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Review Article

Dual inhibition of PI3K and mTOR in cancer therapy: Mechanisms, clinical potential, and future perspectives

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Abstract

The PI3K/AKT/mTOR signaling system is essential for controlling cell growth, survival, proliferation, and metabolism, rendering it a significant therapeutic target in cancer treatment. Dysregulation of this system is commonly reported in numerous cancers, facilitating tumor development and resistance to standard therapy. Dual inhibitors that concurrently target both Phosphatidylinositol 3-Kinase (PI3K) and Mammalian Target of Rapamycin (mTOR) provide a more thorough inhibition of this pathway, reducing the deficiencies of single-agent inhibitors and bypassing compensatory mechanisms that frequently result in therapeutic resistance. This review investigates the molecular basis of dual PI3K/mTOR inhibition, emphasizing its potential to improve cancer treatment effects. We provide a concise overview of the preclinical and clinical data that substantiates the efficacy of dual inhibitors in various malignancies, including breast, prostate, colorectal, pancreatic, ovarian, and lung cancers. Significant antitumor activity has been demonstrated by notable dual inhibitors when combined with chemotherapy or targeted agents. However, challenges such as resistance and toxicity persist. Additional research is required to refine dose protocols, optimize patient selection by biomarker identification, and investigate combination drugs to improve efficacy while reducing undesirable effects. The advancement of nanoformulations has demonstrated potential in enhancing medicine delivery and reducing systemic toxicity. Dual PI3K/mTOR inhibitors constitute a promising therapeutic strategy, providing significant enhancements in tailored cancer treatment, particularly for individuals with resistant or aggressive malignancies.

Keywords: PI3K-mTOR inhibitors; dual inhibition; targeted therapy; oncogenic pathways; molecular signaling; drug resistance

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INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, with an increasing global burden that highlights the urgent need for innovative and effective treatment approaches[1,2]. Cancer develops due to disruptions in signaling networks that regulate key cellular processes such

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as growth, proliferation, metabolism, and survival[3,4]. Among these, the phosphatidylinositol 3-kinase (PI3K)/ Protein Kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway is one of the most commonly dysregulated pathways in cancer and is associated with tumor initiation, progression, and resistance to conventional therapies[5,6].

The PI3K/AKT/mTOR pathway plays a central role in cellular signaling, integrating extracellular and intracellular signals to regulate critical cellular functions. The activation of PI3K is triggered by receptor tyrosine kinases (RTKs) and G-protein-coupled receptors (GPCRs) in response to extracellular growth factors, such as insulin-like growth factors (IGF) and epidermal growth factor (EGF)[7,8]. Upon activation, PI3K catalyses the conversion of phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3), a critical step that facilitates the recruitment and phosphorylation of AKT (Figure 1)[9].

Once activated, AKT phosphorylates downstream targets, including mTOR, a serine/threonine kinase that operates within two distinct complexes: mTORC1 and mTORC2 (Figure 1). These complexes regulate various processes essential for cancer progression. mTORC1 controls protein synthesis, cellular proliferation, and metabolism through effectors such as ribosomal protein S6 kinase (S6K) and eukaryotic translation initiation factor 4E-binding protein (4EBP1) [10]. mTORC2, on the other hand, modulates the actin cytoskeleton, promotes cell survival, and activates AKT in a feedback loop that sustains tumor growth and survival[11,12]. Dysregulation of the PI3K/AKT/mTOR pathway is a hallmark of many cancers. This dysregulation can result from mutations or amplifications in PI3K, AKT, or mTOR genes, or from the loss of tumor suppressors such as Phosphatase and Tensin Homolog (PTEN), which negatively regulates the pathway. Such alterations lead to uncontrolled cellular proliferation, resistance to apoptosis, and enhanced cell survival, making this pathway an attractive target for cancer therapies[13-15].

Given the critical role of the PI3K/AKT/mTOR pathway in tumor progression, various therapeutic strategies have been developed to target its components. These include isoform-specific PI3K inhibitors, such as alpelisib and idelalisib, and

