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Review Article

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SELPERCATINIB: A SYSTEMATIC REVIEW OF NOVEL TARGETED THERAPY FOR RET POSITIVE CANCERS

[1]Neethu R.*, [2]Lokesh. Mahajan and [3]Nishigandh Mokal

[1]Assistance Professor, Department of Pharmacology, [2]Final Year Student, Bachelor of Pharmacy, [3]Final Year Student, Bachelor of Pharmacy, NCRD's Sterling Institute of Pharmacy, Nerul, Navi Mumbai, Maharashtra 400706, India.

***Corresponding Author: Neethu R.**

Assistance Professor, Department of Pharmacology, NCRD's Sterling Institute of Pharmacy, Nerul, Navi Mumbai, Maharashtra 400706, India.

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ABSTRACT

Selpercatinib, marketed as Retevmo or Retsevmo, is an orally administered drug that selectively inhibits the rearranged during transfection (RET) kinase. Its primary indication is the treatment of advanced non-small cell lung cancer (NSCLC) with RET gene fusions. Additionally, selpercatinib has shown efficacy in other clinical applications, including the treatment of medullary thyroid cancer, papillary thyroid cancers, offering a targeted therapeutic option for patients with these RET-driven cancers. Selpercatinib demonstrated a favorable tolerability profile, with most adverse events being manageable through dose adjustments. The safety profile was acceptable, and only a limited number of patients were forced to discontinue treatment due to adverse events related to selpercatinib. This suggests that the benefits of selpercatinib can be achieved while minimizing the impact of treatment-related side effects. Recent clinical trials have confirmed the efficacy of selpercatinib (Retevmo) in treating cancers with RET gene alterations, outperforming standard treatments in prolonging progression-free survival for patients with lung cancer and thyroid cancer. Selpercatinib (Retevmo) is antineoplastic drug approved by FDA. This oral medication has been shown to effectively target and inhibit the abnormal proteins driving tumor growth in solid cancers with RET mutations or fusions, offering a promising therapeutic option for patients with these specific genetic changes.[1] The LIBRETTO-431 trial demonstrated that selpercatinib significantly improved treatment outcomes for patients with advanced non-small cell lung cancer (NSCLC) harboring RET fusions. Specifically, selpercatinib more than doubled the median progression-free survival compared to chemotherapy with or without pembrolizumab (Keytruda).[2] Furthermore, the LIBRETTO-531 trial showed that selpercatinib outperformed two others targeted therapies in patients with advanced medullary thyroid cancer containing RET mutations, achieving superior results in progression-free survival and other key measures.[3] On the basis of results obtained from clinical trials, selpercatinib drug is found to be providing progression free survival, efficacy, safety and have better tolerability profile while minimizing side effects as compared to other cancer treatment options.

KEYWORDS: Selpercatinib, RET Fusion, Selective tyrosine kinase inhibitors, non-small cell lung cancer (NSCLC).

INTRODUCTION

Lung cancer is a significant global health challenge and ranks as the second most common malignant tumor. The long-term prognosis for patients remains challenging, with a notably poor survival rate. Non-small cell lung cancer (NSCLC) makes up about 80% to 85% of lung cancer cases and is frequently diagnosed at a later stage. For advanced NSCLC, treatment commonly involves chemotherapy regimens containing platinum, but the five-year survival rate is still around 15%.

RET gene fusions are present in a small percentage of NSCLC cases, ranging from 0.7% to 2%, and are typically seen in younger patients and those who have never smoked. Among the various fusion genes identified, the most frequently observed partners are KIF5B, CCDC6, and NCOA.[4]

RET mutations are linked to various cancers, particularly medullary thyroid carcinoma (MTC), and can be either germline or somatic.

1. Germline RET Mutations (25%): These are inherited and present in all cells of the body. They are often associated with hereditary cancer syndromes, such as Multiple Endocrine Neoplasia type 2 (MEN2). People with germline mutations are at a higher risk for cancers like MTC, and they can pass the mutation to their children.
2. Somatic RET Mutations (75%): These mutations develop during a person's lifetime and affect only

specific cells, without being passed on to future generations. Somatic mutations are more common in sporadic cases of cancers like MTC and also occur in other types, such as non-small cell lung cancer (NSCLC).[4]

Above classification reflects the general distribution of RET mutations in these cancers.

