Article published on 2025-11-17

Targeting PLK1 in myelodysplastic syndromes: The Role of Rigosertib in Precision Medicine

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Chinese Journal of Applied Physiology, 2025: e20250021

Abstract Rigosertib (ON 01910.Na) is a novel multi-kinase inhibitor initially developed as a non-ATP competitive agent, targeting dysregulated signalling pathways in cancer cells, notably RAS/RAF/MEK/ERK and PI3K/AKT, alongside Polo-like kinase 1 (PLK1). Preclinical studies have demonstrated its potent anticancer effects across various malignancies, including myelodysplastic syndromes (MDS), acute myeloid leukaemia (AML), and solid tumours such as pancreatic, colorectal, and breast cancers, by inducing apoptosis, mitotic arrest, and oxidative stress. Its selective cytotoxicity spares normal cells, making it a promising therapeutic candidate. However, clinical trials have yielded mixed results; while early-phase studies showed promise, particularly in hematologic cancers, phase III trials, such as those in MDS and pancreatic cancer, failed to demonstrate significant survival benefits over standard treatments. Challenges include variable patient responses, potential resistance mechanisms, and manageable but notable toxicities like myelosuppression and fatigue. Emerging evidence suggests rigosertib's potential in paediatric cancers like neuroblastoma and its synergy with therapies such as MEK inhibitors and hypomethylating agents. Future research should focus on optimizing combination strategies, identifying predictive biomarkers, and improving drug delivery to enhance its clinical efficacy and applicability across diverse cancer types.

Keywords Multi-kinase inhibitor, Myelodysplastic Syndromes, Polo-like kinase inhibitor (Plk1)

Introduction

Rigosertib (ON 01910.Na) is a novel compound developed as a multikinase inhibitor, originally designed to be non-ATP competitive. It has demonstrated the ability to induce apoptosis and cell-cycle arrest in various human cancer cell lines, including those from breast cancer, prostate cancer, glioblastoma, non-small cell lung cancer, gastric cancer, colorectal cancer, melanoma, head and neck squamous cell carcinoma, myelodysplastic syndrome, mantle cell lymphoma, pancreatic cancer, chronic lymphocytic leukemia, and chronic myelogenous leukemia. Importantly, rigosertib has minimal impact on normal human cells, including HUVEC[1]. The exact mechanism of action of rigosertib has remained unclear despite extensive research. Early studies suggested that it directly inhibits Polo-like kinase-1

DOI: 10.62958/j.cjap.2025.021
www.cjap.ac.cn

Published by CJAP editorial office and Asian BioMed Innovation Press

(PLK1), but this finding has not been validated in subsequent studies. More recently, rigosertib has been identified as a RAS mimetic, which can affect oncogenic RAS signaling. However, studies show that rigosertib does not induce cell death via inhibition of the RAS pathway in RAS mutated rhabdomyosarcoma (RMS) and neuroblastoma (NB) cells. Interestingly, when combined with the MEK inhibitor trametinib, which has efficacy in RAS-mutated cancers, rigosertib shows a synergistic effect, inhibiting growth in RMS cell lines. This combination also delays tumor growth and extends survival in an RMS xenograft model, suggesting potential for combination therapy[2]. Rigosertib works by binding to the RAS-binding domains of RAS effectors like Raf family members (ARAF, BRAF, and RAF1) and PI3 kinase isoforms, inhibiting their interaction with active RAS. These decreases signaling through the RAS/RAF/MEK/ERK MAPK and PI3 kinase/AKT/mTOR pathways. Rigosertib also induces mitotic and oxidative stress, activating stress MAPKs such as p38 and JNK, which further disrupt signaling in the RAS pathway. The mitotic stress may be due to rigosertib, or its degradation products, binding to a site between α- and β-tubulin, similar to colchicine, which prevents microtubule growth. Preclinically, rigosertib has shown potent anticancer effects in various malignancies. It inhibits tumor growth in models of RAS-mutated colorectal and lung adenocarcinoma and suppresses pancreatic cancer progression in genetically engineered models. Additionally, rigosertib has shown efficacy in hematologic cancers like Hodgkin lymphoma and myelodysplastic syndrome. However, clinical trials combining rigosertib with gemcitabine in patients with metastatic pancreatic cancer did not improve survival or response compared to gemcitabine alone[3]. RAS mutations are common in pediatric cancers, including solid tumors like fusion-negative rhabdomyosarcoma (FN-RMS), malignant peripheral nerve sheath tumors, and neuroblastoma, as well as hematologic cancers like juvenile myelomonocytic leukemia. This study focused on the effects of rigosertib in FN-RMS and NB models that harbor RAS mutations (HRAS, KRAS, or NRAS). Both FN-RMS and NB are embryonal tumors, with origins in skeletal muscle and sympathoadrenal precursors, respectively. The study aimed to explore rigosertib's activity in pediatric solid tumors and investigate its mechanism of action, with the goal of identifying potential biomarkers for future clinical trials in pediatric patient[4].