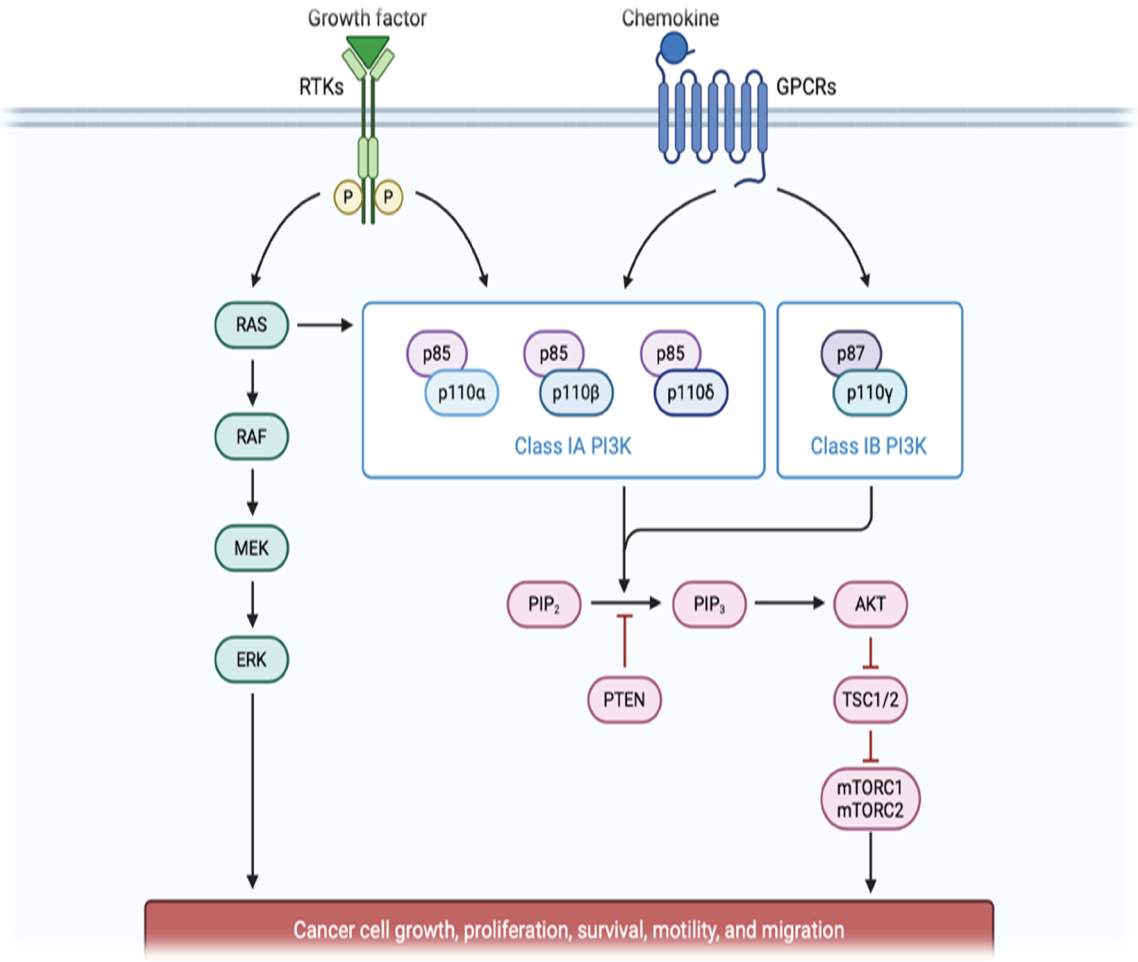

Figure 1. The PI3K/AKT/mTOR pathway activated by receptor tyrosine kinases (RTKs) and GPCRs (G-protein-coupled receptors) promotes cancer cell growth, proliferation, survival, and migration. PTEN negatively regulates PIP_3 generation, while AKT and mTORC1/2 mediate downstream signaling. The RAS-RAF-MEK-ERK pathway is also depicted as a parallel RTK-driven route (This Scheme was created by Biorender).

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mTOR inhibitors like everolimus and temsirolimus[16,17]. While these agents have shown initial promise, their efficacy has been limited by compensatory feedback mechanisms and the activation of alternative survival pathways. For example, mTORC1 inhibitors can inadvertently activate mTORC2, which in turn enhances AKT signaling and restores tumor cell survival. Similarly, PI3K inhibitors often fail to completely suppress downstream signaling through mTOR, leaving critical pro-survival pathways intact[17]. These limitations underscore the need for more comprehensive therapeutic approaches that target multiple components of the pathway simultaneously.

Dual inhibition of PI3K and mTOR has emerged as a promising strategy to overcome the limitations of single-agent therapies. By simultaneously targeting both upstream (PI3K) and downstream (mTOR) components of the pathway, dual inhibitors offer a more complete blockade of the signaling cascade, disrupting key survival and proliferation signals. This approach not only limits compensatory feedback loops but also enhances apoptosis, reduces angiogenesis, and suppresses tumor growth more effectively than single-target therapies[11,12].

Notable dual inhibitors include dactolisib (BEZ235), gedatolisib (PF-05212384), and samotolisib (LY3023414), which have shown preclinical and clinical efficacy in various malignancies such as breast, prostate, lung, colorectal, and ovarian cancers[6,16,18,19]. When combined with other therapies, such as chemotherapy, immune checkpoint inhibitors, or radiotherapy, dual inhibitors further enhance therapeutic responses by modulating the tumor microenvironment and sensitizing cancer cells to treatment[9,20,21].

Dual PI3K/mTOR inhibitors work by blocking critical components of the pathway at multiple levels. For example, PI3K inhibition prevents the production of PIP3, thereby reducing AKT activation and downstream signaling. Concurrently, mTOR inhibition suppresses protein synthesis, metabolism, and angiogenesis, leading to reduced tumor proliferation and survival. This dual action has shown synergistic effects in preclinical models, with significant reductions in tumor growth and increased apoptosis[12,20]. These inhibitors also offer additional therapeutic benefits, such as modulating the immune microenvironment to enhance anti-tumor immunity, and preventing angiogenesis, which starves tumors of essential nutrients and oxygen. Furthermore, dual therapies can overcome resistance mechanisms that often develop with single-agent therapies, making them particularly valuable in treating aggressive and refractory cancers[11,22].

Despite their promise, dual inhibitors face significant challenges, including drug toxicity, resistance, and patient variability. Adverse effects such as hyperglycaemia, fatigue, and gastrointestinal disturbances are common due to the pathway's role in normal cellular processes[23-26]. Resistance mechanisms, such as the activation of alternative signaling pathways like Mitogen-Activated Protein Kinase/ Extracellular Signal-Regulated Kinase (MAPK/ERK) or mutations in target kinases, further complicate their clinical application[27]. To address these challenges, ongoing research focuses on developing personalized treatment protocols, identifying predictive biomarkers, and exploring combination therapies. For instance, nanoformulations that encapsulate dual inhibitors are being developed to enhance drug delivery, reduce systemic toxicity, and improve therapeutic efficacy[28]. These formulations allow for targeted delivery to tumor sites, minimizing off-target effects and increasing drug stability[2, 29-31].

