treatment – typically a combination of surgery, radiotherapy, and chemotherapy – have been made, the 5-year survival rate for HNSCC has remained stalled at approximately 50% for the past 40 years [16]. In the face of this dismal statistic, interest has grown in developing precision medicine approaches and small molecule targeting agents for this disease. In order to develop such drugs, a greater understanding of the genetic changes and molecular mechanisms that drive HNSCC oncogenesis is needed.

The last decade has seen dramatic advancements made in profiling the genomic landscape of HNSCC. In 2015, The Cancer Genome Atlas (TCGA) reported a comprehensive genomic characterization of 279 HNSCC samples that has since been updated to include 530 samples [17-19]. HNSCC was found to have high genomic instability, as demonstrated by a reported mean of 141 copy number alterations (CNAs) and 62 structural aberrations (chromosomal fusions). Notably, the most commonly altered oncogene in HNSCC was found to be *PIK3CA*, which codes for the p110α catalytic subunit of the PI3K enzyme. Genetic alteration of *PIK3CA*, including mutation and/or amplification, was found in 34% of HPV-negative HNSCC tumors, and in 56% of HPV-positive tumors [17,20]. This review will focus on the oncogenic role of *PIK3CA* in HNSCC, agents and strategies that have been developed to target the proteins encoded by wild-type or mutant *PIK3CA*, and ongoing clinical trials involving these agents.

3.1 Classes of PI3K Enzymes

The PI3K enzymes comprise a family of intracellular phosphatidylinositol (PtdIns) kinases that are categorized into three classes based on structure, function, and substrate preference.

Class I PI3Ks are heterodimers that consist of a regulatory subunit and a catalytic subunit and can be further categorized into class IA (PI3Kα, PI3Kβ, PI3Kδ) or IB (PI3Kγ), based on catalytic subunit subtype [21]. In class IA, there are three isoforms of the catalytic subunit – p110α, p110β, and p110γ – respectively encoded by *PIK3CA*, *PIK3CB* and *P1K3CD* and five variants of the regulatory subunit – p85α, p55α, p50α, p85β, and p55δ. Class IB consists of the catalytic subunit, p110γ, encoded by *PIK3CG* and a regulatory subunit – p101 or p76.

Upon activation, class I PI3Ks act at the cellular membrane where they phosphorylate phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4,5-bisphosphate (PIP_3) [22]. Once PIP_3 has locally accumulated at the membrane, the phosphorylated inositol head acts as an anchoring site for proteins that contain pleckstrin homology (PH) domains, leading to activation of these secondary signaling proteins [23] [24]. Among the PH domain-containing effector proteins that become activated are Akt, 3-phosphoinositide-dependent protein kinase 1 (PDK1), and guanosine diphosphate (GDP)-GTP exchange factors for Rac [24-26]. Once activated, these signaling proteins initiate various cellular pathways involved in cell survival, cell cycle, metabolism, and migration, among others.

Class II PI3Ks are monomers of catalytic isoforms and lack regulatory subunits [23]. Though less understood than the class I enzymes, they are thought to be involved in angiogenesis, clathrin-mediated endocytosis, and insulin stimulation [27-31]. Class III PI3Ks are heterodimers of a catalytic and regulatory subunit and are known to convert phosphatidylinositol (PI) to phosphatidylinositol 3-phosphate (PI3P). The Class III PI3Ks are thought to be involved in autophagy induction [32]. This review will focus primarily on the Class IA PI3K containing the p110α catalytic subunit encoded by *PIK3CA*.

3.2 Mutations in PI3K in Head and Neck Cancer

Since publication of the genomic profile of HNSCC tumors by the TCGA in 2015, further studies have corroborated the high frequency of alterations in components of the PI3K signaling pathway in head and neck cancer. In a whole-exome sequencing analysis of 151 HNSCC tumors, the PI3K pathway was found to be the most commonly altered mitogenic pathway (30.5% of tumors) compared to the JAK/STAT pathway (9.3%) and MAPK pathway (8.0%) [20]. Among genes encoding PI3K pathway components, *PIK3CA* was found to be the most frequently mutated (12.6% of tumors), followed by *PIK3CG* and *PTEN* [20]. Additional studies reported similar findings of 7.4%, 10.5%, and 10.4% for *PIK3CA* mutation rates in HNSCC [33-35].

Among the *PIK3CA* mutations observed in HNSCC, 63% occur at three “hotspot” locations in the p110α subunit – E542, E545, and H1047 [18,19]. Collectively, mutations at these three sites are referred to as canonical *PIK3CA* mutations. E542 and E545 are located in the helical domain of p110α and mutations at these sites are known to confer PI3K hyperactivity by disrupting the regulatory impact of p85 on the p110α catalytic subunit [36]. H1047 is located in the p110α kinase domain and mutation at this site is thought to cause a conformational change in the kinase, granting the kinase easier access to its phospholipid substrate [37]. The frequency of *PIK3CA* canonical mutations may also vary by HPV status.

A retrospective study of 87 oropharyngeal cancer samples found only 4 of 41 (9.76%) HPV-negative tumors harbored hotspot mutations versus 13 of 46 (28.2%) HPV-positive tumors [38].

Mutational activation of p110α leads to stimulation of the PI3K-Akt-mTOR signaling pathway, which regulates multiple aspects of cell growth and survival (Figure 1). Notably, Akt mediates phosphorylation of mTOR, a key mediator of cellular metabolism [39]. Akt can also inactivate TSC1-TSC2, thereby promoting Rheb GTPase to activate mTORCl [40]. mTORC1 subsequently inactivates the translational inhibitor 4E-BP1 and activates S6 kinase (S6K), promoting protein synthesis [41]. In addition to effects on cell growth and metabolism, activation of the PI3K-Akt-mTOR pathway has been shown to contribute to regulation of apoptosis and angiogenesis [42-44]. Hence, it is perhaps not surprising that activating mutations in the *PIK3CA* gene form the basis for aberrant tumor growth and metastasis in a variety of cancers.

3.3 GSK-3 in Head and Neck Cancer

While the role of PI3K in head and neck cancer oncogenesis has been well studied, the precise role of GSK-3, downstream of PI3K, is less clear. Confusion surrounding the oncogenic potential of GSK-3 exists for other cancers, as it has been shown to demonstrate both pro- and anti-tumor activity [45]. These conflicting properties are also found in head and neck cancer.

Prior experiments have shown that treatment of four HNSCC cell lines with the GSK3a/p inhibitor, SB 216763, resulted in decreased cell viability and migration [46]. Similar decreases in cell proliferation and migration with GSK-3 β inhibition were found in esophageal squamous cell carcinoma (ESCC) lines; conversely, increased GSK-3β pathway activation in nasopharyngeal carcinoma cell lines resulted in increased proliferation and invasion [47,48]. Clinical samples from HNSCC patients have further supported a potential oncogenic role for GSK-3. Seventy-three percent (11/15) of HNSCC patient samples exhibited aberrant nuclear expression of GSK-3P, whereas all benign samples contained no nuclear GSK-3β [49]. GSK-3β levels were also found to be significantly increased in HNSCC patients presenting with cervical lymph node metastasis, supporting *in vitro* data implicating its role in enhancing cell migration and invasion [50].

Interestingly, GSK-3 also plays a key cancer protective role through cell cycle regulation. As mentioned, GSK-3 inhibits c-Myc, a major oncogenic transcription factor, and is critical in the phosphorylation and subsequent degradation of cyclin D1 and cyclin E [51]. In murine models, deletion of transcription factor Grhl3 in oral epithelium resulted in loss of GSK3β expression independent of PI3K signaling; subsequent accumulation of c-Myc was followed by development of aggressive oral tumors [52]. GSK-3 is also crucial in keeping epithelial-to-mesenchymal transitions (EMT) in check. In ESCC lines, GSK-3β induction resulted in loss of the mesenchymal marker, Snail, and induction of E-cadherin [53]. In oral squamous cell carcinoma lines, Pramanik *et al.* found that inactivation of GSK-3 signaling was strongly associated with increased matrix metalloproteinase-9, an enzyme that digests extracellular matrix [54]. To date, the role of GSK-3 in HNSCC is not yet fully elucidated; further work

in characterizing its oncogenic properties are necessary before it can be pursued as a potential target in HNSCC therapy.

4.1 PI3K Inhibitors

Because this review focuses on the oncogenic effects of *PIK3CA,* this section will review inhibitors that target the PI3Ka enzyme. In presenting the inhibitors below, we begin with PI3K class IA-selective inhibitors, followed by pan-class I inhibitors, and concluding with PI3K/mTOR inhibitors. The structures of the PI3K inhibitors described below are shown in Figure 2 and summaries of clinical trials involving PI3K inhibitors are provided in Tables 1 and 2.

4.1.1 Alpelisib (BYL719)—Alpelisib selectively inhibits pi 10a, the product of *PIK3CA.* Positive association between the efficacy of alpelisib and *PIK3CA* status has been most strongly demonstrated in breast cancer. In a recent Phase III trial, 572 breast cancer patients were randomized to receive alpelisib plus fulvestrant or placebo plus fulvestrant. In a sub-cohort of 341 patients with confirmed *PIK3CA*-mutated cancer, progression-free survival (PFS) was significantly improved compared to patients with wild-type *PIK3CA* cancer (11 months vs 5.7 months) as well as overall response (26.6% vs 12.8%) [55]. Subsequently, in May of 2019, the FDA approved alpelisib in combination with fulvestrant to treat advanced or metastatic breast cancers that express hormone receptor and harbor mutations in *PIK3CA* [56].

Preclinical *in vitro* and *in vivo* data suggest that alpelisib is more active in cells harboring *PIK3CA* mutations. In a pharmacological profiling screen of a large panel of cancer cell lines, alpelisib sensitivity was found to be associated with *PIK3CA* mutation, amplification, and copy number gain [57]. Similar results were observed in *in vivo* mouse models [58]. When six mutant human HNSCC cell lines - two mutant *PIK3CA,* four wild-type *PIK3CA* – were treated with alpelisib *in vitro*, *PIK3CA*-mutant cell lines demonstrated greater inhibition of growth than wild-type cell lines [59].