Development of Rigosertib

A major issue with kinase-inhibition therapies is the development of drug resistance due to mutations in the kinase's ATP binding site. To address this, researchers have focused on creating inhibitors that target areas outside the ATP binding site, which could lead to more effective cancer treatments. Between 2002 and 2003, Reddy et al. developed several small molecule kinase inhibitors based on styryl-benzyl-sulfones[5]. These inhibitors do not compete with ATP but instead allosterically block substrate binding, demonstrating strong antitumor effects. Their efficacy relies on the specific arrangement of the styryl aromatic ring, allowing them to selectively target cancer cells while reducing side effects in healthy tissues, making them a promising alternative to conventional chemotherapy. Rigosertib (ON-01910), also known as Estybon®, is a well-researched styryl-benzyl-sulfone. It is synthesized from ON-01940 through a two-step process. First, ON-01940 reacts with methyl 2-bromo acetate in a mildly basic sodium acetate solution to form ON-01500. In the second step, ON-01500 undergoes hydrolysis with sodium hydroxide in ethanol and dichloromethane, followed by washing with methyl ethyl ketone to yield rigosertib. In studies with tumor cell lines, rigosertib was found to be a potent inhibitor of the mitotic kinase Plk1, leading to mitotic arrest in the cells[6]. Rigosertib also demonstrated some affinity for other kinases such as PDGFR, Abl, Flt-1, CDK1, Plk2, Src, and Fyn, which share similar binding site features. the initial discovery of rigosertib, research has grown significantly, uncovering new details about its mechanisms and potential targets. These include pathways such as PI3K–Akt, the Ras–Raf signaling cascade, and microtubule dynamics[7].

Chemistry

Rigosertib (ON 01910.Na) is a small molecule multi-kinase inhibitor that shows significant promise in cancer treatment, particularly for myelodysplastic syndromes (MDS). Its chemical structure is sodium 4-[(2,4-dioxopyrimidin-1-yl) methyl] benzenesulfonate, with a molecular formula of $C_{12}H_{11}N_2NaO_6S$ and a molecular weight of 334.29 g/mol. The structure consists of three primary components: a pyrimidine-2,4-dione (uracil derivative) core, a benzyl group connected via a methylene (-CH_2-) linker, and a sulfonate group (-SO_3Na).

The pyrimidine-2,4-dione core, an aromatic heterocyclic ring containing two nitrogen atoms and two keto groups, plays a crucial role in binding kinase proteins due to its hydrogen-bond acceptor sites. Its similarity to uracil enhances its interaction with