Oncogenesis involving RET can occur through activating mutations, either germline or somatic, and also via chromosomal rearrangements. These rearrangements lead to the formation of a fusion protein in which the RET kinase domain is linked to another protein with a dimerization domain. The molecular basis for these RET fusions likely arises from errors in the repair of DNA double-strand breaks. Specifically, chromosomal breakpoints result in the joining of the 3′ end of RET, which encodes the kinase domain, to the 5′ end of another gene. This partner gene typically encodes a domain responsible for dimerization and localization, ultimately creating an active fusion protein that drives oncogenic signalling.

The RET oncogene was initially discovered through experiments involving the transfection of NIH3T3 cells in 1985. This proto-oncogene encodes a receptor tyrosine kinase and produces two main isoforms due to alternative splicing: one isoform with 1072 amino acids and a longer one with 1114 amino acids. These isoforms differ in their C-terminal regions, which can influence their functional roles in cellular processes.[5]

RET (Rearranged during Transfection) is activated through DNA rearrangements that involve the 3′ region of the RET proto-oncogene. This rearrangement fuses the RET gene with the 5′ regions of other genes that encode dimerization domains, such as coiled coil domains, which are essential for its constant activation of RAS/MAPK and PI3K/AKT pathways, involved in cell growth, proliferation, differentiation, survival, and migration. Such genetic alterations are found in various human cancers, including those of the thyroid, lung, colorectal, breast, and salivary glands. RET gene mutations are linked to multiple endocrine neoplasia types 2A and 2B, which can result in medullary thyroid cancer and pheochromocytoma. Ongoing research is focused on developing inhibitors that target RET kinase. Additionally, mutations in RET are associated with Hirschsprung's disease, a developmental disorder affecting the enteric nervous system. Currently, RET-selective tyrosine kinase inhibitors (TKIs), such as Selpercatinib, are approved by FDA for treating non-small cell lung cancer (NSCLC) with RET fusions, Medullary thyroid cancer, papillary thyroid cancer and locally advanced or metastatic ret fusion positive solid tumours.[5,6]

Aberrant activation of the RET gene can occur through three main mechanisms: point mutations, gene fusions, and overexpression. Point mutations in RET are commonly associated with specific types of familial and sporadic thyroid cancers, such as multiple endocrine neoplasia type 2 (MEN2), which often involves medullary thyroid cancers and adrenal pheochromocytomas.

RET gene fusions arise from chromosomal rearrangements that create hybrid proteins, combining the kinase domain of RET with parts of other proteins, leading to constant activation of RET signaling. These fusions are frequently seen in papillary thyroid carcinoma and certain types of non-small cell lung cancer (NSCLC).

Additionally, overexpression of RET can occur due to gene amplification or enhanced transcriptional activity, contributing to tumorigenesis. This overactivity has been noted in cancers such as NSCLC and colorectal cancer. Each of these mechanisms—mutations, fusions, and overexpression—plays a role in driving cancer progression and serves as a potential target for therapy.[7]

Selpercatinib has shown a protective effect on the central nervous system (CNS) in clinical trials, where patients exhibited a lower rate of CNS metastases compared to standard treatments. This is particularly important for patients with RET-altered cancers, as CNS metastases are a common complication, especially in advanced stages of diseases like non-small cell lung cancer (NSCLC). Selpercatinib's ability to penetrate the blood-brain barrier and effectively target RET-altered tumors in the CNS contributes to its role in reducing the risk and burden of brain metastases in these patient.[8]