Clinical trials of alpelisib in head and neck cancer are ongoing. In 2014, a Phase Ib/II study of alpelisib in combination with cetuximab in 32 recurrent or metastatic HNSCC patients found that the combination of BYL719 and cetuximab was well tolerated [60]. In a single-institution study of alpelisib in combination with cetuximab and radiation in stage III/IVb HNSCC, 11 patients demonstrated complete response based on posttreatment imaging. Eight of the 11 patients received mutational analysis; one patient was found to have a *PIK3CA* activating mutation and showed rapid response on serial intratreatment MRI scans, suggesting BYL719 may enhance radiosensitivity, particularly in the setting of *PIK3CA* mutation [61].

While no clinical trials in head and neck cancer patients based on *PIK3CA* status have been completed, the TRanslational biomarker driven UMbrella Project for Head and neck (TRIUMPH) trial, which will screen and assign head and neck cancer patients to one of several molecularly defined subtrials with matched targeted agents, including alpelisib, is currently in progress [62].

4.1.2 Buparlisib (BKM120)—Buparlisib is a class I pan-PI3K inhibitor that targets the ATP binding site in the kinase domain of all four p110 isoforms [63]. Buparlisib is absorbed rapidly following oral administration and demonstrates dose-dependent accumulation in serum [63]. Preclinical data demonstrated anti-proliferative and anti-tumor activity, as well as anti-angiogenic activity in glioma cell lines and anti-microtubular activity in melanoma cell lines [64,65]. In two HNSCC cell lines, buparlisib enhanced sensitivity to radiotherapy [66].

An open-label, Phase I clinical study of buparlisib in advanced solid tumors was completed in Japan in 2014, and found the maximum daily dose to be 100 mg. Of the 15 patients included in the study, two were head and neck cancer patients [67]. In 2017, a pilot dose-escalation study investigating the efficacy of buparlisib plus cetuximab was conducted in recurrent or metastatic head and neck cancer patients. While treatment was well tolerated with no grade 4–5 adverse effects, clinical efficacy was limited [68]. A Phase Ib dose expansion study then evaluated buparlisib in combination with high-dose carboplatin and paclitaxel in patients with advanced solid tumors versus buparlisib in combination with standard dose carboplatin and paclitaxel in patients selected for PTEN loss, a negative regulator of PI3K. There was no significant difference in clinical response between those with PTEN loss and those without [69]. The BERIL-I Phase II trial in 2017 studied the efficacy and safety of buparlisib plus paclitaxel in recurrent or metastatic head and neck cancer patients previously treated with platinum. Results showed increased PFS from 3–5 months to 4–6 months (p=0.011). Similar proportions in buparlisib and placebo groups harbored *PIK3CA* mutations (11% vs 13%) and loss of PTEN expression (1% vs 1%); authors did not report on the utility of *PIK3CA* mutation as a predictive biomarker of buparlisib efficacy [70].

More recently, clinical trials have begun to stratify head and neck cancer patients based on *PIK3CA* and PTEN status. A Phase II multi-center clinical trial in France treated 58 head and neck cancer patients who had failed platinum and cetuximab-based therapy with buparlisib monotherapy based on the status of canonical *PIK3CA* mutations. Results from the trial showed no difference in the primary endpoint of disease control rate at two months between those harboring canonical *PIK3CA* mutations and those with wild-type *PIK3CA* (36.4% vs 38.9%) [71].

4.1.3 PX-866—PX-866 was developed in 2004 as an analog to wortmannin, a potent, irreversible class I pan-isoform PI3K inhibitor, that is limited to use as a tool compound due to liver toxicity [72,73]. Like wortmannin, after oral administration, PX-866 inhibits PI3K by covalently binding to a critical lysine residue in the catalytic domain. Preclinical data was initially promising. *In vitro* studies demonstrated the ability of PX-866 to inhibit anchorage-independent colony formation and cell migration in glioblastoma, prostate, breast, and colon cancer cell lines [73]. Phase I clinical studies also demonstrated a favorable side effect profile [74].

However, Phase II studies of PX-866 have shown limited clinical efficacy. In 2015, 85 patients with locally advanced, recurrent, or metastatic HNSCC who had failed at least one, and no more than two, systemic treatment regimens were randomized to receive docetaxel

either with or without PX-866. There was no significant difference in response rate (RR), PFS, and overall survival (OS) between treatment arms. Four of 49 tumors that were sequenced were found to harbor *PIK3CA* mutations. Due to its rarity, no association could be found between *PIK3CA* mutational status and clinical response [75]. In another Phase II study, 83 HNSCC patients were assigned to cetuximab either with or without PX-866. Again, no significant difference was found in RR, PFS, and OS between the two groups. Of the 46 tumors that were sequenced, eight were found to contain *PIK3CA* exon mutations; none of the eight patients showed a treatment response [74]. PX-866 is no longer being developed for HNSCC.

4.1.4 Copanlisib (BAY 80-6946)—Copanlisib is an intravenous class I pan-isoform PI3K inhibitor with preference towards a and y isoforms. In 2017, this drug was FDA-approved for adult patients with follicular lymphoma who have failed at least two therapy regimens [76]. In a profiling screen, copanlisib potently inhibited cell proliferation in multiple hematological, breast, and endometrial cancer cell lines [77]. *In vitro* studies showed that copanlisib halts cell cycle progression and induces apoptosis in multiple myeloma cells and *in vivo* studies demonstrated its anti-proliferative effects in murine xenograft models [78].

In a clinical trial of copanlisib, 57 patients (9 with non-Hodgkin's lymphoma, 48 with solid tumors) were treated in a dose-escalation study. Copanlisib showed particular efficacy in hematological malignancies (RR 67%) with less activity in solid tumors (RR 6%). *PIK3CA* mutational status was determined via sequencing of circulating tumor DNA or tumor tissue in all 57 patients. 12 were found to harbor *PIK3CA* mutations while 45 contained wild-type *PIK3CA*. Of the three solid tumor patients who had treatment response, one patient (endometrial cancer) showed complete response and was found to harbor a *PIK3CA* mutation [79]. An ongoing study testing copanlisib plus cetuximab in patients with recurrent or metastatic HNSCC that harbor *PIK3CA* mutations, amplification, or PTEN loss is currently active (NCT02822482).

4.1.5 SF1126—2-(4-morpholinyl)-8-phenyl-4H-lbenzopyran-4-one (LY294002) is a dual PI3K and mTOR inhibitor, but is not a viable clinical drug due to its poor solubility and short half- life [80]. In 2008, SF1126 was developed as a more pharmacokinetically favorable, water-soluble prodrug of LY294002. SF1126, which is intravenously administered, contains an RGDS peptide that targets integrins (αvβ3/α5β1) expressed on endothelial and tumor cells, allowing for enhanced tumor uptake. Preclinical data shows anti-tumor and anti-angiogenic effects in preclinical *in vivo* models of glioma and breast cancer [81]. SF1126 was also shown to inhibit cell proliferation *in vitro* in breast, renal, and colon cancer cell lines [80,82].

In clinical trials, SF1126 treatment resulted in stable disease (as best response) in 19 of 33 (58%) patients with advanced B cell malignancies or solid tumors, and demonstrated a favorable safety profile [83]. One ongoing clinical trial is evaluating the efficacy of SF1126 in combination with nivolumab in hepatocellular carcinoma (NCT03059147). A Phase II study investigating SF1126 in recurrent or refractory HNSCC with *PIK3CA* mutations was initiated in 2015, but due to slow recruitment, was terminated in 2018 (NCT02644122).

4.1.6 Dactolisib (BEZ-235)—Dactolisib, an oral dual class I PI3K and mTOR inhibitor, competitively binds to the ATP cleft of these enzymes. *In vitro*, dactolisib induces G_1 cell cycle arrest in prostate cancer and glioblastoma cell lines. Treatment with dactolisib also demonstrated dose-dependent anti-tumor or activity against PC3M xenograft tumors [84]. Interestingly, HNSCC SCC25 cells engineered to express the H1047R p110α mutation showed increased sensitivity to dactolisib whereas cell lines expressing the E545K mutation only demonstrated modestly increased sensitivity relative to parental SCC25 cells, without a clear understanding of how each mutation mediated drug response [85].

Clinical trials of dactolisib, however, have been less than promising. A Phase Ib study in patients with advanced renal cell carcinoma was terminated prematurely due to serious adverse effects. The authors reported grade 3-4 adverse effects in 50% of their patients without objective responses. Most common dose-limiting toxicities included fatigue, rash, nausea and vomiting, diarrhea, and mucositis [86]. Additional studies reported similar limitations due to toxicities. In a Phase II trial of dactolisib in patients with pancreatic neuroendocrine tumor patients, treatment was discontinued in 39% of patients due to poor tolerance and grade 3-4 adverse effects were reported in 84% of patients [87]. One case of HNSCC was included in a Phase Ib study for advanced solid tumors; however, dactolisib again displayed poor tolerability and modest efficacy and is no longer in development [88].

4.1.7 Gedatolisib (PF-05212384)—Gedatolisib is an intravenous dual PI3K and mTOR inhibitor. Synthesized in 2010, gedatolisib was first shown to decrease cell survival and proliferation in breast and prostate cancer cell lines and to demonstrate anti-tumor efficacy against breast cancer xenograft tumors [89]. In HNSCC cell lines resistant to epidermal growth factor receptor (EGFR) inhibitors, treatment with gedatolisib enhanced sensitivity to cetuximab, resulting in increased apoptosis [90]. In mice harboring EGFR inhibitor-resistant esophageal tumors, treatment with gedatolisib and cetuximab resulted in tumor growth inhibition and prolonged survival of the mice [90]. Additionally, pre-treatment of HNSCC cell lines with gedatolisib has been shown to result in significant sensitization to radiotherapy, with minimal radiosensitization in normal fibroblasts [91].

In a Phase I study, gedatolisib monotherapy exhibited manageable safety profiles and good anti-tumor efficacy (part 2 of study) in 78 patients with advanced solid tumors, including two cases of salivary gland cancer. There was no association between *PIK3CA* mutational status and treatment response, though the authors note this is likely due to the low number of *PIK3CA* mutant tumors (n=4) [92]. A Phase Ib study to investigate gedatolisib in combination with paclitaxel and carboplatin in patients with advanced head and neck, breast, ovarian or endometrial, or non-small cell and small cell lung cancers was recently completed (NCT02069158). Another clinical study incorporating the CDK4/6 inhibitor palbociclib in combination with gedatolisib in advanced head and neck cancer and other solid tumors is actively recruiting (NCT03065062).