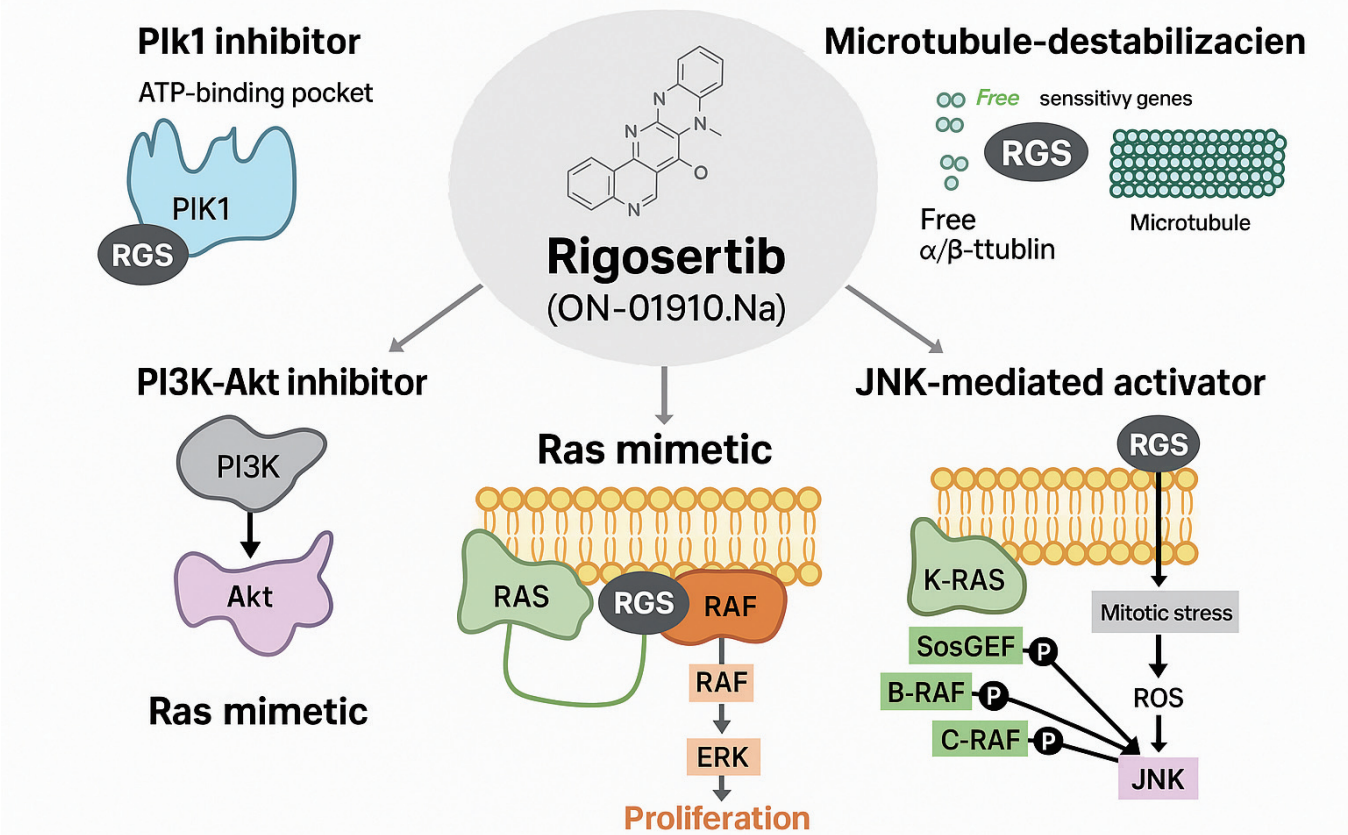

Figure 1. Scheme of development of the rigosertib molecule

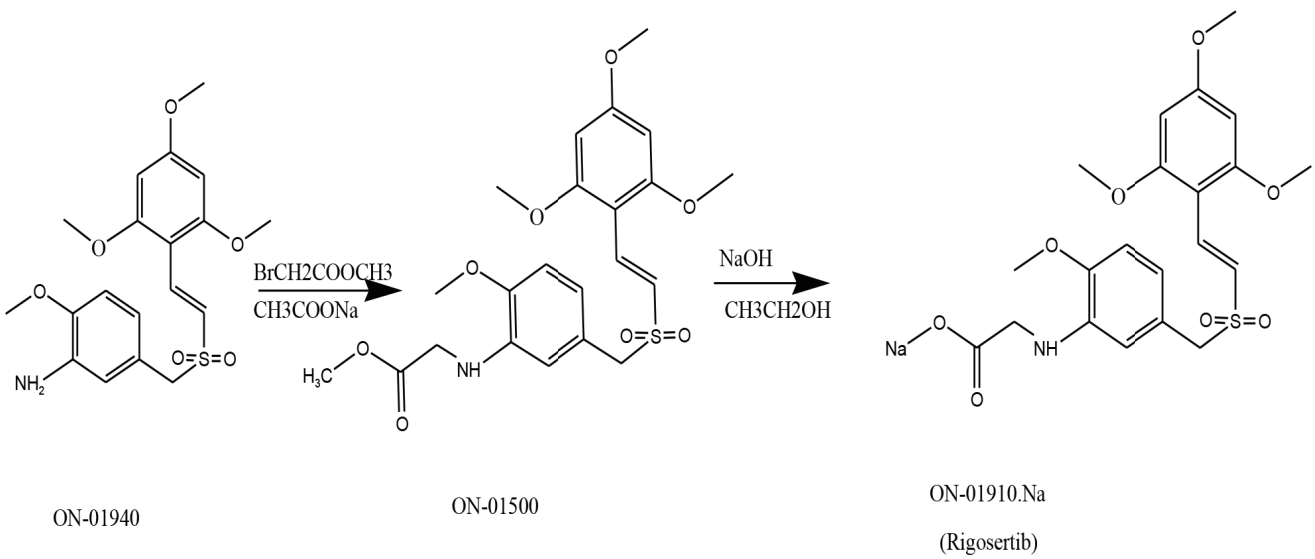

Figure 2. Synthesis of rigosertib

nucleotide-binding domains. The benzyl group adds hydrophobic properties and contributes to binding efficiency through π-π interactions. The sulfonate group provides excellent water solubility, making the drug suitable for intravenous administration. The sodium ion neutralizes the negative charge of the sulfonate group, ensuring stability and compatibility in physiological environments. Overall, the molecule's design balances hydrophobic and hydrophilic properties, contributing to its bioavailability and therapeutic effectiveness.

The drug's synthesis involves a systematic approach. The pyrimidine-2,4-dione core is created by cyclizing urea with β-dicarbonyl compounds. The

resulting pyrimidine ring is then alkylated with benzyl halides to introduce the benzyl group. Finally, the benzylated intermediate undergoes sulfonation with chlorosulfonic acid, followed by neutralization with sodium hydroxide, yielding the final compound. This process ensures the production of a stable, bioactive molecule suitable for pharmaceutical use[8].

Mechanism of Action

Mechanism action of myelodysplastic syndromes