The dual inhibition of PI3K and mTOR represents a significant advancement in targeted cancer therapy, offering a more comprehensive approach to blocking critical signaling pathways involved in tumor growth, survival, and resistance. By addressing the limitations of single-agent therapies, dual inhibitors have demonstrated potential across a range of cancers, particularly when used in combination with other treatments[22]. However, challenges such as toxicity, resistance, and patient selection must be addressed through continued research and innovation. The development of nanoformulations, the identification of biomarkers, and the integration of personalized medicine approaches will be crucial in realizing the full therapeutic potential of dual PI3K/mTOR inhibitors[13]. In this review, we aim to explore the possibility of dual inhibition of PI3K and mTOR for cancer therapy and discuss the rationale for their concurrent action on both pathways.

PI3K Inhibitors

PI3Ks constitute a family of lipid kinases that regulate numerous essential cellular functions, such as cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking[11]. Activation of PI3K is initiated by several extracellular signals, including growth factors, cytokines, and other stimuli that engage RTKs or GPCRs on the cell membrane[8]. Upon activation, PI3K catalyzes the conversion of phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-triphosphate (PIP3), an essential process in the transmission of downstream signals[6,16]. This conversion results in the recruitment and activation of AKT, which associates with PIP3 through its pleckstrin homology (PH) domain[32]. AKT is fully activated via phosphorylation at two critical sites: Ser473 by mTORC2 and Thr308 by 3-phosphoinositide-dependent protein kinase-1 (PDK1)[33]. AKT modulates various downstream pathways associated with cell survival, metabolism, and proliferation upon activation, facilitating tumor growth[17,34].

PI3K inhibitors function by obstructing the catalytic activity of PI3K, inhibiting the synthesis of PIP3 and the subsequent activation of AKT and its downstream signaling pathways[35]. This inhibition affects critical biological functions, including cell growth, survival, and metabolism, frequently resulting in heightened apoptosis and reduced tumor proliferation. Numerous isoform-specific PI3K inhibitors have been created to selectively target specific PI3K isoforms, thereby improving therapeutic efficacy and reducing unwanted effects[36]. Examples comprise idelalisib, which targets PI3Kδ, and Alpelisib, which inhibits explicitly PI3Kα[37]. Alpelisib received approval for the management of advanced or metastatic breast cancer linked to PIK3CA mutations, especially in instances that are HER2-negative and hormone receptor-positive (HR+). Through the targeted inhibition of the commonly mutated PI3Kα isoform, alpelisib successfully restricts tumor proliferation. Idelalisib,

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an isoform-specific inhibitor, is utilized in treating conditions including follicular lymphoma, small lymphocytic lymphoma, and chronic lymphocytic leukemia (CLL). It inhibits PI3Kδ, an essential component in B-cell receptor signaling, vital for the survival and growth of malignant B cells (Glaviano et al., 2023).

mTOR Inhibitors

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase essential for integrating signals from nutrients, growth factors, and cellular energy status to regulate essential processes, including cell growth, proliferation, survival, and metabolism. mTOR operates via two separate complexes: mTORC1 and mTORC2[38]. mTORC1 mainly controls protein synthesis by phosphorylating downstream targets, such as eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) and ribosomal protein S6 kinase 1 (S6K1). This phosphorylation facilitates cell growth, enhances protein synthesis, and supports proliferation[39]. Furthermore, mTORC1 inhibits autophagy, a process of cellular degradation and recycling, by phosphorylating and inactivating Unc-51 Like Autophagy Activating Kinase-1 (ULK1), a kinase that plays a crucial role in the initiation of autophagy[40,41]. Conversely, mTORC2 plays a role in the regulation of the actin cytoskeleton and the activation of AKT via phosphorylation at Ser473, a modification essential for the complete activation of AKT, thereby promoting cell survival and proliferation[33,37].

mTOR inhibitors, including rapamycin (sirolimus) and its analogs (everolimus and temsirolimus), primarily focus on mTORC1. These inhibitors create a complex with FK506-binding protein 12 (FKBP12), which subsequently binds to and inhibits mTORC1[42]. The reduction in phosphorylation of S6K1 and 4EBP1 results in diminished protein synthesis, a deceleration of cell growth, and an enhancement of autophagy, which may promote the death of cancer cells[43]. Everolimus has received clinical approval for the treatment of various cancer types, such as renal cell carcinoma, breast cancer, and pancreatic neuroendocrine tumors. By inhibiting mTORC1, everolimus interferes with essential signaling pathways that facilitate tumor growth and survival. Similarly, temsirolimus, utilized for the treatment of advanced renal cell carcinoma, acts by inhibiting mTORC1, leading to a reduction in cell proliferation and the induction of autophagy, thereby enhancing its antitumor effects[44].