4.2 Limitations of PI3K inhibitors in the clinic

4.2.1 Toxicities—The breadth of functions that class I PI3K enzymes perform is reflected in the wide array of toxicities observed with pan-PI3K inhibitors. The most

commonly reported adverse effects include nausea and vomiting, diarrhea, fatigue, rash, anorexia, and elevated transaminase enzymes [93]. The four isoforms of PI3K p110 subunit (α, β, γ, δ) demonstrate tissue-specific expression and perform distinct functions. Thus, the isoform that is inhibited informs the toxicities observed for its unique inhibitor. We will focus on hyperglycemia, the adverse effect that is common to PI3Kα inhibitors and impinges on GSK-3 signaling.

PI3Kα is expressed ubiquitously and involved in insulin signaling and metabolic regulation. After insulin binds to the insulin receptor (IR), the PI3K pathway becomes activated when IRS1/2 binds to the regulatory subunit of PI3K, p85. Akt is subsequently activated and phosphorylates GSK-3, which increases glycogen synthesis through GYS1 (Figure 1). Disruption of this pathway, thereby, causes hyperglycemia [94].

Hyperglycemia is largely specific for inhibitors of the PI3Kα isoform. In an *in vivo* study, deletion of p110α expression in the liver of mice resulted in significant moderation of insulin signaling, as well as loss of PI3K pathway products. These defects could not be rescued by overexpression of p110β [95]. In a separate study, mice with muscle-specific alterations in PI3Kα signaling demonstrated whole-body glucose intolerance [96]. These results have been further corroborated in clinical studies. PI3K inhibitors with higher potency for PI3Kα manifest higher incidences of hyperglycemia [93]. For instance, the half maximal inhibitory concentration (IC_{50}) for PI3Kα of copanlisib is 0.5 nmol/L whereas buparlisib has an IC_{50} of 52 nmol/L [97]. As such, 63% of subjects in a Phase I trial for copanlisib experienced hyperglycemia (30% Grade 3-4), whereas only 6.7% of subjects in Phase I trials for buparlisib reported hyperglycemia (100% Grade 3-4) [67,79].

The use of PI3K inhibitors as a whole has been limited by intolerable toxicities, resulting in suboptimal dosing and dosing schedules. Thus, studies have begun to explore intermittent dosing schedules to limit adverse effects. For instance, intermittent dosing of buparlisib (5 of 7 days) in breast cancer patients compared to daily dosing resulted in lower frequency of adverse effects with no significant difference in clinical benefit [98]. Further trials are needed to determine optimal dosing schedules that minimize toxicities without compromising efficacy.

4.2.2 Mechanisms of resistance—While toxicities have limited the use of PI3K inhibitors, resistance has also proven to be a major obstacle to their application in the clinic. The complexities of the PI3K pathway and its extensive interactions with other signaling networks have made it difficult to elucidate consistent mechanisms of resistance.

Some possible mechanisms involve rebound activation from loss of negative feedback loops in the PI3K pathway. For instance, Akt phosphorylates FOXO1 proteins. Once phosphorylated, these proteins are unable to upregulate PI3K-activating RTKs – including EGFR, IR, and HER3 – thereby repressing the PI3K pathway in a negative feedback manner [99,100]. Akt also activates mTORC1 and S6K, which then suppress IRS1 expression as another regulatory mechanism [101]. When PI3K inhibitors are introduced into this complex system, negative feedback from FOXO proteins, TORC1, and S6K is lost, resulting in unchecked RTK activation and IRS1 expression.

Other resistance mechanisms involve aberrant upregulation or activation of AXL, RAS, or MAPK. For instance, in head and neck and esophageal squamous cell carcinomas resistant to PI3Kα inhibition, the receptor tyrosine kinase AXL promotes resistance by activating PLCγ and PKC, resulting in PI3K-independent mTOR activation [102]. Repression of AXL was found to restore sensitivity to PI3Kα inhibition [103]. Compensatory activation of complementary pathways closely interconnected with the PI3K pathway also contributes to inhibitor resistance. For example, HRAS mutant HNSCC cell lines that were resistant to alpelisib were shown to have reduced Akt phosphorylation; however, expression of downstream proteins, such as phosphorylated S6, was maintained. Additionally, ERK-TSC2 signaling through the MAPK pathway can activate mTOR independent of PI3K [104]. In another study, PI3K inhibition induced upregulation of HER3 receptors in HPV-positive HNSCC cell lines. HER3 overexpression subsequently increased expression of E6 and E7, which in turn promoted hyperactivation the PI3K pathway. HER3 suppression was able to reduce E6 and E7 levels and restore PI3K inhibitor sensitivity [105].

5 Conclusion

Overall, the success of PI3K inhibitors has been largely limited by their modest efficacy in clinical trials, toxicities, and acquired resistance. One reason for these disappointing results is the current lack of biomarkers that can be used to reliably predict sensitivity to PI3K inhibitors. Several candidates have been evaluated as possible biomarkers, of which *PIK3CA* mutation has proven to be the most consistent in preclinical experiments and clinical trials. However, published trials have been constrained by small numbers of patients with positive biomarkers and thus lack the power necessary to definitively answer whether *PIK3CA* mutation is a useful predictor of inhibitor sensitivity. Of the 14 ongoing clinical trials evaluating PI3Kα inhibitors in head and neck cancer, 5 involve restricting patients to those with positive biomarkers, including *PIK3CA* mutation, PTEN loss, and alterations in PI3K pathway (Tables 1 and 2). The results from these trials will perhaps shed light on the utility of these biomarkers in predicting the efficacy of PI3Kα inhibitors in patients with head and neck cancer.

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References

[1]. Yao HB, Shaw PC, Wong CC, Wan DCC, Expression of glycogen synthase kinase-3 isoforms in mouse tissues and their transcription in the brain, J. Chem. Neuroanat 23 (2002) 291–297. 10.1016/S0891-0618(02)00014-5. [PubMed: 12048112]

[2]. Sutherland C, What are the bona fide GSK3 substrates?, Int. J. Alzheimers. Dis. 2011 (2011). 10.4061/2011/505607.

[3]. Voskas D, Ling LS, Woodgett JR, Does GSK-3 provide a shortcut for PI3K activation of Wnt signalling?, F1000 Biol. Rep 2 (2010) 2–5. 10.3410/B2-82. [PubMed: 20948813]

[4]. Parr BA, McMahon AP, Wnt genes and vertebrate development, Curr. Opin. Genet. Dev 4 (1994) 523–528. 10.1016/0959-437X(94)90067-D. [PubMed: 7950319]

[5]. Cantley LC, The phosphoinositide 3-kinase pathway, Science (80-.). 296 (2002) 1655–1657. 10.1126/science.296.5573.1655.

[6]. Embi P, Rylatt Noor., Cohen Dennis B., Glycogen synthase kinase-3 from rabbit skeletal muscle. Separation from cyclic-AMP-dependent protein kinase and phosphorylase kinase., Eur. J. Biochem 107 (1980) 519–527. 10.1080/15225437.1889.10502791. [PubMed: 6249596]

[7]. Liu X, Xu Y, Zhou Q, Chen M, Zhang Y, Liang H, Zhao J, Zhong W, Wang M, PI3K in cancer: Its structure, activation modes and role in shaping tumor microenvironment, Futur. Oncol 14 (2018) 665–674. 10.2217/fon-2017-0588.

[8]. Zheng Y, Peng M, Wang Z, Asara JM, Tyner AL, Protein Tyrosine Kinase 6 Directly Phosphorylates AKT and Promotes AKT Activation in Response to Epidermal Growth Factor, Mol. Cell. Biol 30 (2010) 4280–4292. 10.1128/mcb.00024-10. [PubMed: 20606012]

[9]. Martini M, De Santis MC, Braccini L, Gulluni F, Hirsch E, PI3K/AKT signaling pathway and cancer: An updated review, Ann. Med 46 (2014) 372–383. 10.3109/07853890.2014.912836. [PubMed: 24897931]

[10]. Vanhaesebroeck B, Stephens L, Hawkins P, PI3K signalling: The path to discovery and understanding, Nat. Rev. Mol. Cell Biol 13 (2012) 195–203. 10.1038/nrm3290. [PubMed: 22358332]

[11]. Hermida MA, Dinesh Kumar J, Leslie NR, GSK3 and its interactions with the PI3K/AKT/mTOR signalling network, Adv. Biol. Regul 65 (2017) 5–15. 10.1016/j.jbior.2017.06.003. [PubMed: 28712664]

[12]. Patel P, Woodgett JR, Glycogen Synthase Kinase 3: A Kinase for All Pathways?, 1st ed., Elsevier Inc., 2017 10.1016/bs.ctdb.2016.11.011.