Rigosertib exerts its therapeutic effects in myelodysplastic syndromes (MDS) through a dual mechanism of action that combines RAS-mimetic activity with inhibition of Polo-like kinase 1 (PLK1). These complementary actions enable it to target abnormal signaling pathways and disrupt malignant cell division, making it particularly effective in addressing the pathological features of MDS[9].

PLK1 is a vital regulator of the cell cycle, particularly during mitosis, and is commonly overexpressed in MDS. Its overactivity contributes to abnormal cell division and genomic instability, hallmarks of the disease. Rigosertib directly targets PLK1, interfering with mitotic spindle assembly and arresting cells at the G2/M checkpoint of the cell cycle. This interruption in mitotic progression results in mitotic failure, increased production of reactive oxygen species, and ultimately, apoptosis of the affected malignant cells[10].

Selective Cytotoxicity

Rigosertib's unique ability to target highly proliferative and dysregulated cells makes it particularly effective in treating higher-risk subtypes of MDS. By exploiting the vulnerabilities in both the RAS and PLK1 pathways, it specifically targets the malignant clonal populations responsible for disease progression[11]. This selective mechanism helps suppress clonal expansion, reduce the disease burden, and improve haematopoiesis, ultimately benefiting patients with MDS by promoting healthier blood cell production and improving overall outcomes[12].