PI3K and mTOR Dual Inhibition

The Rationale Behind Combining PI3K and mTOR Inhibition

The PI3K/AKT/mTOR signaling pathway serves as a crucial regulator of cellular growth, metabolism, survival, and proliferation, and it is often found to be dysregulated in various human cancers. Targeting this pathway presents a promising approach for cancer treatment. Nonetheless, single-agent inhibitors frequently encounter constraints stemming from the activation of compensatory pathways, which diminish their long-term effectiveness[12.] PI3K inhibitors, like alpelisib and idelalisib, function by inhibiting the initial phases of the pathway, which prevents the release of PIP3 and consequent activation of AKT[45,46]. While PI3K inhibition may show initial effectiveness, it can trigger feedback mechanisms or alternative survival pathways that diminish its therapeutic efficacy over time. mTOR inhibitors, especially those targeting mTORC1 such as everolimus and temsirolimus, hinder downstream signaling crucial for protein synthesis, cell growth, and metabolism by diminishing the phosphorylation of S6K1 and 4E-BP1[22]. Nevertheless, the inhibition of mTORC1 may occasionally lead to the activation of mTORC2, resulting in the phosphorylation of AKT and a partial restoration of signaling[35].Dual inhibitors, including dactolisib (BEZ235) and samotolisib, simultaneously target PI3K and mTORC1/2, providing a more comprehensive range of inhibition by restricting feedback activation and improving antitumor effects such as apoptosis and decreased proliferation[47,48].

The dual inhibition strategy offers a more thorough pathway blockage, leading to increased antitumor efficacy and minimizing the potential for resistance[5]. Resistance to single-agent therapies may develop due to genetic mutations, alternative pathways like MAPK/ERK activation, or feedback mechanisms that reinstate PI3K or AKT signaling. Dual inhibition addresses these adaptive mechanisms by targeting essential components in the PI3K/AKT/mTOR pathway, enhancing both the initial response and sustained effectiveness[27].

Research conducted in preclinical and clinical settings has demonstrated that the combination of PI3K and mTOR inhibitors results in synergistic effects. This combination leads to enhanced inhibition of tumor growth, increased rates of apoptosis, and more significant reductions in cell proliferation compared to the use of either inhibitor individually[27]. For instance, the combination of Alpelisib, a PI3Kα inhibitor, with everolimus has shown improved antitumor effects in breast cancer models, reinforcing the clinical justification for dual inhibition[49]. Current clinical trials are assessing the safety and effectiveness of this method across different types of cancer, such as breast, colorectal, and renal cell carcinomas, with preliminary findings indicating potential benefits[37].

Recent research tries to identify biomarkers that can predict responses to dual inhibition and personalize treatment according to each tumor's genetic and molecular features to enhance outcomes. Ongoing research aims to comprehend and address resistance mechanisms, examine next-generation inhibitors, and explore innovative drug combinations [9, 17]. Moreover, dual inhibition can potentially improve the effectiveness of chemotherapy, radiotherapy, and immunotherapy by making cancer cells more responsive to these treatments and altering the immune microenvironment, thereby providing further therapeutic advantages[16].

Chemical and Natural Sources of Dual PI3K/mTOR Inhibitors

Various dual PI3K/mTOR inhibitors can be classified according to their chemical structure. For example, sulfonamide methoxypyridine derivatives, created through scaffold-hopping strategies, demonstrate strong inhibitory activity against PI3Kα and mTOR[50]. Quinoline derivatives have been recognized as potent dual inhibitors, demonstrating strong binding affinity to the ATP-binding sites of PI3K and mTOR, thereby effectively inhibiting their activity[51]. Compounds such as Samotolisib and

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GSK2126458 have shown significant effectiveness in preclinical models[48,52]. Furthermore, morpholino-pyrimidine derivatives featuring sulfonyl side chains have demonstrated significant antitumor activity and enhanced bioavailability in clinical trials [53]. Additionally, analogs of pictilisib, which share structural similarities with the PI3K inhibitor pictilisib, have been altered to target mTOR, thereby improving anticancer effectiveness and minimizing resistance in comparison to single-target inhibitors[54].

Natural substances and plant extracts demonstrate significant potential as dual PI3K/mTOR pathway inhibitors. Curcumin, a polyphenol extracted from turmeric (*Curcuma longa*), has shown efficacy in inhibiting both PI3K and mTOR pathways, hence diminishing tumor development and promoting apoptosis in multiple cancer cell lines[55-57].

Resveratrol, present in grapes, berries, and peanuts, inhibits the PI3K/AKT/mTOR system by diminishing AKT and mTOR phosphorylation, thereby restraining cancer cell growth and facilitating apoptosis. It has demonstrated efficacy in preclinical tests against breast, prostate, and colon cancers[58,59]. Epigallocatechin-3-gallate (EGCG), a catechin derived from green tea, also inhibits this pathway, leading to reduced cell proliferation and death in breast, prostate, and lung malignancies[60].

Berberine, an alkaloid derived from plants like Berberis species, has demonstrated the ability to decrease the phosphorylation of PI3K, AKT, and mTOR. This action contributes to inhibiting tumor growth and promoting apoptosis, especially in breast, prostate, and colorectal cancers[15,61]. Scutellarein, a natural product with anticancer potential, exerts its effects on colorectal cancer cells by targeting the PI3K/AKT/mTOR pathway. It upregulates PTEN while downregulating PI3K, AKT, and phosphorylated mTOR, effectively inhibiting cancer cell growth, migration, and invasion. This highlights the potential of scutellarein as a therapeutic agent within the scope of PI3K/mTOR dual inhibitors for cancer treatment[34]. Finally, fisetin, a flavonoid present in a range of fruits and vegetables, influences the PI3K/AKT/mTOR pathway, leading to a decrease in cancer cell proliferation and the induction of apoptosis, showing potential effectiveness against breast, lung, and prostate cancers[62 63].