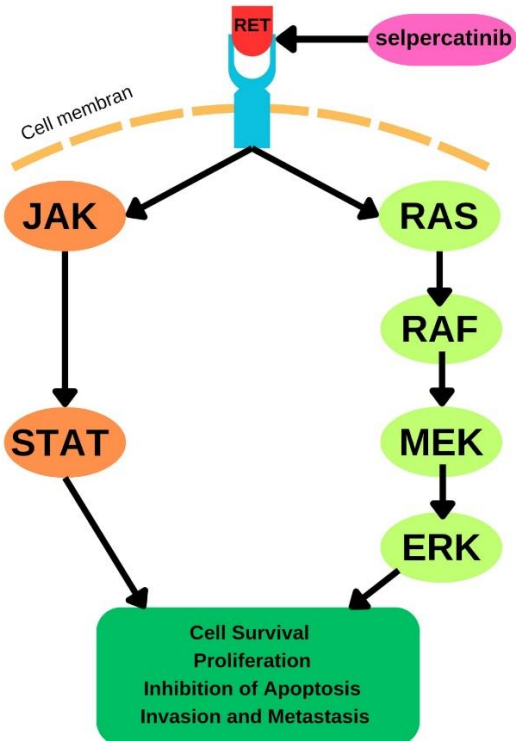
REGULATORY HISTORY

In 2018, selpercatinib received breakthrough therapy designation for treating patients with specific types of cancer, including metastatic non-small cell lung cancer (NSCLC) with RET fusion, medullary thyroid cancer (MTC) with RET mutation, and thyroid cancer with RET fusion. This designation was based on promising early results from the LIBRETTO-001 study. The FDA held multiple meetings with LOXO Oncology Inc., now a subsidiary of Eli Lilly and Company, in 2018 and 2019 to discuss the new drug application (NDA) and potential confirmatory trials. The NDA was submitted on December 4, 2019, and received priority review. The applicant also submitted an Assessment Aid to facilitate the FDA's evaluation.[9,10]

MECHANISM OF ACTION

Selpercatinib's mechanism of action involves selectively inhibiting the enzymatic activity of the RET tyrosine kinase, a key driver of certain cancers, including non-small cell lung cancer (NSCLC) and medullary thyroid cancer (MTC). By occupying the ATP-binding site of the RET protein, selpercatinib prevents the receptor from phosphorylating downstream signalling molecules, thereby disrupting critical pathways like mitogen-

activated protein kinase/extracellular signal-regulated kinase (ERK), the phosphatidylinositol-3 kinase/protein kinase B (AKT), and the Janus kinase/signal transducer and activator of transcription pathways. These pathways play a central role in cell survival, proliferation, and differentiation, and their dysregulation can lead to tumour development and progression. Selpercatinib's high selectivity for RET is a significant advantage, as it minimizes off-target effects and reduces the risk of adverse events associated with less specific tyrosine kinase inhibitors. This selectivity is achieved through a unique chemical structure that precisely fits the ATP-binding pocket of the RET kinase domain, allowing for targeted inhibition with minimal impact on other kinases. Additionally, selpercatinib has shown activity against a range of RET mutations and fusions, making it a promising therapeutic option for patients with RET-altered cancers.[11,15]



It is a potent kinase inhibitor that targets wild-type RET and various mutated RET isoforms, as well as VEGFR1 and VEGFR3 (vascular endothelial growth factor receptor is responsible for signalling tumor angiogenesis), with IC50 values ranging from 0.92 to 67.8 nmol/L. Additional in vitro enzyme assays revealed that selpercatinib also inhibits FGFR1, 2, and 3(Fibroblast Growth Factor Receptor), albeit at higher concentrations. Notably, cellular assays demonstrated that selpercatinib exhibits a higher affinity for RET, inhibiting it at concentrations approximately 60-fold lower than those required for FGFR1 and 2, and 8-fold lower than those required for VEGFR3. Certain genetic alterations, including point mutations and chromosomal rearrangements, can lead to constitutive activation of RET kinase, driving tumor cell proliferation. Selpercatinib has shown antitumor activity in various in vitro and in vivo tumour models, including those with RET V804M, RET M918T, CCDC6-RET, and KIF5B-RET alterations, which are characterized by constitutive activation of RET proteins.[9]