The Pharmacodynamics and Pharmacokinetics of Rigosertib

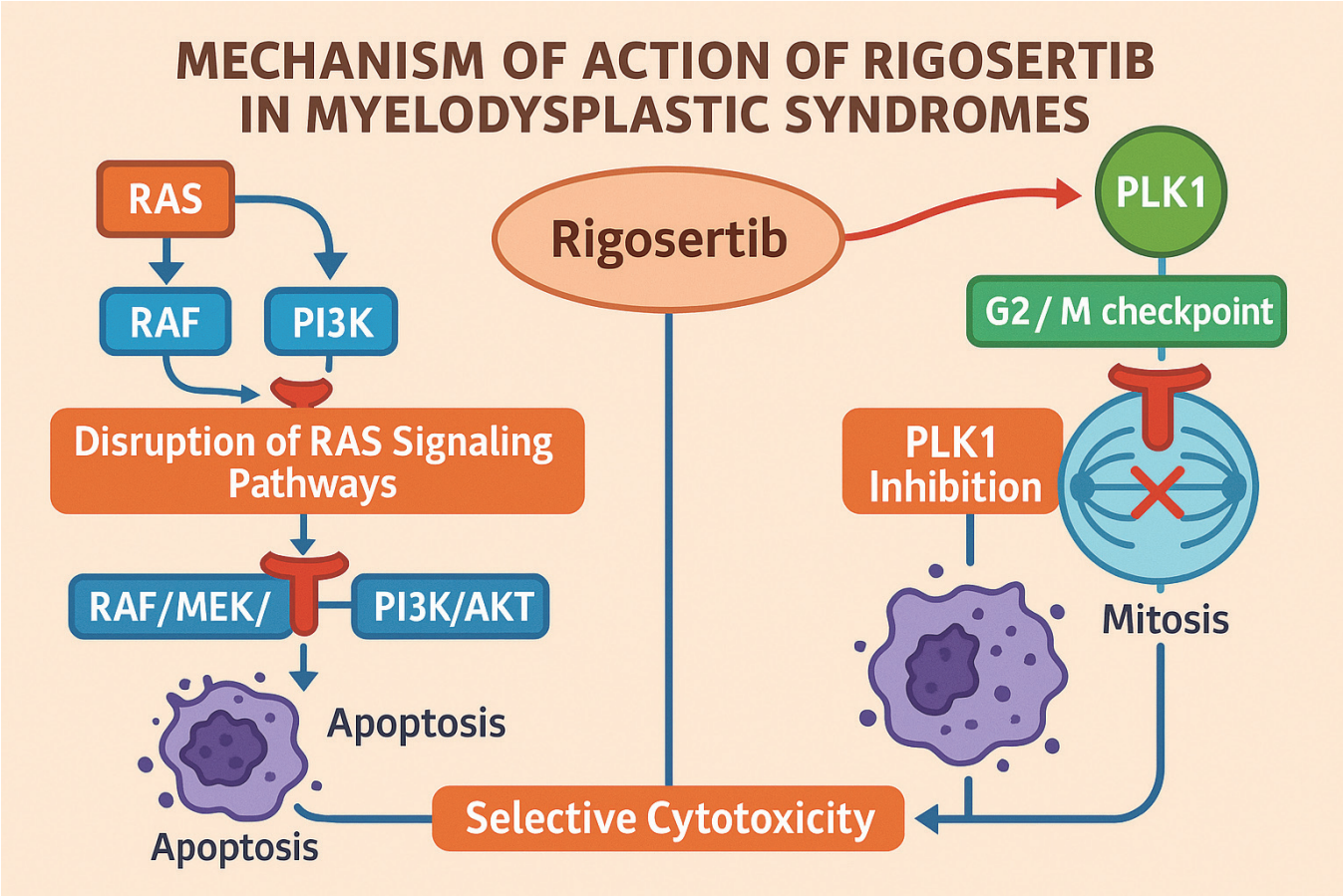

Figure 3. Mechanism action of myelodysplastic syndromes

Pharmacodynamics of Rigosertib

Rigosertib is a small molecule with a distinctive mechanism of action that influences multiple critical signaling pathways in cancer cells, making it a promising therapeutic agent for various malignancies, especially those involving mutations in the Ras signaling pathway[13].

1. Inhibition of PI3K-AKT and Ras Pathways: One of the primary mechanisms of rigosertib is its ability to disrupt key oncogenic pathways, particularly the Ras-Raf-MEK-ERK and PI3K-AKT pathways. These pathways are frequently deregulated in cancer cells, contributing to uncontrolled cell proliferation and survival. Rigosertib inhibits the activation of these pathways, thereby reducing cell growth and inducing apoptosis in tumor cells.

2. Binding to RAF's Ras-Binding Domain: Rigosertib has a specific binding site in the Ras-binding domain of RAF proteins. By preventing the interaction between RAS and RAF, the drug effectively blocks RAF activation and its downstream signaling. This disruption of signaling pathways helps reduce the tumor cells' ability to proliferate and survive, particularly in cancers driven by RAS mutations, such as pancreatic and lung cancer.

3. Mitotic Arrest and DNA Repair Inhibition: Rigosertib also targets the cell cycle by interfering with the mitotic process. It disrupts spindle assembly and chromosome segregation, leading to mitotic arrest. As a result, cancer cells cannot complete cell division, which forces them into apoptosis. Additionally, rigosertib inhibits DNA repair mechanisms, further compounding its anti-cancer effects by preventing the repair of damaged DNA in rapidly dividing tumor cells.

4. Impact on the Tumor Microenvironment: Rigosertib's action extends beyond individual cancer cells. It may also alter the tumor microenvironment by modulating key signaling pathways involved in cell survival, migration, and invasion. Through this modulation, rigosertib could help to enhance the immune response against the tumor and suppress factors that promote tumor progression, such as immunosuppressive cytokines.