Nanoparticle formulations of dual PI3K/mTOR inhibitors

A promising approach in cancer therapy entails the development of nanoformulations that include dual PI3K/mTOR inhibitors. Nanotechnology improves the safety, effectiveness, distribution and the pharmacokinetics of dual PI3K/mTOR inhibitors by enhancing their water solubility and stability[31]. Nanoformulations have the potential to enhance the precision of delivering these inhibitors directly to tumor locations, thereby decreasing off-target effects and limiting systemic toxicity[30]. This targeted strategy guarantees that elevated medication levels are delivered to the tumor, consequently enhancing treatment results[64-66]. For instance, the encapsulation of gedatolisib within nanoparticles has demonstrated promising outcomes by enhancing the therapeutic index and minimizing toxicity in early clinical trials[28 67].

A notable example is the development of NanoGe, disulphide-crosslinked polyethylene glycol polymeric micelles designed to overcome the solubility limitations of gedatolisib[68]. NanoGe, with a diameter of approximately 23 nm, remains stable in circulation but break up in the reductive tumor microenvironment, releasing gedatolisib preferentially at the tumor site[28,69]. This design enhanced antitumor efficacy and cytotoxicity than free drug at prostate cancer cells due to improved cellular uptake and PI3K/mTOR inhibition[70]. Thus, NanoGe exemplifies how redox-sensitive polymeric micelles can dramatically improve solubility, tumor targeting and efficacy of dual inhibitors[28].

Liposomal nanocarriers enhance the solubility and circulation of hydrophobic dual inhibitors. Despite its potent anticancer activity, dactolisib (BEZ235) is highly hydrophobic, with poor solubility and bioavailability limiting its clinical application[71]. Liposomal formulations, such as liposomal BEZ235 (L-BEZ), improve its dispersibility by incorporating the hydrophobic compound into a lipid bilayer[71,72]. Preclinical studies demonstrate superior efficacy of L-BEZ, especially when combined with electroporation, achieving complete tumor regression in models where oral BEZ235 or electroporation alone was ineffective[71]. In head-and-neck cancer, irreversible electroporation with L-BEZ eradicated HN5 tumors with no recurrence after two months[71]. Other liposomal systems, such as those incorporating the PI3K/mTOR inhibitor PI-103, have shown improved systemic delivery and therapeutic outcomes compared to free drugs[73,74]. Liposomes offer advantages like high drug loading, reduced toxicity, and passive tumor targeting via the enhanced permeability and retention effect.

Biodegradable polymer base nanoparticles, such as Polyethylene Glycol–Poly(lactic-co-glycolic acid (PEG-PLGA) and polyesters, enable sustained release and targeted delivery of different targets including kinase inhibitors. For instance, PEG–PLGA nanoparticles loaded with dactolisib, delivered using a dual-antibody pre-targeting strategy, showed enhanced tumor binding and superior antitumor activity compared to free dactolisib[68]. Similarly, polymeric nanoparticle formulation of gedatolisib improved circulation, biodistribution, and safety[75]. These nanoparticles exploit the enhanced permeability and retention effect to concentrate drugs in tumors, increase half-life, and reduce off-target toxicity, as demonstrated by PLGA–PEG particles effectively targeting cancer cells with higher efficiency than free drugs[68,76]. Numerous dual inhibitors exhibit inadequate solubility and stability in physiological environments, limiting their therapeutic efficacy. Advanced nanoformulations could protect these medications from degradation, enhance their solubility, and facilitate a more stable, extended release of the active ingredient. For example, phenylsulfonylurea derivatives in nanoformulations have improved pharmacokinetics and increased antitumor activity of these dual inhibitors[77].

Nanoparticles contribute to modifying drug resistance by facilitating the more effective delivery of dual PI3K/mTOR inhibitors to tumor cells, thereby sustaining therapeutic levels

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for extended durations. This sustained release could inhibit cancer cells from engaging alternative survival pathways, thus enhancing the overall effectiveness of treatment[68]. Furthermore, integrating dual inhibitors within a single nanoformulation can yield synergistic effects, resulting in enhanced anticancer activity through the suppression of tumor growth, the induction of apoptosis, and the inhibition of metastasis. Preclinical investigations utilizing nanoparticle-encapsulated dual inhibitors have demonstrated notable tumor suppression[77]. Liposome-based formulations that encapsulate dual inhibitors to prevent them from degradation have shown encouraging outcomes in preclinical studies aimed at enhancing drug delivery to cancer cells[78,79].

Therapeutic Potential of PI3K-mTOR Dual Inhibitors

PI3K-mTOR dual inhibitors demonstrate potential in the treatment of several types of cancer, such as breast, lung, ovarian, prostate, and pancreatic cancers. Preclinical studies indicate that these inhibitors may improve the efficacy of radiation and chemotherapy.

PI3K-mTOR Dual Inhibitors in Prostate Cancer Treatment

Prostate cancer, the predominant malignancy in males, frequently entails disruption of the PI3K-mTOR pathway, especially in castration-resistant instances. Preclinical and clinical investigations have examined the efficacy of PI3K-mTOR dual inhibitors in the treatment of prostate cancer[80,81]. BEZ235 (Dactolisib) has demonstrated the ability to decrease the proliferation of prostate cancer cells by obstructing the PI3K-mTOR pathway in both in vitro and in vivo models[81]. In preclinical investigations, GSK2126458 similarly diminished prostate cancer cell proliferation and tumor formation[82].