[13]. Marur S, Forastiere AA, Head and neck cancer: Changing epidemiology, diagnosis, and treatment, Mayo Clin. Proc 83 (2008) 489–501. 10.4065/83.4.489. [PubMed: 18380996]

[14]. Torre A, Bray Linsey A., Siegel Freddie.. Ferlay Rebecca L., Lortet-Tieulent Jacques., Jemal Joannie., Global Cancer Statistics, CA Cancer J Clin. 65 (2015) 87–108. 10.3322/caac.21262. [PubMed: 25651787]

[15]. Kreimer AR, Clifford GM, Boyle P, Franceschi S, Human papillomavirus types in head and neck squamous cell carcinomas worldwide: A systemic review, Cancer Epidemiol. Biomarkers Prev 14 (2005) 467–475. 10.1158/1055-9965.EPI-04-0551. [PubMed: 15734974]

[16]. Siegel A, Miller Rebecca L., Jemal Kimberly D., Cancer Statistics, 2017, CA Cancer J Clin. 67 (2017) 7–30. 10.3322/caac.21387. [PubMed: 28055103]

[17]. Lawrence MS, Sougnez C, Lichtenstein L, Cibulskis K, Lander E, Gabriel SB, Getz G, Ally A, Balasundaram M, Birol I, Bowlby R, Brooks D, Butterfield YSN, Carlsen R, Cheng D, Chu A, Dhalla N, Guin R, Holt RA, Jones SJM, Lee D, Li HI, Marra MA, Mayo M, Moore RA, Mungall AJ, Robertson AG, Schein JE, Sipahimalani P, Tam A, Thiessen N, Wong T, Protopopov A, Santoso N, Lee S, Parfenov M, Zhang J, Mahadeshwar HS, Tang J, Ren X, Seth S, Haseley P, Zeng D, Yang L, Xu AW, Song X, Pantazi A, Bristow CA, Hadjipanayis A, Seidman J, Chin L, Park PJ, Kucherlapati R, Akbani R, Casasent T, Liu W, Lu Y, Mills G, Motter T, Weinstein J, Diao L, Wang J, Hong Fan Y, Liu J, Wang K, Auman JT, Balu S, Bodenheimer T, Buda E, Hayes DN, Hoadley KA, Hoyle AP, Jefferys SR, Jones CD, Kimes PK, Liu Y, Marron JS, Meng S, Mieczkowski PA, Mose LE, Parker JS, Perou CM, Prins JF, Roach J, Shi Y, Simons JV, Singh D, Soloway MG, Tan D, Veluvolu U, Walter V, Waring S, Wilkerson MD, Wu J, Zhao N, Cherniack AD, Hammerman PS, Tward AD, Pedamallu CS, Saksena G, Jung J, Ojesina AI, Carter SL, Zack TI, Schumacher SE, Beroukhim R, Freeman SS, Meyerson M, Cho J, Noble MS, DiCara D, Zhang H, Heiman DI, Gehlenborg N, Voet D, Lin P, Frazer S, Stojanov P, Liu Y, Zou L, Kim J, Muzny D, Doddapaneni HV, Kovar C, Reid J, Morton D, Han Y, Hale W, Chao H, Chang K, Drummond JA, Gibbs RA, Kakkar N, Wheeler D, Xi L, Ciriello G, Ladanyi M, Lee W, Ramirez R, Sander C, Shen R, Sinha R, Weinhold N, Taylor BS, Aksoy BA, Dresdner G, Gao J, Gross B, Jacobsen A, Reva B, Schultz N, Sumer SO, Sun Y, Chan TA, Morris LG, Stuart J, Benz S, Ng S, Benz C, Yau C, Baylin SB, Cope L, Danilova L, Herman JG, Bootwalla M, Maglinte DT, Laird PW, Triche T, Weisenberger DJ, Van Den Berg DJ, Agrawal N, Bishop J, Boutros PC, Bruce JP, Byers LA, Califano J, Carey TE, Chen Z, Cheng H, Chiosea SI, Cohen E, Diergaarde B, Egloff AM, El-Naggar AK, Ferris RL, Frederick MJ, Grandis JR, Guo Y, Haddad RI, Harris T, Hui ABY, Lee JJ, Lippman SM, Liu FF, McHugh JB, Myers J, Ng PKS, Perez-Ordonez B, Pickering

CR, Prystowsky M, Romkes M, Saleh AD, Sartor MA, Seethala R, Seiwert TY, Si H, Van Waes C, Waggott DM, Wiznerowicz M, Yarbrough WG, Zhang J, Zuo Z, Burnett K, Crain D, Gardner J, Lau K, Mallery D, Morris S, Paulauskis J, Penny R, Shelton C, Shelton T, Sherman M, Yena P, Black AD, Bowen J, Frick J, Gastier-Foster JM, Harper HA, Leraas K, Lichtenberg TM, Ramirez NC, Wise L, Zmuda E, Baboud J, Jensen MA, Kahn AB, Pihl TD, Pot DA, Srinivasan D, Walton JS, Wan Y, Burton RA, Davidsen T, Demchok JA, Eley G, Ferguson ML, Mills Shaw KR, Ozenberger BA, Sheth M, Sofia HJ, Tarnuzzer R, Wang Z, Yang L, Zenklusen JC, Saller C, Tarvin K, Chen C, Bollag R, Weinberger P, Golusiński W, Golusiński P, Ibbs M, Korski K, Mackiewicz A, Suchorska W, Szybiak B, Curley E, Beard C, Mitchell C, Sandusky G, Ahn J, Khan Z, Irish J, Waldron J, William WN, Egea S, Gomez-Fernandez C, Herbert L, Bradford CR, Chepeha DB, Haddad AS, Jones TR, Komarck CM, Malakh M, Moyer JS, Nguyen A, Peterson LA, Prince ME, Rozek LS, Taylor EG, Walline HM, Wolf GT, Boice L, Chera BS, Funkhouser WK, Gulley ML, Hackman TG, Hayward MC, Huang M, Rathmell WK, Salazar AH, Shockley WW, Shores CG, Thorne L, Weissler MC, Wrenn S, Zanation AM, Brown BT, Pham M, Comprehensive genomic characterization of head and neck squamous cell carcinomas, Nature. 517 (2015) 576–582. 10.1038/nature14129. [PubMed: 25631445]

[18]. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy A, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, Antipin Y, Reva B, Goldberg AP, Sander C, Schultz N, The cBio Cancer Genomics Portal: An Open Platform for exploring Multidimensional Cancer Genomics Data, CANCER Discov.|. 401 (2012). 10.1158/2159-8290.CD-12-0095.

[19]. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, Cerami E, Sander C, Schultz N, Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal, Sci. Signal 6 (2013). 10.1126/scisignal.2004088.

[20]. Lui VWY, Hedberg ML, Li H, Vangara BS, Pendleton K, Zeng Y, Lu Y, Zhang Q, Du Y, Gilbert BR, Freilino M, Sauerwein S, Peyser ND, Xiao D, Diergaarde B, Wang L, Chiosea S, Seethala R, Johnson JT, Kim S, Duvvuri U, Ferris RL, Romkes M, Nukui T, Ng PKS, Garraway LA, Hammerman PS, Mills GB, Grandis JR, Frequent mutation of the PI3K pathway in head and neck cancer defines predictive biomarkers, Cancer Discov. 3 (2013) 761–769. 10.1158/2159-8290.CD-13-0103. [PubMed: 23619167]

[21]. Jung K, Kang H, Mehra R, Targeting phosphoinositide 3-kinase (PI3K) in head and neck squamous cell carcinoma (HNSCC), Cancers Head Neck. (2018) 1–13. [PubMed: 29951282]

[22]. Lee JY, Engelman JA, Cantley LC, PI3K charges ahead, Science (80-.). 317 (2007) 206–207. 10.1126/science.1146073.

[23]. Vanhaesebroeck B, Waterfield MD, Signaling by distinct classes of phosphoinositide 3-kinases, Exp. Cell Res 253 (1999) 239–254. 10.1006/excr.1999.4701. [PubMed: 10579926]

[24]. Miao B, Skidan I, Yang J, Lugovskoy A, Reibarkh M, Long K, Brazell T, Durugkar KA, Maki J, Ramana CV, Schaffhausen B, Wagner G, Torchilin V, Yuan J, Degterev A, Small molecule inhibition of phosphatidylinositol-3,4,5-triphosphate (PIP3) binding to pleckstrin homology domains, Proc. Natl. Acad. Sci. U. S. A 107 (2010) 20126–20131. 10.1073/pnas.1004522107. [PubMed: 21041639]

[25]. Salim K, Bottomley MJ, Querfurth E, Zvelebil MJ, Gout I, Scaife R, Margolis RL, Gigg R, Smith CI, Driscoll PC, Waterfield MD, Panayotou G, Distinct specificity in the recognition of phosphoinositides by the pleckstrin homology domains of dynamin and Bruton's tyrosine kinase., EMBO J. 15 (1996) 6241–6250. 10.1002/j.1460-2075.1996.tb01014.x. [PubMed: 8947047]

[26]. Scheid MP, Marignani PA, Woodgett JR, Multiple Phosphoinositide 3-Kinase-Dependent Steps in Activation of Protein Kinase B, Mol. Cell. Biol 22 (2002) 6247–6260. 10.1128/mcb.22.17.6247-6260.2002. [PubMed: 12167717]

[27]. Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, Yamauchi M, Imamura Y, Qian ZR, Baba Y, Shima K, Sun R, Nosho K, Meyerhardt JA, Giovannucci E, Fuchs CS, Chan AT, Ogino S, Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival, N. Engl. J. Med 367 (2012) 1596–1606. 10.1056/NEJMoa1207756. [PubMed: 23094721]

[28]. Zeng Y, Lu Y, Zhang Q, Du Y, Gilbert B, Chiosea S, Seethala R, Johnson JT, Kim S, Garraway LA, Hammerman PS, Mills GB, Grandis JR, Defines Predictive Biomarkers, 3 (2014) 761–769. 10.1158/2159-8290.CD-13-0103.Frequent.

[29]. Gulluni F, De Santis MC, Margaria JP, Martini M, Hirsch E, Class II PI3K Functions in Cell Biology and Disease, Trends Cell Biol. 29 (2019) 339–359. 10.1016/j.tcb.2019.01.001. [PubMed: 30691999]

[30]. Brown RA, Domin J, Arcaro A, Waterfield MD, Shepherd PR, Insulin activates the α isoform of class II phosphoinositide 3-kinase, J. Biol. Chem 274 (1999) 14529–14532. 10.1074/jbc.274.21.14529. [PubMed: 10329640]

[31]. Yoshioka K, Yoshida K, Cui H, Wakayama T, Takuwa N, Okamoto Y, Du W, Qi X, Asanuma K, Sugihara K, Aki S, Miyazawa H, Biswas K, Nagakura C, Ueno M, Iseki S, Schwartz RJ, Okamoto H, Sasaki T, Matsui O, Asano M, Adams RH, Takakura N, Takuwa Y, Endothelial PI3K-C2α, a class II PI3K, has an essential role in angiogenesis and vascular barrier function, Nat. Med 18 (2012) 1560–1569. 10.1038/nm.2928. [PubMed: 22983395]

[32]. Backer JM, The regulation and function of Class III PI3Ks: Novel roles for Vps34, Biochem. J 410 (2008) 1–17. 10.1042/BJ20071427. [PubMed: 18215151]

[33]. Thongwatchara P, Thongsuksai P, Dechaphunkul T, Dechaphunkul A, Frequency of PIK3CA mutations in head and neck squamous cell carcinoma (HNSCC) in southern Thailand, Ann. Oncol 29 (2018) 388 10.1093/annonc/mdw585.