5. Autophagy Inhibition: Another notable effect of rigosertib is its ability to influence autophagy, a process that cancer cells often use to survive under stress. By inhibiting autophagy, rigosertib weakens cancer cells' ability to cope with stress and forces them to undergo programmed cell death, thus contributing to its anti-tumor activity.

Due to these diverse effects on cellular signaling, mitosis, DNA repair, and the tumor microenvironment, rigosertib holds significant promise for treating cancers with RAS mutations, such as pancreatic cancer and non-small cell lung cancer. It has been studied in clinical trials for both hematologic cancers, such as myelodysplastic syndromes, and solid tumors[14].

Pharmacokinetics of Rigosertib

Understanding the pharmacokinetic properties of rigosertib is essential for optimizing its dosing regimen and clinical efficacy. Here's a detailed look at its absorption, distribution, metabolism, and elimination[15]:

1. Absorption: Rigosertib is typically administered orally, either in the form of a tablet or a suspension. Although its exact bioavailability is not fully defined, rigosertib is absorbed through the gastrointestinal tract after oral administration. Peak plasma concentrations are usually reached within 2 to 4 hours (Tmax), indicating a relatively fast absorption profile[16].

2. Distribution: Once absorbed, rigosertib is widely distributed throughout the body, including to tumor tissues. It has a high volume of distribution (Vd), which suggests that it is well-dispersed into different tissues, a key characteristic for its efficacy against solid tumors. The drug is highly bound to plasma proteins, which may affect its distribution, therapeutic action, and potential drug interactions. Although specific tissue concentration data are limited, rigosertib is expected to penetrate tumor tissues effectively due to its molecular structure.

3. Metabolism: Rigosertib undergoes metabolism primarily in the liver via the cytochrome P450 enzyme system. Although the specific CYP enzymes involved are not entirely clarified, it is known that the drug itself is the main active form, with its metabolites being less potent or inactive. This metabolism process is crucial in determining the drug's overall therapeutic effect and potential interactions with other medications.

4. Elimination: Rigosertib has a half-life ranging from 8 to 12 hours, which supports intermittent dosing schedules. It is primarily eliminated through the feces, with a smaller portion excreted in the urine. This indicates that rigosertib is mainly processed and eliminated by the liver, with the kidneys playing a secondary role in its excretion.

5. Dose and Administration: The dosing of rigosertib is often determined based on body surface area (BSA) or fixed doses, depending on the specific clinical scenario and patient characteristics. Given its pharmacokinetic profile, dose adjustments may be required in individuals with liver dysfunction, as the

liver is the primary organ responsible for metabolizing the drug. Additionally, monitoring for toxicity is necessary, particularly for patients with pre-existing conditions that could affect drug metabolism or elimination[17].

Preclinical studies on rigosertib

Preclinical studies of rigosertib have provided extensive evidence of its potential as a therapeutic agent in various cancers, particularly those with mutations in the Ras and PI3K-AKT signaling pathways. These studies have elucidated the drug's mechanisms of action, demonstrated its efficacy across a range of cancer models, and explored its potential for combination therapies. Below is a detailed summary of these preclinical findings, focusing on rigosertib' s mechanisms of action, its effects in solid and hematologic cancer models, its combination potential, and its safety profile[18].

Rigosertib Clinical Trials for Cancer Therapy

Preclinical in vivo studies established that rigosertib possesses a favourable safety profile, demonstrating no significant toxic effects such as myelotoxicity, neuropathy, or cardiotoxicity. Additionally, it was found to effectively inhibit the growth of several cancers, including liver, breast, and pancreatic tumors. Based on these promising results, rigosertib was swiftly introduced into clinical trials to assess its therapeutic potential across a broad range of cancers, including both solid tumors and hematological malignancies[19].

Safety and Toxicity Considerations

One of the key factors influencing the clinical development of rigosertib is its safety profile. While generally manageable, the drug is associated with several adverse effects. Common toxicities observed in clinical trials include myelosuppression, gastrointestinal disturbances, and fatigue. These side effects, while expected in many anticancer agents, can be particularly concerning for elderly or immunocompromised patients, such as those with MDS.

More severe adverse events, including sepsis and neutropenia, have also been reported. Such complications highlight potential risks associated with rigosertib treatment, especially in vulnerable patient populations. Given these concerns, further efforts are needed to optimize dosing strategies, identify patients who are most likely to tolerate treatment, and explore combination therapies that might mitigate toxicity while enhancing efficacy[22].