In clinical trials, dactolisib shown limited antitumor efficacy in patients with metastatic castration-resistant prostate cancer, achieving a median progression-free survival of 3.7 months in a phase II trial[83]. Additional dual inhibitors, including GSK2126458 and PF-04691502, have demonstrated potential in preclinical research and are currently being evaluated in prostate cancer clinical trials[48,84]. PI3K-mTOR dual inhibitors present a potential strategy for the treatment of advanced and metastatic prostate cancer. Nonetheless, additional clinical research is required to ascertain their efficacy and safety and to find biomarkers that predict therapeutic response.

PI3K-mTOR Dual Inhibitors in Breast and Ovarian Cancer Treatment

Breast cancer, recognized as the most prevalent cancer among women globally, often involves the activation of the PI3K-mTOR pathway, especially in hormone receptor-positive, HER2-negative subtypes. This activation is associated with resistance to endocrine therapy, which is the standard treatment for estrogen receptor-positive breast cancer. Various mTOR inhibitors, including everolimus and temsirolimus, have demonstrated the ability to overcome endocrine resistance and enhance survival rates in cases of advanced breast cancer[6,22,45]. Combining mTOR inhibitors with other targeted therapies, such as PI3K inhibitors, has significantly improved antitumor effects. Clinical trials have demonstrated that PI3K-mTOR dual inhibitors, particularly when combined with endocrine therapy, are effective in treating hormone receptor-positive, HER2-negative breast cancer[22]. The BOLERO-2 trial demonstrated that the combination of everolimus and exemestane markedly enhanced progression-free survival (PFS) in postmenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer[85]. Although effective, these inhibitors may induce side effects, including gastrointestinal complications, tiredness, and immunosuppression.

A phase I study demonstrated that the combination of the PI3K-mTOR inhibitor gedatolisib and the CDK4/6 inhibitor palbociclib in patients with hormone receptor-positive, HER2-negative advanced breast cancer resulted in a 60% response rate, accompanied by a manageable safety profile[86]. In the same manner, phase II studies revealed the effectiveness of dactolisib in conjunction with fulvestrant and GSK2126458 paired with tamoxifen, resulting in response rates of 37% and 47%, respectively[81,87]. The results underscore the clinical value of PI3K-mTOR inhibitors in breast cancer; however, further evaluation through larger randomized trials is necessary to understand their efficacy and safety better. A 2024 study on gedatolisib with palbociclib and endocrine therapy in metastatic breast cancer (103 participants) reported objective response rates of 85.2% (first-line) and 25–61.5% (later lines). Common grade 3–4 adverse events included neutropenia (63%), stomatitis (27%), and rash (20%). Despite manageable toxicities, the regimen showed promising efficacy compared to standard treatment[86].

Ovarian cancer, a malignancy frequently associated with the activation of the PI3K-mTOR pathway, has been investigated for treatment using PI3K-mTOR dual inhibitors[88]. Research involving PKI-587 and GDC-0980 in ovarian cancer models has demonstrated notable suppression of tumor growth and enhanced apoptosis, indicating their potential application in ovarian cancer treatment[89]. Moreover, the combination of PI3K-mTOR inhibitors with PARP inhibitors such as olaparib has shown improved antitumor effects in preclinical models[90,91]. A clinical trial of gedatolisib in patients with recurrent ovarian cancer demonstrated that the drug was well-tolerated, with several patients showing partial responses[92]. The findings suggest that PI3K-mTOR dual inhibitors may be beneficial in treating ovarian cancer; however, further clinical studies are necessary to determine their long-term effectiveness and safety.

PI3K-mTOR Dual Inhibitors in Lung Cancer Treatment

Lung cancer, which entails non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), stands as the principal cause of cancer-related fatalities globally. Despite progress in surgical techniques, radiation, chemotherapy, targeted therapies, and immunotherapy, the prognosis of lung cancer continues to be unfavorable, underscoring the critical necessity for novel treatment approaches. The PI3K-mTOR signaling pathway is essential for the growth, survival, and metabolism of cancer cells, and it is often found to be dysregulated in cases of lung cancer. PI3K-mTOR dual inhibitors present a promising

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therapeutic approach by concurrently blocking essential pathways that promote cancer[93].

Preclinical and clinical investigations have supported the efficacy of PI3K-mTOR dual inhibitors in treating lung cancer. In NSCLC, the dual inhibitor BEZ235 has demonstrated the ability to reduce cell proliferation and induce apoptosis in preclinical models, indicating its potential as a therapeutic alternative[94]. During a phase I clinical trial, PF-05212384 demonstrated anticancer efficacy in patients with advanced solid tumors, including lung cancer, with partial responses noted in certain NSCLC patients[95]. In SCLC, the PI3K-mTOR dual inhibitor GSK2126458 demonstrated the ability to inhibit cell proliferation and promote apoptosis in preclinical investigations, suggesting its therapeutic promise for this more aggressive variant of lung cancer[96]. Although these findings are encouraging, further clinical trials are required to evaluate the efficacy and safety of PI3K-mTOR dual inhibitors in lung cancer, determine optimal treatment modalities, and identify biomarkers that predict patient response.