[34]. Qiu W, Schönleben F, Li X, Ho DJ, Close LG, Manolidis S, Bennett BP, Su GH, PIK3CA mutations in head and neck squamous cell carcinoma, Clin. Cancer Res 12 (2006) 1441–1446. 10.1158/1078-0432.CCR-05-2173. [PubMed: 16533766]

[35]. Kozaki KI, Imoto I, Pimkhaokham A, Hasegawa S, Tsuda H, Omura K, Inazawa J, PIK3CA mutation is an oncogenic aberration at advanced stages of oral squamous cell carcinoma, Cancer Sci. 97 (2006) 1351–1358. 10.1111/j.1349-7006.2006.00343.x. [PubMed: 17052259]

[36]. Miled N, Yan Y, Hon WC, Perisic O, Zvelebil M, Inbar Y, Schneidman-Duhovny D, Wolfson HJ, Backer JM, Williams RL, Mechanism of two classes of cancer mutations in the phosphoinositide 3-kinase catalytic subunit, Science (80-.). 317 (2007) 239–242. 10.1126/science.1135394.

[37]. Mandelker D, Gabelli SB, Schmidt-Kittler O, Zhu J, Cheong I, Huang CH, Kinzler KW, Vogelstein B, Amzel LM, A frequent kinase domain mutation that changes the interaction between PI3Kα and the membrane, Proc. Natl. Acad. Sci. U. S. A 106 (2009) 16996–17001. 10.1073/pnas.0908444106. [PubMed: 19805105]

[38]. Nichols Anthony C., Palma David A., Chow W, High Frequency of Activating PIK3CA Mutations in Human Papillomavirus-Positive Oropharyngeal Caner, J. Am. Assoc. Otolaryngoloy 139 (2013) 617–622.

[39]. Ra S, Dm S, mTOR Signaling in Growth, Metabolism and Disease, Cell. 168 (2017) 960–976. 10.1016/j.cell.2017.02.004.mTOR. [PubMed: 28283069]

[40]. Inoki K, Li Y, Xu T, Guan KL, Rheb GTpase is a direct target of TSC2 GAP activity and regulates mTOR signaling, Genes Dev. 17 (2003) 1829–1834. 10.1101/gad.1110003. [PubMed: 12869586]

[41]. Hay N, Sonenberg N, Upstream and downstream of mTOR. Genes Dev. 2004, 18, 1926–1945, Genes Dev. 18 (2004) 1926–1945. 10.1101/gad.1212704.hibiting. [PubMed: 15314020]

[42]. Chang F, Lee JT, Navolanic PM, Steelman LS, Shelton JG, Blalock WL, Franklin RA, McCubrey JA, Involvement of PI3K/Akt pathway in cell cycle progression, apoptosis, and neoplastic transformation: A target for cancer chemotherapy, Leukemia. 17 (2003) 590–603. 10.1038/sj.leu.2402824. [PubMed: 12646949]

[43]. Xue G, Hemmings BA, PKB/akt-dependent regulation of cell motility, J. Natl. Cancer Inst 105 (2013) 393–404. 10.1093/jnci/djs648. [PubMed: 23355761]

[44]. Karar J, Maity A, PI3K/AKT/mTOR Pathway in Angiogenesis, Front. Mol. Neurosci 4 (2011) 1–8. 10.3389/fnmol.2011.00051. [PubMed: 21441980]

[45]. Mancinelli R, Carpino G, Petrungaro S, Mammola CL, Tomaipitinca L, Filippini A, Facchiano A, Ziparo E, Giampietri C, Multifaceted Roles of GSK-3 in Cancer and Autophagy-Related Diseases, Oxid. Med. Cell. Longev 2017 (2017) 4629495 10.1155/2017/4629495. [PubMed: 29379583]

[46]. Schulz L, Pries R, Lanka AS, Drenckhan M, Rades D, Wollenberg B, Inhibition of GSK3alpha/beta impairs the progression of HNSCC., Oncotarget. 9 (2018) 27630–27644. 10.18632/oncotarget.25250. [PubMed: 29963225]

[47]. Hu W, Xiao L, Cao C, Hua S, Wu D, UBE2T promotes nasopharyngeal carcinoma cell proliferation, invasion, and metastasis by activating the AKT/GSK3beta/beta-catenin pathway., Oncotarget. 7 (2016) 15161–15172. 10.18632/oncotarget.7805. [PubMed: 26943030]

[48]. Gao S, Li S, Duan X, Gu Z, Ma Z, Yuan X, Feng X, Wang H, Inhibition of glycogen synthase kinase 3 beta (GSK3beta) suppresses the progression of esophageal squamous cell carcinoma by modifying STAT3 activity., Mol. Carcinog 56 (2017) 2301–2316. 10.1002/mc.22685. [PubMed: 28574599]

[49]. Ugolkov AV, Matsangou M, Taxter TJ, O'Halloran TV, Cryns VL, Giles FJ, Mazar AP, Aberrant expression of glycogen synthase kinase-3beta in human breast and head and neck cancer., Oncol. Lett 16 (2018) 6437–6444. 10.3892/ol.2018.9483. [PubMed: 30405781]

[50]. Matsuo FS, Andrade MF, Loyola AM, da Silva SJ, Silva MJB, Cardoso SV, de Faria PR, Pathologic significance of AKT, mTOR, and GSK3beta proteins in oral squamous cell carcinoma-affected patients., Virchows Arch. 472 (2018) 983–997. 10.1007/s00428-018-2318-0. [PubMed: 29713826]

[51]. Mishra R, Glycogen synthase kinase 3 beta: can it be a target for oral cancer., Mol. Cancer 9 (2010) 144 10.1186/1476-4598-9-144. [PubMed: 20537194]

[52]. Georgy SR, Cangkrama M, Srivastava S, Partridge D, Auden A, Dworkin S, McLean CA, Jane SM, Darido C, Identification of a Novel Proto-oncogenic Network in Head and Neck Squamous Cell Carcinoma., J. Natl. Cancer Inst 107 (2015). 10.1093/jnci/djv152.

[53]. Paccez JD, Duncan K, Vava A, Correa RG, Libermann TA, Parker MI, Zerbini LF, Inactivation of GSK3beta and activation of NF-kappaB pathway via Axl represents an important mediator of tumorigenesis in esophageal squamous cell carcinoma., Mol. Biol. Cell 26 (2015) 821–831. 10.1091/mbc.E14-04-0868. [PubMed: 25568334]

[54]. Pramanik KK, Nagini S, Singh AK, Mishra P, Kashyap T, Nath N, Alam M, Rana A, Mishra R, Glycogen synthase kinase-3beta mediated regulation of matrix metalloproteinase-9 and its involvement in oral squamous cell carcinoma progression and invasion., Cell. Oncol. (Dordr) 41 (2018) 47–60. 10.1007/s13402-017-0358-0. [PubMed: 29134466]

[55]. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, Iwata H, Conte P, Mayer IA, Kaufman B, Yamashita T, Lu YS, Inoue K, Takahashi M, Pápai Z, Longin AS, Mills D, Wilke C, Hirawat S, Juric D, Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer, N. Engl. J. Med 380 (2019) 1929–1940. 10.1056/NEJMoa1813904. [PubMed: 31091374]

[56]. Markham A, Alpelisib: First Global Approval, Drugs. 79 (2019) 1249–1253. 10.1007/s40265-019-01161-6. [PubMed: 31256368]

[57]. Huang A, Fritsch C, Wilson C, Reddy A, Liu M, Lehar J, Quadt C, Hofmann F, Schlegel R, Abstract 3749: Single agent activity of PIK3CA inhibitor BYL719 in a broad cancer cell line panel, Cancer Res. 72 (2012) 3749 LP–3749. 10.1158/1538-7445.AM2012-3749.

[58]. Fritsch C, Huang A, Chatenay-Rivauday C, Schnell C, Reddy A, Liu M, Kauffmann A, Guthy D, Erdmann D, De Pover A, Furet P, Gao H, Ferretti S, Wang Y, Trappe J, Brachmann SM, Maira SM, Wilson C, Boehm M, Garcia-Echeverria C, Chene P, Wiesmann M, Cozens R, Lehar J, Schlegel R, Caravatti G, Hofmann F, Sellers WR, Characterization of the novel and specific PI3Ka inhibitor NVP-BYL719 and development of the patient stratification strategy for clinical trials, Mol. Cancer Ther 13 (2014) 1117–1129. 10.1158/1535-7163.MCT-13-0865. [PubMed: 24608574]

[59]. Keam B, Kim S, Ahn YO, Kim TM, Lee SH, Kim DW, Heo DS, In vitro anticancer activity of PI3K alpha selective inhibitor BYL719 in head and neck cancer, Anticancer Res. 35 (2015) 175–182. [PubMed: 25550549]

[60]. Abdul Razak AR, Souliéres D, Laurie SA, Hotte SJ, Singh S, Winquist E, Chia S, Tourneau CL, Nguyen-Tan PF, Chen EX, Chan KK, Wang T, Giri N, Mormont C, Quinn S, Siu LL, A phase II trial of dacomitinib, an oral pan-human EGF receptor (HER) inhibitor, as first-line treatment in recurrent and/or metastatic squamous-cell carcinoma of the head and neck, Ann. Oncol 24 (2013) 761–769. 10.1093/annonc/mds503. [PubMed: 23108949]

[61]. Dunn LA, Riaz N, Fury MG, Sean M, Michel L, Lee NY, Sherman EJ, Baxi SS, Haque SS, Katabi N, Wong RJ, A Phase Ib Study of Cetuximab and BYL719 (Alpelisib) Concurrent with Intensity-Modulated Radiation Therapy in Stage III-IVB Head and Neck Squamous Cell Carcinoma, Int. J. Radiat. Oncol. • Biol. • Phys 719 (2019). 10.1016/j.ijrobp.2019.09.050.

