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Targeting PI3 kinase in cancer☆

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ABSTRACT

The PI3K/Akt/mTOR pathway is the most frequently known activated aberrant pathway in human cancers. Pathologic activation can occur at multiple levels along the signaling pathway by a variety of mechanisms, including point mutations, amplifications, and inactivation of tumor suppressor genes. This pathway is also a known resistance pathway, as it can be activated by both receptor tyrosine kinases and other oncogenes. mTOR inhibitors were the first targeted molecules in this pathway, and have already been FDA-approved in multiple indications. Because of the broad potential applications of inhibiting this pathway upstream of mTOR, multiple compounds targeting PI3K are in development. In this review, we discuss the clinical development of these inhibitors, including dual PI3K/mTOR inhibitors, pan-PI3K inhibitors, and isoform-selective PI3K inhibitors. Common adverse events, including rash, nausea, vomiting, diarrhea, and hyperglycemia, have created a narrow therapeutic window for all classes of PI3K inhibitors. Furthermore, single agent clinical activity has also been limited, with the exception of isoform-selective inhibitors, particularly the PI3Kδ and PI3Kγ inhibitors in hematologic malignancies. The future role of inhibitors of the PI3K/Akt/mTOR pathway in the clinical practice of oncology likely depends on the development of patient selection strategies and the results of combination trials that are currently ongoing.

Contents

1. PI3K signaling in cancer

In more than 20 years since its discovery, studies have established the central role of phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling in cancer growth, metabolism, survival, and motility (Katso et al., 2001; Vivanco & Sawyers, 2002; Engelman et al., 2006; Zhao & Vogt, 2008). The PI3K/Akt/mTOR pathway is likely the most frequently activated pathway in human cancers, affecting some 30–50% of tumors (Samuels et al., 2004), making it an attractive target for oncology drug development. Inhibition of signaling along this pathway can result in both decreased cellular proliferation and promotion of cellular death (Hennessy et al., 2005).

Abbreviations: AE, Adverse event; ALT, Alanine transaminase; AST, Aspartate transaminase; CLL, Chronic lymphocytic leukemia; DLT, Dose-limiting toxicity; FDA, Food and Drug Administration; GIST, Gastrointestinal stromal tumor; MTD, Maximum tolerated dose; mTOR, Mammalian target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; NHL, Non-Hodgkin's lymphoma; NSCLC, Non-small cell lung cancer; ORR, Objective response rate; PD, Pharmacodynamics; PI3K, Phosphatidylinositol 3-kinase; PK, Pharmacokinetics; PTEN, Phosphatase and tensin homolog; RECIST, Response Evaluation Criteria in Solid Tumors; RTK, Receptor tyrosine kinase.

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There are three known classes of PI3 kinases, classes I, II, and III, categorized by structure and function. Of these, class I PI3 kinases are the most clearly implicated in human cancer, and will be the focus of this review (Yuan & Cantley, 2008). There are three class IA PI3K isoforms (PI3Kα, PI3Kβ, and PI3Kδ). PI3Kγ represents the only enzyme in class 1B of the PI3Ks (Pacold et al., 2000). In addition, there are three isoforms of Akt: Akt1, Akt2, and Akt3. Completing the signaling cascade, mTOR is comprised of two known complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (Hardt et al., 2011).

Pathologic activation of the PI3K/Akt/mTOR pathway can arise in a number of ways, with the most common being point mutations of PI3K, inactivation of the tumor suppressor phosphatase and tensin homolog (PTEN), and amplification or mutation of Akt (Hennessy et al., 2005). Point mutations in *PIK3CA*, the gene encoding the p110α subunit of PI3K, are among the most commonly documented mutations in cancer (Samuels et al., 2004). Though these mutations have been described in nearly every major tumor type, those with the highest prevalence include breast, endometrium, colon, and head and neck cancers.

Unlike PI3Kα, mutations in PI3Kδ and PI3Kγ are uncommon. PI3Kδ is preferentially expressed in leukocytes, and is important in B cell activation, proliferation, survival, and lymphoid tissue homing (Fung-Leung, 2011). PI3Kδ is activated by cellular receptors through interaction with the SH2 domains of the PI3K p85 regulatory subunit, or directly through *RAS* (Hsu et al., 2004). PI3Kδ signaling is known to be particularly hyperactive in many B cell malignancies. Numerous preclinical studies illustrated that isoform-specific inhibition of PI3Kδ resulted in cytotoxicity of B cells while sparing toxicity to other hematopoietic cell types (Deane & Fruman, 2004; Fruman, 2004; Vanhaesebroeck et al., 2005). PI3Kγ is associated with G-protein coupled receptors and is responsible for the very rapid induction of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) and can also be activated by RAS downstream of other receptors. Similar to PI3Kδ, PI3Kγ is preferentially expressed in leukocytes, and is central to the growth and survival of B cell malignancies. PI3Kγ is also known to have a role in the maintenance of the tumor microenvironment and involved in T cell development and survival.

PTEN is an antagonist of PI3K signaling, and loss of function of this tumor suppressor gene leads to increased downstream activation (Maehama & Dixon, 1998; Chow & Baker, 2006; Engelman et al., 2006). Mutations in PTEN have been demonstrated in numerous cancers, most notably endometrial, central nervous system, skin, and prostate cancers. While somatic mutations are more common, germline loss of PTEN results in Cowden syndrome (Zbuk & Eng, 2007; Suzuki et al., 2008). Loss of PTEN can also develop due to deletions, transcriptional silencing, or protein instability due to post-translational modification (Ali et al., 1999).