MECHANISM OF RESISTANCE

Resistance to selective RET inhibitors, such as selpercatinib, can emerge through multiple mechanisms, including RET solvent front mutations, which alter the drug-binding site. Although these mutations occur relatively infrequently, they can significantly compromise treatment efficacy. More commonly, resistance develops independently of RET, through acquired amplification of alternative oncogenic drivers like Mesenchymal epithelial transition (MET) or Kirsten rat sarcoma virus (KRAS). This highlights the need for next-generation RET inhibitors with improved potency against resistance mutations, as well as combination therapy strategies to address the complex mechanisms driving resistance. By targeting multiple pathways and leveraging synergistic effects, these approaches can enhance treatment outcomes for patients with RET-altered cancers, including non-small cell lung cancer (NSCLC) and medullary thyroid cancer (MTC).[12,13,22]

PHARMACODYNAMICS

A clinical trial was conducted to assess the effects of a drug on the heart's electrical activity. The study involved:

- 32 healthy participants
- Randomized and double-blind design
- Placebo and positive controls
- Four-way crossover ECG assessment

This means that each participant received four different treatments (including placebo and positive controls) in a random order, and their ECG readings were taken after each treatment. The study aimed to evaluate the drug's effects on the heart's electrical activity in a controlled and unbiased manner.

This study tested the effects of selpercatinib (a cancer drug) on the heart's electrical activity in 32 healthy people. The results showed that high doses of selpercatinib (320mg and 640mg) slightly increased the time it takes for the heart to recharge between beats (called QTcF interval). This increase was more noticeable with the higher dose.

It produces following results.

- High doses of selpercatinib prolonged the QTcF interval by 8-10 milliseconds (a small increase).
- The higher dose (640mg) caused a slightly greater increase.
- A mathematical model predicted that the recommended dose (160mg twice daily) would cause a smaller increase (around 10-17 milliseconds).

- In a separate study with cancer patients, the recommended dose caused an increase of around 22 milliseconds after 8 days of treatment.

Overall, the study suggests that selpercatinib can affect the heart's electrical activity, but the impact is relatively small and may not be clinically significant.[14]

PHARMOKINETICS

Selpercatinib's pharmacokinetics were assessed in patients with advanced solid tumors receiving 160 mg twice daily. It is observed that

- Steady-state exposure increased slightly more than proportionally with dose escalation (20 mg-240 mg twice daily).
- Steady-state was achieved within 7 days.
- Median accumulation ratio: 3.4-fold (AUC) and 2.66-fold (Cmax) with 160 mg twice daily.
- Mean steady-state parameters:
- Cmax: 2,980 ng/mL
- AUC0-24h: 51,600 ng*h/mL
- Half-life (t½): 24.5 hours
- Clearance (CLss/F): 6 L/hr

Pharmacokinetic profiles were similar between cancer patients and healthy volunteers.[14,1]

Pharmacokinetic Parameters

- **Absorption**

The pharmacokinetics of selpercatinib, a targeted cancer therapy, have been extensively characterized. Following oral administration, selpercatinib is rapidly absorbed, reaching peak plasma concentrations within approximately 2 hours. Its absolute oral bioavailability is 73.2%, indicating a relatively high extent of absorption.

Food intake can influence selpercatinib's pharmacokinetics. When administered with a high-fat, high-calorie meal, the area under the plasma concentration-time curve (AUC) increases by 9%, while the peak concentration (Cmax) decreases by 14%. Additionally, the time to reach peak concentration (Tmax) is delayed from 1.5 to 4 hours.

- **Distribution**

Selpercatinib's distribution is characterized by an apparent volume of distribution (Vss/F) of 191 litres, indicating extensive tissue distribution. The drug is highly bound to plasma proteins (97%), which is independent of concentration. The blood-to-plasma concentration ratio is 0.7.

- **Metabolism**

These studies reveal that selpercatinib is primarily metabolized by the cytochrome P450 enzyme CYP3A4. Following administration of a radiolabelled dose, unchanged selpercatinib accounts for 86% of the radioactive drug components in plasma.