[62]. Keam B, Kim HR, Yun HT, Triumph trial: One small step could become one giant leap for precision oncology in head and neck cancer, Cancer Res. Treat 51 (2019) 413–414. 10.4143/crt.2018.335. [PubMed: 30064199]

[63]. Maira SM, Pecchi S, Huang A, Burger M, Knapp M, Sterker D, Schnell C, Guthy D, Nagel T, Wiesmann M, Brachmann S, Fritsch C, Dorsch M, Chène P, Shoemaker K, De Pover A, Menezes D, Martiny-Baron G, Fabbro D, Wilson CJ, Schlegel R, Hofmann F, García-Echeverría C, Sellers WR, Voliva CF, Identification and characterization of NVP-BKM120, an orally available pan-class I PI3-kinase inhibitor, Mol. Cancer Ther 11 (2012) 317–328. 10.1158/1535-7163.MCT-11-0474. [PubMed: 22188813]

[64]. Koul D, Fu J, Shen R, LaFortune T, Wang S, Tiao N, Kim Y-W, Liu J-L, Maira S-M, Yung WKA, Antitumor Activity of NVP-BKM120–A Selective Pan Class I PI3 Kinase Inhibitor Showed Differential Forms of Cell Death Based on p53 Status of Glioma Cells Dimpy, 18 (2012) 184–195. 10.1016/j.cortex.2009.08.003.Predictive.

[65]. Brachmann SM, Kleylein-Sohn J, Gaulis S, Kauffmann A, Blommers MJJ, Kazic-Legueux M, Laborde L, Hattenberger M, Stauffer F, Vaxelaire J, Romanet V, Henry C, Murakami M, Guthy DA, Sterker D, Bergling S, Wilson C, Brümmendorf T, Fritsch C, Garcia-Echeverria C, Sellers WR, Hofmann F, Maira SM, Characterization of the mechanism of action of the pan class i PI3K inhibitor NVP-BKM120 across a broad range of concentrations, Mol. Cancer Ther. 11 (2012) 1747–1757. 10.1158/1535-7163.MCT-11-1021. [PubMed: 22653967]

[66]. Blas K, Wilson TG, Tonlaar N, Galoforo S, Hana A, Marples B, Wilson GD, Dual blockade of PI3K and MEK in combination with radiation in head and neck cancer, Clin. Transl. Radiat. Oncol 11 (2018) 1–10. 10.1016/j.ctro.2018.04.003. [PubMed: 30014041]

[67]. Ando Y, Inada-inoue M, Mitsuma A, Yoshino T, Ohtsu A, Suenaga N, Sato M, Kakizume T, Robson M, Quadt C, Doi T, Phase I dose-escalation study of buparlisib (BKM120), an oral pan-class I PI3K inhibitor, in Japanese patients with advanced solid tumors, Cancer Sci. 105 (2014) 347–353. 10.1111/cas.12350. [PubMed: 24405565]

[68]. Brisson RJ, Kochanny S, Arshad S, Dekker A, DeSouza JA, Saloura V, Vokes EE, Seiwert TY, A pilot study of the pan-class I PI3K inhibitor buparlisib in combination with cetuximab in patients with recurrent or metastatic head and neck cancer, Head Neck. (2019) 3842–3849. 10.1002/hed.25910. [PubMed: 31486207]

[69]. Smyth LM, Monson KR, Jhaveri K, Drilon A, Li BT, Abida W, Iyer G, Gerecitano JF, Gounder M, Harding JJ, Voss MH, Makker V, Ho AL, Razavi P, Iasonos A, Lacouture ME, Teitcher JB, Erinjeri JP, Katabi N, Fury MG, Hyman DM, A phase 1b dose expansion study of the pan-Class I PI3K inhibitor buparlisib (BKM120) plus carboplatin and paclitaxel in PTEN deficient tumors and with dose intensified carboplatin and paclitaxel Lillian, Invest New Drugs. 35 (2017) 742–750. 10.1007/s10637-017-0445-0.A. [PubMed: 28281183]

[70]. Soulières D, Faivre S, Mesía R, Remenár É, Li SH, Karpenko A, Dechaphunkul A, Ochsenreither S, Kiss LA, Lin JC, Nagarkar R, Tamás L, Kim SB, Erfán J, Alyasova A, Kasper S, Barone C, Turri S, Chakravartty A, Chol M, Aimone P, Hirawat S, Licitra L, Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial, Lancet Oncol. 18 (2017) 323–335. 10.1016/S1470-2045(17)30064-5. [PubMed: 28131786]

[71]. Fayette D, Digue J, Ségura-Ferlay L, Treilleux C, Wang I, Lefebvre Q, Daste G, Even A, Couchon C, Thaunat S, Guyemion A, Peyrade F, Cupissol D, You B, Le Tourneau C, Jaouen L, Grinand E, Tabone-Eglinger S, arin G, Buparlisib (BKM120) in refractory head and neck squamous cell carcinoma harbouring or not a PI3KCA mutation: a phase II multicenter trial, in: Buparlisib Refract. Head Neck Squamous Cell Carcinoma Harbouring or Not a PI3KCA Mutat. a Phase II Multicent. Trial, 2019.

[72]. Cleary JM, Shapiro GI, Development of Phosphoinositide-3 Kinase Pathway Inhibitors for Advanced Cancer, Curr Oncol Rep. 12 (2017) 1–13. 10.1007/s11912-010-0091-6.

[73]. Koul D, Shen R, Kim YW, Kondo Y, Lu Y, Bankson J, Ronen SM, Kirkpatrick DL, Powis G, Yung WKA, Cellular and in vivo activity of a novel PI3K inhibitor, PX-866, against human glioblastoma, Neuro. Oncol 12 (2010) 559–569. 10.1093/neuonc/nop058. [PubMed: 20156803]

[74]. Bowles DW, Senzer N, Hausman D, Peterson S, Vo A, Walker L, Cohen RB, Jimeno A, A multicenter phase 1 study of PX-866 and cetuximab in patients with metastatic colorectal

carcinoma or recurrent/metastatic squamous cell carcinoma of the head and neck, Invest. New Drugs 32 (2014) 1197–1203. 10.1007/s10637-014-0124-3. [PubMed: 24916771]

[75]. Jimeno A, Bauman J, Weissman C, Adkins D, Schnadig I, Beauregard P, Bowles DW, Spira A, Levy B, Seetharmu N, Hausman D, Walker L, Rudin CM, Shirai K, A randomized, phase 2 trial of docetaxel with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer, Oral Oncol. 51 (2015) 383–388. 10.1016/j.oraloncology.2014.12.013. A. [PubMed: 25593016]

[76]. Markham A, Copanlisib: First Global Approval, Drugs. 77 (2017) 2057–2062. 10.1007/s40265-017-0838-6. [PubMed: 29127587]

[77]. Bush TL, Payton M, Heller S, Chung G, Hanestad K, Rottman JB, Loberg R, Friberg G, Kendall RL, Saffran D, Radinsky R, AMG 900, a small-molecule inhibitor of aurora kinases, potentiates the activity of microtubule-targeting agents in human metastatic breast cancer models, Mol. Cancer Ther 12 (2013) 2356–2366. 10.1158/1535-7163.MCT-12-0993-T. [PubMed: 23990115]

[78]. Ye L, Mayerle J, Ziesch A, Reiter FP, Gerbes AL, De Toni EN, The PI3K inhibitor copanlisib synergizes with sorafenib to induce cell death in hepatocellular carcinoma, Cell Death Discov. 5 (2019). 10.1038/s41420-019-0165-7.

[79]. Patnaik A, Appleman LJ, Tolcher AW, Papadopoulos KP, Beeram M, Rasco DW, Weiss GJ, Sachdev JC, Chadha M, Fulk M, Ejadi S, Mountz JM, Lotze MT, Toledo FGS, Chu E, Jeffers M, Peña C, Xia C, Reif S, Genvresse I, Ramanathan RK, First-in-human phase I study of copanlisib (BAY 80-6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas, Ann. Oncol 27 (2016) 1928–1940. 10.1093/ANNONC/MDW282. [PubMed: 27672108]

[80]. Vlahos CJ, Matter WF, Hui KY, Brown RF, A specific inhibitor of phosphatidylinositol 3-kinase, 2-(4-morpholinyl)- 8-phenyl-4H-1-benzopyran-4-one (LY294002), J. Biol. Chem 269 (1994) 5241–5248. [PubMed: 8106507]

[81]. Garlich JR, De P, Dey N, Jing DS, Peng X, Miller A, Murali R, Lu Y, Mills GB, Kundra V, Shu HK, Peng Q, Durden DL, A vascular targeted pan phosphoinositide 3-kinase inhibitor prodrug, SF1126, with antitumor and antiangiogenic activity, Cancer Res. 68 (2008) 206–215. 10.1158/0008-5472.CAN-07-0669. [PubMed: 18172313]

[82]. Joshi S, Singh AR, Durden DL, Pan-PI-3 kinase inhibitor SF1126 shows antitumor and antiangiogenic activity in renal cell carcinoma, Cancer Chemother. Pharmacol 75 (2015) 595–608. 10.1007/s00280-014-2639-x. [PubMed: 25578041]

[83]. Mahadevan D, Chiorean E. g., Harris WB, Von Hoff DD, Stejskal-Barnett A, Qi W, Anthony SP, Younger AE, Ramanathan RK, Phase I pharmacokinetic and pharmacodynamic study of the pan-PI3K/mTORC vascular targeted pro-drug SF1126 in patients with advanced solid tumours and B-cell malignancies, Eur J Cancer. 48 (2012). 10.1038/jid.2014.371.