All three isoforms of Akt have demonstrated amplification in various malignancies. Akt1 amplification has been reported in gastric carcinoma, glioblastoma, and gliosarcoma. Akt2 amplification has been identified in head and neck squamous cell carcinoma, pancreatic, ovarian, and breast cancers. Mutations in Akt have also been identified, but are less common than the frequency observed with *PIK3CA* (Cheung & Testa, 2013). Similarly, mutations in mTOR are rare (Hardt et al., 2011).

In addition to inherent aberrations in members of the PI3K/Akt/mTOR pathway, pathologic signaling through this pathway can also occur by other means, including receptor tyrosine kinases (RTKs), G protein-coupled receptors, and other oncogenes (e.g. RAS) (Skolnik et al., 1991; Katso et al., 2001; Kang et al., 2006; Shaw & Cantley, 2006; Zhao & Vogt, 2008). For example, RTKs can become constitutively activated, resulting in increased PI3K signaling. Indeed, this has been described as a resistance mechanism to tyrosine kinase inhibitors, such as in gastrointestinal stromal tumors (GIST) after exposure to imatinib (Bauer et al., 2006). Also, PI3K signaling can be upregulated via cross talk from other oncogenes. This interaction has been best described between the RAS and PI3K pathways, where Ras-GTP can allosterically activate PI3K after direct binding (Kodaki et al., 1994; Rodriguez-Viciana et al., 1994; Suire et al., 2002), resulting in pathologic activation of the pathway.

2. Inhibitors of PI3K pathway signaling

With the pivotal role this pathway plays in cancer biology, the ability to effectively inhibit PI3K/Akt/mTOR signaling is an attractive anti-cancer strategy across multiple tumor types (Miled et al., 2007). Selective mTOR inhibitors were the first compounds developed to target this pathway. Rapamycin analogues, such as temsirolimus and everolimus, specifically inhibit mTORC1 and are already United States FDA-approved in renal cell carcinoma, subependymal giant cell astrocytoma, pancreatic neuroendocrine tumors, and hormone receptor-positive HER2-negative breast cancer in combination with exemestane (Hudes et al., 2007; Motzer et al., 2008; Yao et al., 2011; Baselga et al., 2012; Franz et al., 2013). Compounds that target mTORC2 in addition to mTORC1, including INK128, AZD2014, and CC-223, are also in development (Banerji et al., 2012; Shih et al., 2012; Patel, Patel, et al., 2013). Selective Akt inhibitors, such as MK-2206, AZD5363, and GSK690693, are also in phase 1 and 2 clinical trials (Altomare et al., 2010; Yap et al., 2011; Davies et al., 2012). As much research and other review articles have focused on these agents, this review will specifically focus on inhibitors of PI3K.

3. Clinical development of dual PI3K/mTOR inhibitors

The ability to effectively target PI3K and mTOR simultaneously has potential to fully inhibit signaling through the entire pathway. Since PI3K and mTOR share several structural similarities, some compounds were developed to inhibit both the class I PI3K isoforms and mTORC1 and mTORC2 (Sturgill & Hall, 2009). Multiple of these dual PI3K/mTOR inhibitors are in clinical development (Table 1).

BEZ235 (Novartis) is a reversible, orally bioavailable selective inhibitor of PI3K and mTORC1 and mTORC2. Fifty-nine patients were enrolled in the first-in-human trial using a hard-gelatin capsule across doses ranging from 10 mg daily to 1100 mg daily without identification of the maximum tolerated dose (MTD) (Burris et al., 2010). The most common toxicities were usually grade 1/2, and included nausea, vomiting, diarrhea, fatigue/asthenia, and anorexia. There were no dose-limiting toxicities (DLTs). Fifty-one patients were evaluable, with two reaching partial response, 16 with a minor response, and 14 who demonstrated stable disease ≥ 4 months. Non-proportional pharmacokinetic (PK) exposure, with high inter- and intrapatient variability, leads to development of a solid dispersion system (SDS) sachet formulation. The adverse event (AE) profile remained similar, with an MTD of 1600 mg daily, with DLTs of grade 3 fatigue and asthenia (2) and grade 3 thrombocytopenia (1) (Peyton et al., 2011). Recently, Arkenau et al. showed that twice-daily dosing at 600 mg was more tolerable than once-daily dosing, while retaining pharmacodynamic (PD) activity and demonstrating preliminary signs of clinical benefit (Arkenau et al., 2012). BEZ235 is undergoing further clinical development in phase I and phase II studies, both alone and in combination with hormonal agents and cytotoxic chemotherapeutics for the treatment of multiple malignancies.

XL765 (Exelixis/Sanofi-Aventis) is also a potent and selective inhibitor of class I PI3K isoforms, mTORC1, and mTORC2. Seventy-nine patients treated in the dose escalation revealed an MTD of 50 mg orally twice-daily (Brana et al., 2010). Common AEs were similar to those of BEZ235, with nausea, vomiting, diarrhea, anorexia, and skin disorders. Four patients demonstrated ≥grade 3 liver transaminase elevations (three patients at 120 mg twice-daily and one at 50 mg twice-daily). Exposures increased appropriately with increasing doses, with a half-life of 3–9 h. Serial tumor biopsies showed modulation of downstream targets, with reductions in pAkt-T308 (57–76%), and p4EBP1 (62–80%). There were no partial responses, but seven patients were on study for ≥6 months. Ongoing phase I and phase II trials of XL765 are evaluating this compound