Dual PI3K-mTOR Inhibitors in the Treatment of Colorectal and Anal Cancers

Dual PI3K-mTOR inhibitors exhibit therapeutic potential in colorectal and anal malignancies, which are linked to the deregulation of the PI3K-mTOR system. Dactolisib, a dual inhibitor, has demonstrated efficacy in colon cancer models, especially in tumors containing PIK3CA mutations[47]. Preclinical investigations revealed its capacity to diminish tumor proliferation and trigger apoptosis, especially in combination with chemotherapy. Nonetheless, early clinical trials involving patients with metastatic colorectal cancer demonstrated considerable side effects, including mucositis and gastrointestinal complications, which restricted its application[97]. Likewise, PF-05212384 (Gedatolisib) has been investigated in colorectal cancer models, demonstrating a reduction in tumor growth and an augmentation in chemotherapy efficacy. Despite exhibiting acceptable side effects in clinical studies, its overall efficacy was constrained when evaluated alongside the FOLFIRI regimen[97].

Recent Phase I/II trials of dual PI3K/mTOR inhibitors have shown promising antitumor activity. WX390, a potent PI3K-mTOR dual inhibitor targeting pan-PI3K and mTOR, is currently undergoing Phase I/II clinical trials for various indications [98]. Notable studies include a Phase II trial investigating WX390 in combination with toripalimab for advanced gastric-type cancers. Earlier Phase Ib trials demonstrated its manageable safety profile, ability to modulate the tumor immune microenvironment by reducing tumor Treg cells, and promising antitumor effects[98,99]. WX390 is also being evaluated in Phase II trials for gynecological cancers[100], Preclinical and early clinical data support its high potency and efficacy in xenograft models[101]. Current research emphasizes combination strategies—such as pairing these inhibitors with immunotherapy (e.g., Anti-Programmed Death-1 agents (anti-PD-1 agents)) or chemotherapy—to enhance efficacy and overcome resistance mechanisms[102].

The incidence of anal cancer has been increasing among high-risk populations, highlighting the urgent need for innovative therapies, particularly for advanced or metastatic cases where existing treatments yield unsatisfactory results. The PI3K-mTOR pathway has emerged as a significant target because of its common deregulation in anal cancer[103]. PI3K-mTOR dual inhibitors present an opportunity to inhibit various signaling pathways that contribute to tumor growth and survival, potentially leading to more extensive therapeutic outcomes. Research on these inhibitors in anal cancer remains in its preliminary phases; however, initial studies indicate their possible effectiveness[103]. A Phase I study of bimiralisib, a pan-PI3K/mTOR inhibitor, in advanced solid tumors identified the maximum tolerated dose (MTD) for the continuous schedule as 80 mg, with grade 3 fatigue as the dose-limiting toxicity. Hyperglycemia was the most common treatment-emergent adverse event[104]. A phase II trial of BEZ235 in patients with advanced solid tumors, including anal cancer, demonstrated encouraging outcomes: two of nine anal cancer patients exhibited partial responses, while four others attained stable disease, resulting in a median progression-free survival (PFS) of 3.9 months[83,105]. The application of PI3K-mTOR dual inhibitors in anal cancer remains in preliminary stages; nonetheless, these investigations indicate potential efficacy in managing advanced disease stages. However, additional clinical trials are required to enhance the understanding of their efficacy and safety in colorectal and anal malignancies.

PI3K-mTOR Dual Inhibitors in Pancreatic Cancer Treatment

The PI3K-mTOR pathway is often activated in pancreatic cancer, rendering it a compelling therapeutic target. Preclinical studies indicate that PI3K-mTOR dual inhibitors can effectively suppress pancreatic cancer proliferation in vitro and in vivo, frequently enhancing the efficacy of conventional chemotherapeutic drugs such as gemcitabine. A study showed that combining BEZ235, a dual PI3K-mTOR inhibitor, and erlotinib triggered apoptosis and inhibited tumor development in pancreatic cancer cells, indicating a potential treatment strategy[11,12,49,82]. Clinical trials have commenced assessing the efficacy of PI3K-mTOR dual inhibitors in pancreatic cancer. A trial examining GDC-0980 in conjunction with chemotherapy (gemcitabine and nab-paclitaxel) for metastatic pancreatic cancer demonstrated encouraging outcomes, with a median progression-free survival of 7.6 months, and the treatment was well tolerated[106,107]. Preclinical studies have shown that dual inhibitors of the PI3K-mTOR pathway can impede tumor development and spread in mouse models of pancreatic cancer.

While initial trials have demonstrated promising outcomes, the application of PI3K-mTOR dual inhibitors in treating pancreatic cancer remains in its early phases. Although certain patients have shown partial responses, additional research is essential to assess their long-term efficacy and safety comprehensively. In summary, PI3K-mTOR dual inhibitors show significant potential, especially when utilized alongside other treatment modalities. Nevertheless, further comprehensive research is required to investigate their potential and tackle any related challenges thoroughly[107].

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Challenges and opportunities in the clinical development of dual PI3k-mTOR inhibitors for cancer therapy

The clinical development of dual PI3K-mTOR inhibitors involves various challenges, such as managing toxicity, understanding resistance mechanisms, and selecting appropriate patients. Although dual inhibitors demonstrate considerable antitumor efficacy in a range of cancers, their capacity to engage multiple pathways frequently leads to pronounced side effects. These inhibitors interfere with the PI3K and mTOR signaling pathways, which are essential for the growth and survival of cancer cells. However, they also impact normal cells, resulting in shared toxicities, including mucositis, hyperglycemia, nausea, and fatigue. These adverse effects restrict both the dosage and duration of treatment, presenting a notable obstacle to their wider clinical use.