[84]. Maira SM, Stauffer F, Brueggen J, Furet P, Schnell C, Fritsch C, Brachmann S, Chène P, De Pover A, Schoemaker K, Fabbro D, Gabriel D, Simonen M, Murphy L, Finan P, Sellers W, García-Echeverría C, Identification and characterization of NVP-BEZ235, a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent in vivo antitumor activity, Mol. Cancer Ther 7 (2008) 1851–1863. 10.1158/1535-7163.MCT-08-0017. [PubMed: 18606717]

[85]. Wirtz ED, Hoshino D, Maldonado AT, Tyson DR, Weaver AM, Response of head and neck squamous cell carcinoma cells carrying PIK3CA mutations to selected targeted therapies, JAMA Otolaryngol - Head Neck Surg. 141 (2015) 543–549. 10.1001/jamaoto.2015.0471. [PubMed: 25855885]

[86]. Carlo MI, Molina AM, Lakhman Y, Patil S, Woo K, DeLuca J, Lee C-H, Hsieh JJ, Feldman DR, Motzer RJ, Voss MH, A Phase Ib Study of BEZ235, a Dual Inhibitor of Phosphatidylinositol 3-Kinase (PI3K) and Mammalian Target of Rapamycin (mTOR), in Patients With Advanced Renal Cell Carcinoma, Oncologist. 21 (2016) 787–788d. 10.1634/theoncologist.2016-0145. [PubMed: 27286790]

[87]. Salazar R, Garcia-Carbonero R, Libutti SK, Hendifar AE, Custodio A, Guimbaud R, Lombard-Bohas C, Ricci S, Klümpen H, Capdevila J, Reed N, Walenkamp A, Grande E, Safina S, Meyer T, Kong O, Salomon H, Tavorath R, Yao JC, Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Naïve Advanced Pancreatic

Neuroendocrine Tumors, Oncologist. 23 (2018) 766–e90. 10.1634/theoncologist.2017-0144. [PubMed: 29242283]

[88]. Rodon J, Pérezfidalgo A, Krop IE, Burris H, Guerrero A-, Britten CD, Becerra C, Schellens J, Richards DA, Phase 1/1b dose escalation and expansion study of BEZ235, a dual PI3K/mTOR inhibitor, in patients with advanced solid tumors including patients with advanced breast cancer, Cancer Chemother Pharmacol. 82 (2018) 285–298. 10.1007/s00280-018-3610-z.Phase. [PubMed: 29882016]

[89]. Venkatesan AM, Dehnhardt CM, Delos Santos ED, Chen Z, Dos Santos OD, Ayral-Kaloustian S, Khafizova G, Brooijmans N, Mallon R, Hollander I, Feldberg L, Lucas J, Yu K, Gibbons J, Abraham RT, Chaudhary I, Mansour TS, Bis(morpholino-l,3,5-triazine) derivatives: Potent adenosine 5′-triphosphate competitive phosphatidylinositol-3-kinase/mammalian target of rapamycin inhibitors: Discovery of compound 26 (PKI-587), a highly efficacious dual inhibitor, J. Med. Chem 53 (2010) 2636–2645. 10.1021/jm901830p. [PubMed: 20166697]

[90]. D'Amato V, Rosa R, D'Amato C, Formisano L, Marciano R, Nappi L, Raimondo L, Di Mauro C, Servetto A, Fusciello C, Veneziani BM, De Placido S, Bianco R, The dual PI3K/mTOR inhibitor PKI-587 enhances sensitivity to cetuximab in EGFR-resistant human head and neck cancer models, Br. J. Cancer 110 (2014) 2887–2895. 10.1038/bjc.2014.241. [PubMed: 24823695]

[91]. Leiker AJ, DeGraff W, Choudhuri R, Thetford A, Sowers A, Cook JA, Van Waes C, Mitchell JB, Radiation Enhancement of Head and Neck Squamous Cell Carcinoma by the Dual PI3K/mTOR Inhibitor PF-05212384 Andrew, Clin Cancer Res. 21 (2015) 2792–2801. 10.1158/1078-0432.CCR-14-3279.Radiation. [PubMed: 25724523]

[92]. Shapiro GI, Bell-McGuinn KM, Molina JR, Bendell J, Spicer J, Kwak EL, Pandya SS, Millham R, Borzillo G, Pierce KJ, Han L, Houk BE, Gallo JD, Alsina M, Braña I, Tabernero J, First-in-human study of PF-05212384 (PKI-587), a small-molecule, intravenous, dual inhibitor of PI3K and mTOR in patients with advanced cancer, Clin. Cancer Res 21 (2015) 1888–1895. 10.1158/1078-0432.CCR-14-1306. [PubMed: 25652454]

[93]. Zhang Y, Yan H, Xu Z, Yang B, Luo P, He Q, Molecular basis for class side effects associated with PI3K/AKT/mTOR pathway inhibitors, Expert Opin. Drug Metab. Toxicol 15 (2019) 767–774. 10.1080/17425255.2019.1663169. [PubMed: 31478386]

[94]. Schultze SM, Hemmings BA, Niessen M, Tschopp O, PI3K/AKT, MAPK and AMPK signalling: Protein kinases in glucose homeostasis, Expert Rev. Mol. Med 14 (2012). 10.1017/S1462399411002109.

[95]. Sopasakis VR, Liu P, Suzuki R, Kondo T, Winnay J, Tran TT, Asano T, Smyth G, Sajan MP, Farese RV, Kahn CR, Zhao JJ, Specific Roles of the p110α Isoform of Phosphatidylinsositol 3-Kinase in Hepatic Insulin Signaling and Metabolic Regulation Victoria, Cell Metab. 11 (2010) 220–230. 10.1016/j.cmet.2010.02.002.Specific. [PubMed: 20197055]

[96]. Luo J, Sobkiw CL, Hirshman MF, Logsdon MN, Li TQ, Goodyear LJ, Cantley LC, Loss of class IA PI3K signaling in muscle leads to impaired muscle growth, insulin response, and hyperlipidemia, Cell Metab.3 (2006) 355–366. 10.1016/j.cmet.2006.04.003. [PubMed: 16679293]

[97]. Janku F, Phosphoinositide 3-kinase (PI3K) pathway inhibitors in solid tumors: From laboratory to patients, Cancer Treat. Rev 59 (2017) 93–101. 10.1016/j.ctrv.2017.07.005. [PubMed: 28779636]

[98]. Ma CX, Luo J, Naughton M, Ademuyiwa F, Suresh R, Griffith M, Griffith OL, Skidmore ZL, Spies NC, Ramu A, Trani L, Pluard T, Nagaraj G, Thomas S, Guo Z, Hoog J, Han J, Mardis E, Lockhart C, Ellis MT, A phase I trial of BKM120 (Buparlisib) in combination with fulvestrant in postmenopausal women with estrogen receptor-positive metastatic breast cancer, Clin. Cancer Res 22 (2016) 1583–1591. 10.1158/1078-0432.CCR-15-1745. [PubMed: 26563128]

[99]. Chakrabarty A, Sánchez V, Kuba MG, Rinehart C, Arteaga CL, Feedback upregulation of HER3 (ErbB3) expression and activity attenuates antitumor effect of PI3K inhibitors, Proc. Natl. Acad. Sci. U. S. A 109 (2012) 2718–2723. 10.1073/pnas.1018001108. [PubMed: 21368164]

[100]. Chandarlapaty S, Sawai A, Scaltriti M, Rodrik-Outmezguine V, Grbovic-Huezo O, Serra V, Majumder PK, Baselga J, Rosen N, AKT inhibition relieves feedback suppression of receptor tyrosine kinase expression and activity, Cancer Cell. 19 (2011) 58–71. 10.1016/j.ccr.2010.10.031. [PubMed: 21215704]

[101]. O'Reilly KE, Rojo F, She Q-B, Solit D, Mills GB, Smith D, Lane H, Hofmann F, Hicklin DJ, Ludwig DL, Baselga J, Rosen N, mTOR Inhibition Induces Upstream Receptor Tyrosine Kinase Signaling and Activates Akt, Cancer Res. 66 (2006) 1500–1508. 10.1161/CIRCULATIONAHA.110.956839. [PubMed: 16452206]

[102]. Elkabets M, Pazarentzos E, Juric D, Sheng Q, Pelossof RA, Brook S, Benzaken AO, Rodon J, Morse N, Yan JJ, Liu M, Das R, Chen Y, Tam A, Wang H, Liang J, Gurski JM, Kerr DA, Rosell R, Teixidó C, Huang A, Ghossein RA, Rosen N, Bivona TG, Scaltriti M, Baselga J, AXL mediates resistance to PI3Kα inhibition by activating the EGFR/PKC/mTOR Axis in Head and neck and esophageal squamous cell carcinomas, Cancer Cell. 27 (2015) 533–546. 10.1016/j.ccell.2015.03.010. [PubMed: 25873175]

[103]. Badarni M, Prasad M, Balaban N, Zorea J, Yegodayev KM, Joshua BZ, Dinur AB, Grénman R, Rotblat B, Cohen L, Elkabets M, Repression of AXL expression by AP-1/JNK blockage overcomes resistance to PI3Ka therapy, JCI Insight. 4 (2019). 10.1172/jci.insight.125341.

[104]. Ruicci KM, Pinto N, Khan MI, Yoo J, Fung K, MacNeil D, Mymryk JS, Barrett JW, Nichols AC, ERK-TSC2 signalling in constitutively-active HRAS mutant HNSCC cells promotes resistance to PI3K inhibition, Oral Oncol. 84 (2018) 95–103. 10.1016/j.oraloncology.2018.07.010. [PubMed: 30115483]

[105]. Brand TM, Hartmann S, Bhola NE, Li H, Zeng Y, O'Keefe RA, Ranall MV, Bandyopadhyay S, Soucheray M, Krogan NJ, Kemp C, Duvvuri U, LaVallee T, Johnson DE, Ozbun MA, Bauman JE, Grandis JR, Cross-talk Signaling between HER3 and HPV16 E6 and E7 Mediates Resistance to PI3K Inhibitors in Head and Neck Cancer Toni, Cancer Res. 78 (2018) 2383–2395. 10.1158/0008-5472.CAN-17-1672. [PubMed: 29440171]

[106]. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L, Zhang J, Bolton EE, PubChem 2019 update: improved access to chemical data, Nucleic Acids Res. 47 (2019) D1102–D1109. 10.1093/nar/gky1033. [PubMed: 30371825]

Highlights:

- GSK-3 is negatively regulated by the PI3K pathway
- *PIK3CA* encoding the catalytic subunit of PI3K is commonly altered in HNSCC
- Past clinical trials of PI3K inhibitors have demonstrated limited efficacy
- Biomarkers identifying patients sensitive to PI3K inhibitors are needed