- **Elimination**

It occurs primarily through faecal excretion, with 69% of the administered radioactivity recovered in faeces, while 24% is recovered in urine. These findings provide valuable insights into selpercatinib's pharmacokinetic properties, informing dosing strategies and potential interactions.[20]

CLINICAL INDICATIONS

- Non-Small Cell Lung Cancer (NSCLC**):** Selpercatinib is indicated for adults with locally advanced or metastatic NSCLC harboring a RET gene fusion, confirmed via an FDA-approved test.
- Medullary Thyroid Cancer (MTC**):** Approved for adults and children (aged 2 years and older) with advanced or metastatic MTC involving a RET mutation, requiring systemic therapy. This was initially approved under an accelerated pathway based on response rate and duration, with continued approval contingent on clinical benefit confirmation in future trials.
- RET Fusion-Positive Thyroid Cancer**:** Suitable for adults and children (aged 2 years and older) with advanced or metastatic thyroid cancer, characterized by a RET gene fusion, who have not responded to radioactive iodine treatment and require systemic therapy.
- RET Fusion-Positive Solid Tumors**:** Indicated for adults and children (aged 2 years and older) with locally advanced or metastatic solid tumors that have a RET gene fusion and have either progressed after prior treatment or lack satisfactory alternative options. Approved under an accelerated pathway based on response rate and duration, with continued approval depending on the confirmation of clinical benefit in subsequent trials.[20]

SAFETY AND EFFICACY

Selpercatinib, a first-in-class RET kinase inhibitor, has demonstrated efficacy in treating RET fusion-positive lung and thyroid cancers. Its safety and efficacy were evaluated in the LIBRETTO-001 trial, a phase I/II, open-label, single-arm study that included patients with RET-altered cancers. The trial analyzed patients with RET fusion-positive NSCLC, including 69 patients without prior treatment and 247 who had previously received platinum-based chemotherapy. The primary endpoint was the objective response rate (ORR), evaluated using RECIST v1.1 criteria by an independent review committee. Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival, and safety.

- Patients without Prior Treatment**:** The ORR was 84% (95% CI: 73–92), with 6% achieving complete responses (CRs). The median DoR was 20.2 months (95% CI: 13.0 to not reached), with 40% of responses ongoing at the data cutoff (median follow-up of 20.3 months). The median PFS was 22.0 months, with 35% of patients remaining alive and progression-free (median follow-up of 21.9 months).

- Previously Treated Patients**:** The ORR was 61% (95% CI: 55–67), with 7% achieving CRs. The median DoR was 28.6 months (95% CI: 20.4 to not reached), and 49% of responses were ongoing (median follow-up of 21.2 months). The median PFS was 24.9 months, with 38% of patients alive and progression-free (median follow-up of 24.7 months).
- Patients with CNS Metastasis**:** For 26 patients with measurable baseline CNS metastasis, the intracranial ORR was 85% (95% CI: 65–96), with 27% achieving CRs.

The safety profile of selpercatinib aligned with previous findings, with common adverse events including hypertension (22%), elevated alanine aminotransferase (16%), and elevated aspartate aminotransferase (13%). No treatment-related deaths were reported. These results suggest that selpercatinib may be effective in treating RET-altered cancers beyond lung and thyroid tumors. Comprehensive genomic testing is essential for identifying eligible patients.[17,18,21]

DOSE AND ADMINISTRATION

Selpercatinib can be taken with or without food, except when using proton pump inhibitors (PPIs), which may require separate administration. The recommended dosage varies by body weight for adults and pediatric patients aged 12 years or older.

- **Patients <50 kg:** 120 mg orally twice daily
- **Patients ≥50 kg:** 160 mg orally twice daily

Dose adjustments may be necessary for patients with severe hepatic impairment to ensure safety and efficacy.[20]

DOSAGE FORM AND STRENGTH

Selpercatinib is available in capsule form with strengths of 40 mg or 80 mg.[20]

ADVERSE DRUG REACTIONS

Potential adverse reactions to selpercatinib include.

1. Hepatotoxicity
2. Interstitial lung disease/pneumonia
3. Hypertension
4. QT interval prolongation
5. Hemorrhagic events
6. Hypersensitivity reactions
7. Hypothyroidism
8. Tumor lysis syndrome
9. Impaired wound healing
10. Other adverse reactions[19]