Conclusion

Rigosertib represents a promising yet complex

Table 1. Preclinical Studies on Rigosertib Chart

Category	Details
Mechanisms of Action	Binds RAF Ras-binding domain; blocks downstream signaling; reduces proliferation & induces apoptosis (esp. Ras-driven cancers). - PI3K-AKT Inhibition: Reduces AKT phosphorylation; impairs survival & promotes cell death. - Mitotic Disruption & DNA Repair Inhibition: Interferes with spindle assembly; causes mitotic arrest and DNA damage accumulation. - Autophagy Inhibition: Blocks survival mechanism in stressed cancer cells; increases apoptosis.
Efficacy Solid Tumors	Pancreatic Cancer: Effective in KRAS-mutant PDAC; inhibits growth and induces apoptosis. - NSCLC: Reduces proliferation in Ras/EGFR mutant tumors; enhances chemotherapy sensitivity. - Colorectal Cancer: Targets Ras/PI3K-AKT pathways; synergistic effects with chemotherapy.
Efficacy Hematologic Cancers	MDS: Inhibits abnormal growth; improves blood cell differentiation; supports clinical development. - AML: Induces apoptosis & cell cycle arrest; reverses chemo-resistance.
Combination Therapy Potential	With Chemotherapy: Enhances effects of drugs like gemcitabine; overcomes resistance. - With Targeted Therapies: Synergizes with MEK & PI3K inhibitors. - With Immunotherapy: Modulates tumor microenvironment; improves response to immune checkpoint inhibitors.
Safety & Toxicity Profile	Well Tolerated in animal studies. - Mild GI and Hematologic Toxicities at high doses or in combinations. - Importance of Dosing Optimization to reduce adverse effects in future clinical use.

Table 2. Rigosertib Clinical Trials for Cancer Therapy

Phase	Cancer Type	Administration	Trial Results	Notable Findings
Preclinical	Liver, Breast, Pancreatic (mouse models)	IV	Inhibited tumor growth, minimal toxicity	No myelotoxicity, neuropathy, or cardiotoxicity
Phase I	Solid Tumors & Haematological	IV (1800 mg/24h, 3-day infusion, biweekly)	Well tolerated; common AEs: fatigue, GI, urinary symptoms	Rare thrombocytopenia and myelosuppression; promising for MDS patients
Phase I	Solid Tumors & Haematological	Oral (560 mg b.i.d.)	Mild toxicities (urinary, GI, hypotension, anorexia)	Dose-limiting toxicity at 700 mg b.i.d[20].
Phase II	NSCLC, Squamous Cell Carcinomas, MDS, Leukemia	IV & Oral	Some hematological response in MDS and leukemias	Monotherapy and combination trials (with azacitidine, decitabine)
Phase III	MDS	IV	Median OS: 8.2 months (vs. 5.9 in control); no CR or PR	Modest bone marrow blast reduction; no significant survival benefit[21]
Phase III	Pancreatic Adenocarcinoma	IV + Gemcitabine	No improvement in survival or response rate	Clinical results did not reflect preclinical promise

anticancer agent with a multifaceted mechanism of action, targeting critical oncogenic pathways such as RAS/RAF/MEK/ERK, PI3K/AKT, and PLK1, while demonstrating selective cytotoxicity against malignant cells in preclinical models. Its ability to induce apoptosis, disrupt mitosis, and modulate the tumor microenvironment has shown significant potential in a wide range of cancers, including myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and certain solid tumors like neuroblastoma and breast cancer. However, the translation of these preclinical successes into clinical benefits has been inconsistent, as evidenced by the failure of phase III trials in MDS and pancreatic cancer to improve overall survival compared to standard therapies. Factors such as suboptimal patient selection, pharmacokinetic limitations, and emerging resistance mechanisms may contribute to these disappointing outcomes. Despite these setbacks, rigosertib's favourable safety profile and synergistic potential with therapies like hypomethylating agents, chemotherapy, and targeted inhibitors underscore its continued relevance. Moving forward, optimizing rigosertib's clinical utility will require a focus on combination strategies, the identification of predictive biomarkers to enhance patient stratification, and advancements in drug formulations to improve bioavailability and reduce toxicity. While challenges remain, rigosertib's unique mechanism and preclinical efficacy suggest it could still play a valuable role in personalized cancer therapy, particularly for hematologic malignancies and RAS-driven cancers, pending further research and refinement.

Conflict of interest

The authors declare that there is no conflict of interest.

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