The emergence of resistance to dual inhibitors presents a significant challenge, as tumors may evolve mechanisms to circumvent therapeutic interventions. As time progresses, cancer cells can initiate alternative signaling pathways, develop mutations in target kinases, or utilize feedback loops within the PI3K-mTOR network, which ultimately diminishes the effectiveness of the inhibitors. This resistance constrains the sustained advantages of dual inhibitors and underscores the necessity for continuous investigation into strategies to surmount these mechanisms. Choosing the right patient population is essential for fully exploiting the therapeutic potential of dual inhibitors. Identifying and validating biomarkers that can predict patient responses to these therapies is crucial, yet it continues to pose significant challenges. The absence of dependable biomarkers makes it difficult to identify which patients are likely to benefit most, thereby adding complexity to the clinical application of dual PI3K-mTOR inhibitors.

Despite these challenges, dual inhibitors such as gedatolisib (PF-05212384), samotolisib (LY3023414), and dactolisib (NVP-BEZ235) have exhibited efficacy in both preclinical and clinical trials, demonstrating potential when utilized in combination with chemotherapy or as monotherapies in malignancies including colorectal cancer and triple-negative breast cancer. Nonetheless, adverse effects remain a considerable worry, especially when dual inhibitors are utilized with other treatments. For instance, the combination of PI3K and mTOR inhibitors, such as buparlisib and everolimus, might intensify adverse effects, including hyperglycemia and elevate the risk of infections. In contrast, dual BRAF and MEK inhibitors may improve survival but are associated with heightened risks of fever, cardiac problems, and dermatological difficulties. Effective management solutions are important to mitigate these toxicity risks. This entails consistent patient monitoring, dose adjustments as required, and supportive care to alleviate undesirable effects. Current clinical trials are essential for refining dosing protocols and calibrating the equilibrium between efficacy and safety. By enhancing these approaches, dual PI3K-mTOR inhibitors may establish themselves as a fundamental component of cancer therapy, providing more efficacious treatment alternatives while minimizing the related risks.

Future Perspectives

The future of dual PI3K-mTOR inhibitors in cancer treatment is promising; however, numerous important challenges must be resolved to realize their full potential. An important domain for the future of these drugs is the oversight of toxicity resulting from the simultaneous targeting of numerous pathways. Optimizing dosage methods, including intermittent dosing and innovative formulations promoting tumor-targeted medication delivery, may reduce side effects and increase patient tolerance. Moreover, integrating dual inhibitors with other medicines at lower doses may maintain their effectiveness while mitigating adverse effects.

A crucial domain for future research is predicting and validating predictive biomarkers. Biomarkers are essential for identifying individuals most likely to benefit from dual PI3K-mTOR inhibition, facilitating a more customized therapy strategy. Cancer polymorphism is a significant challenge; identifying the tumor subtypes most sensitive to dual inhibition will be crucial for enhancing outcomes and refining treatment options. Addressing resistance mechanisms becomes another critical area of attention. Resistance frequently arises from the activation of alternate signaling pathways or mutations in the target kinases, constraining dual inhibitors' long-term effectiveness. Investigating combination therapy with additional targeted medicines, immunotherapies, or radiation may mitigate these resistance mechanisms and improve the therapeutic window.

Furthermore, although dual PI3K-mTOR inhibitors have demonstrated potential in breast, prostate, colorectal, and pancreatic cancers, extending their use to additional tumor types, including ovarian cancer, may enhance their clinical applicability; however, more extensive, randomized trials will be essential to thoroughly determine their efficacy and clarify their position within broader cancer treatment approaches. Finally, continuous advancements in nanotechnology may significantly transform the therapeutic application of dual inhibitors. The advancement of novel nanoformulations aimed at improving drug solubility, stability, and tumor selectivity would enhance therapeutic efficacy while minimizing systemic toxicity, hence rendering therapies safer and more effective for patients.

CONCLUSION

The dual inhibition of the PI3K-mTOR pathway signifies notable progress in targeted cancer therapy, providing a more thorough blockage of essential signaling pathways that contribute to tumor growth, survival, and resistance. Research in both preclinical and clinical settings has shown the therapeutic potential of dual inhibitors like dactolisib, gedatolisib, and samotolisib across a range of cancers, including breast, prostate, colorectal, pancreatic, and ovarian tumors. These inhibitors demonstrate improved effectiveness relative to single-agent therapies by addressing compensatory mechanisms and diminishing tumor

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progression. Still, obstacles like drug resistance, toxicity, and selecting appropriate patients continue to pose considerable challenges to the broader implementation in clinical settings. Resolving these challenges via biomarker identification, refined dosing strategies, and integration with additional therapeutic approaches will be essential for enhancing these inhibitors' long-term effectiveness and safety. Ongoing research and advancement, especially in drug delivery and personalized medicine, will be crucial to fully utilize the therapeutic potential of dual PI3K-mTOR inhibitors and enhance outcomes for patients facing resistant and aggressive cancers.

CONFLICT OF INTEREST

The authors declare that they have no competing interests

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

QuillBot and ChatGPT were used to refine the language and improve readability. The authors thoroughly reviewed and edited all content and take full responsibility for its accuracy and integrity.

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