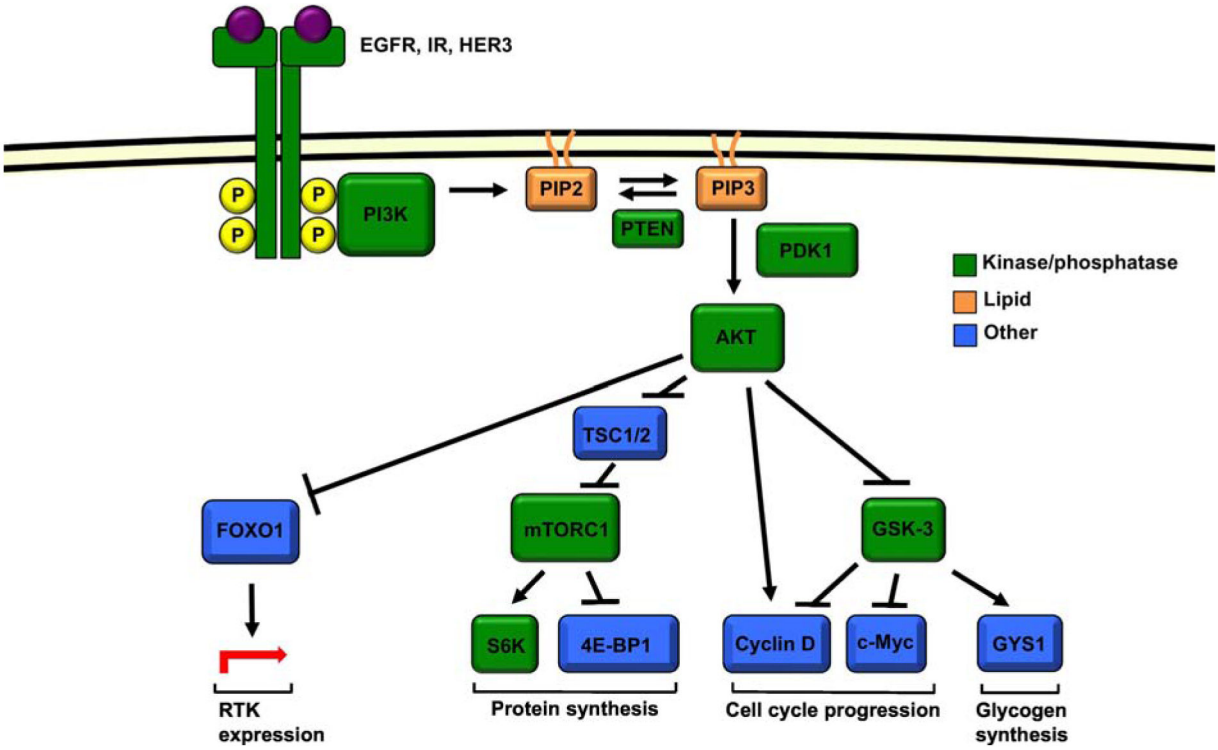

Figure 1. The PI3K signaling pathway.

PI3K converts $PIP_2$to PIP_3, leading to the activation of Akt. Akt inhibits FOXO1, which when active, increases expression of various RTKs including EGFR, IR, and HER3. Akt also activates mTORC1 via inhibition of TSC1/2, leading to stimulation of protein synthesis via activation of S6K and inhibition of 4E-BP1. Inhibition of GSK-3 by Akt results in increased expression of cyclin D and c-Myc and decreased glycogen synthesis.

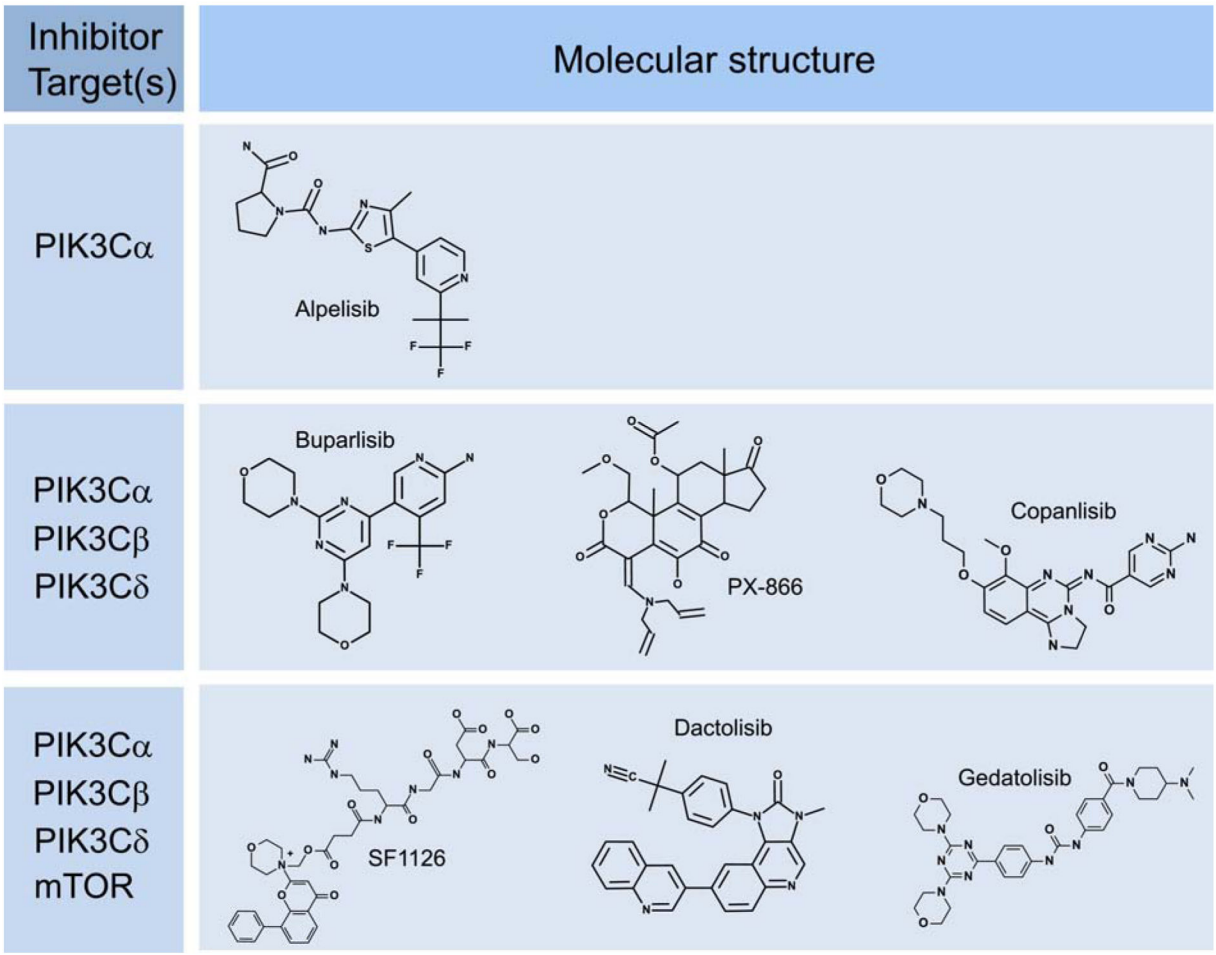

Figure 2. Inhibitory activities and molecular structures of class IA PI3K/mTOR inhibitors.

Different classes of inhibitors target different PI3K isoforms. Alpelisib specifically targets PI3Kα while buparlisib, PX-866, and copanlisib are pan-class IA PI3K inhibitors. SF1126, dactolisib, and gedatolisib are dual class IA PI3K/mTOR inhibitors. Molecular structures were created on PubChem [106].

Table 1.

Ongoing clinical trials evaluating PI3Kα inhibitors in patients with head and neck cancer exclusively.

PI3Kα inhibitor	Other interventions	HNSCC conditions	PI3K Biomarker	Phase	Status	Clinical trial identifier
Alpelisib		All	PI3K pathway alterations	II	Recruiting	NCT03292250
Alpelisib		Recurrent or metastatic	None	II	Recruiting	NCT02145312
Alpelisib	Cisplatin, intensity modulated radiotherapy (IMRT)	Locally advanced	None	I	Active, not recruiting	NCT02537223
Buparlisib	Cetuximab	Recurrent or metastatic	None	I/II	Active, not recruiting	NCT01816984
Buparlisib	Cisplatin, IMRT	All	None	I	Active, not recruiting	NCT02113878
Copanlisib	Cetuximab	Recurrent or metastatic	PI3K mutation/ amplification and/or PTEN loss	I/II	Active, not recruiting	NCT02822482

Table 2.

Ongoing clinical trials evaluating PI3Kα inhibitors in cancer, including patients with head and neck cancer.

PI3Kα inhibitor	Other interventions	Conditions	PI3K Biomarker	Phase	Status	Clinical trial identifier
Alpelisib		Advanced solid tumors	*PIK3CA* mutation	I	Active, not recruiting	NCT01219699
Buparlisib	Gefitinib	Non-small cell lung cancer (NSCLC), enriched with solid tumors	Hyperactive PI3K pathway, historic EGFR mutation	I	Active, not recruiting	NCT01570296
Copanlisib	Nivolumab	Metastatic solid tumors, lymphomas	None	I	Recruiting	NCT03502733
Copanlisib		Solid tumors, lymphomas	None	I/II	Recruiting	NCT03458728
Copanlisib	Olaparib, durvalumab	Metastatic or unresectable solid tumors	None	I	Recruiting	NCT03842228
Copanlisib	Nivolumab	Metastatic or unresectable microsatellite stable (MSS) solid tumors, MSS colon cancer	None	I/II	Recruiting	NCT03711058
Copanlisib, GSK2636771, Taselisib		Refractory solid tumors, lymphomas, multiple myeloma	*PIK3CA* mutation or PTEN mutation/loss (copanlisib), PTEN mutation/loss (GSK2636771), *PIK3CA* mutations without *RAS* mutation or PTEN loss (taselisib)	II	Recruiting	NCT02465060
Gedatolisib	Palbociclib	Head and neck, lung, pancreatic, other solid tumors	None	I	Recruiting	NCT03065062