DOSE MODIFICATIONS AND SAFETY CONSIDERATIONS

- Hepatotoxicity**:** Monitor ALT and AST levels prior to starting selpercatinib, every 2 weeks for the first 3 months, then monthly or as clinically indicated. Adjust treatment based on severity.
- Interstitial Lung Disease (ILD)/Pneumonitis**:** Monitor for respiratory symptoms. Modify or discontinue treatment based on severity.
- Hypertension**:** Ensure blood pressure is controlled before treatment. Monitor regularly, adjusting treatment as needed.
- QT Interval Prolongation**:** Monitor QT interval, electrolytes, and TSH levels regularly. Increase monitoring when co-administering with CYP3A inhibitors or QT-prolonging drugs. Adjust based on severity.
- Hemorrhagic Events**:** Discontinue permanently in cases of severe hemorrhage.
- Hypersensitivity Reactions**:** Withhold treatment and initiate corticosteroids upon reaction. Gradually resume at reduced doses upon resolution.
- **T**umor Lysis Syndrome**:** Closely monitor at-risk patients and manage clinically as needed.
- Impaired Wound Healing: Withhold selpercatinib 7 days prior to elective surgery. Avoid administration for 2 weeks post-major surgery or until adequate wound healing.
- Embryo-Fetal Toxicity: Selpercatinib may cause fetal harm. Advise females of reproductive potential to use effective contraception and discuss potential fetal risks.[19,20]

DRUG INTERACTIONS

Effects of Other Drugs on Selpercatinib

1. Antacids.

Concurrent use reduces selpercatinib plasma levels, potentially decreasing RETEVMO's anti-tumor efficacy. Avoid coadministration with PPIs, H2 receptor antagonists, and antacids. If necessary, administer RETEVMO with food (with PPIs) or adjust timing (with H2 receptor antagonists or antacids).

2. Strong/Moderate CYP3A Inhibitors

Concomitant use increases selpercatinib plasma levels, elevating the risk of adverse reactions, including QTc interval prolongation. Avoid coadministration. If unavoidable, reduce RETEVMO dosage and monitor QT interval with ECGs.

3. Strong/Moderate CYP3A Inducers

Concurrent use decreases selpercatinib plasma levels, potentially reducing RETEVMO's anti-tumor efficacy. Avoid coadministration.

Effects of selpercatinib on Other Drugs

1. CYP2C8 and CYP3A Substrates

Selpercatinib inhibits CYP2C8 and CYP3A, increasing substrate plasma levels and potentially elevating adverse reaction risk. Avoid coadministration with sensitive substrates. If necessary, follow labeling recommendations.

2. Certain P-glycoprotein (P-gp) Substrates

Selpercatinib inhibits P-gp, increasing substrate plasma levels and potentially elevating adverse reaction risk.

Avoid coadministration with sensitive substrates. If necessary, follow labeling recommendations.

Drugs responsible for prolonging QT
Selpercatinib may prolong QTc interval. Monitor QT interval with ECGs when co-administering medications that also prolong QT interval.[20]

STORAGE
Capsules of selpercatinib are stored at room temperature between 20 degree C to 25 degree C.

FUTURE DIRECTIONS
Continued research is essential to further confirm the benefits of selpercatinib in broader patient populations, especially under real-world conditions. Ongoing studies may also clarify its role as a first-line treatment and its long-term safety. The development of combination therapies involving selpercatinib could be an exciting area of future exploration, potentially improving outcomes even further.

CONCLUSION
In conclusion, Selpercatinib (RETEVMO) marks a significant paradigm shift in the treatment of RET fusion-positive non-small cell lung cancer (NSCLC) as well as in Medullary thyroid cancer (MTC). By selectively inhibiting RET kinase, Selpercatinib demonstrates remarkable efficacy, with overall response rates and durable responses in patients with advanced disease, including those pretreated with platinum-based chemotherapy and immunotherapy. Its favourable safety profile, characterized by manageable adverse events and low discontinuation rates, enhances patient quality of life. Notably, Selpercatinib's oral administration and lack of requirement for routine monitoring of QTc interval prolongation facilitate outpatient management. Ongoing research will continue to explore Selpercatinib's potential in combination regimens, earlier lines of treatment, and other RET-driven cancers, such as thyroid and pancreatic tumors. As the first FDA-approved selective RET inhibitor, Selpercatinib sets a new standard of care for RET fusion-positive NSCLC, addressing a critical unmet need and offering hope for improved outcomes in this patient population.

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