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Review Article

A Comprehensive Review of Thyroid Cancer Management using the RET Inhibitor Selpercatinib: Therapeutic and Analytical Perspectives

A Rajasekaran*, V S Thiruvengadarajan, I Ponnilavarasan, S Sabitha

KMCH College of Pharmacy, Kalapatti Road, Kovai Estate, Coimbatore, Tamil Nadu 641-048.

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ABSTRACT

Thyroid cancer, a common malignancy, often involves the Rearranged During Transfection (RET) proto-oncogene, which drives tumorigenesis through the MAPK signalling cascade. Multikinase inhibitors such as vandetanib, regorafenib, and cabozantinib, which block the RET receptor, have been used for treatment but demonstrated limited efficacy due to nonspecific target interactions. Selpercatinib, a highly selective RET receptor tyrosine kinase (RTK) inhibitor, has emerged as a promising therapeutic agent. Initially developed for the treatment of non-small cell lung cancer, it is now employed in managing thyroid cancer, particularly the papillary thyroid cancer and medullary thyroid cancer variants, in both adults and pediatric patients above two years of age. Selpercatinib acts by inhibiting tyrosine kinase mutations, thereby preventing oncogene-driven proliferation. Its effectiveness is further supported by studies that have characterized the RET proto-oncogene expression profiles in normal versus cancerous tissues. Currently marketed under the brand name Retevmo, selpercatinib is available in tablet and capsule forms (40 mg and 80 mg). Typical side effects include musculoskeletal discomfort, diarrhea, headache, nausea, vomiting, fever (pyrexia), and bleeding, underscoring the need for therapeutic drug monitoring to optimize treatment outcomes. Analytical methodologies, such as Reverse Phase High-Performance Liquid Chromatography (RP–HPLC), Liquid Chromatography–Tandem Mass Spectrometry (LC-MS/MS), and Nuclear Magnetic Resonance (NMR), have been developed and validated for determining selpercatinib and its degradation products. Additionally, bio-analytical methods for pharmacokinetic studies have been established and validated to ensure accurate drug monitoring and analysis.

INTRODUCTION

The thyroid gland is a butterfly-shaped endocrine organ located at the root of the neck, positioned on either side of the trachea and just below the thyroid cartilage (commonly known as Adam's apple). It consists of two lobes connected by a thin structure

***Corresponding Author:** A Rajasekaran
Address: *KMCH College of Pharmacy, Kalapatti Road, Kovai Estate, Coimbatore, Tamil Nadu 641-048.*
Email : principal@kmchcop.ac.in

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called the isthmus.[1]. In adults, the gland typically weighs between 20 and 40 grams.

The thyroid gland is composed of numerous follicles, which are lined with cuboidal epithelial cells known as follicular cells. In addition, parafollicular cells (C cells) are interspersed between the follicles.

Functions of Thyroid Cells:

- **Follicular Cells:** Utilize iodine to synthesize thyroid hormones, namely triiodothyronine (T3) and thyroxine (T4).
- **Parafollicular Cells (C cells):** Secrete calcitonin, a hormone that plays a crucial role in calcium homeostasis[2].

The pituitary gland regulates thyroid function by releasing **Thyroid Stimulating Hormone** (TSH), which controls the secretion of T3 and T4 from the thyroid gland. [2]

Thyroid hormones are essential for a wide range of physiological functions, including Regulating growth and metabolism, Controlling body weight and hormonal production, Supporting fetal development, Facilitating muscle contraction and heart rate and Managing blood pressure and body temperature[3]

1.1 THYROID CANCER:

Thyroid cancer – starts in thyroid gland, most thyroid cancers are differentiated cancers. Develops from thyroid follicular cells, it's a form of malignant cancer. A lump may be present (may be solid or fluid filled) at thyroid nodules are common, which may or may not be cancerous.[3]

Thyroid cancers are described as either well-differentiated, poorly differentiated, and undifferentiated. Women are more likely prone to develop thyroid cancer at three to one (3:1) ratio, it occurs in any age group but mostly after 30, and its aggressiveness increases after 55 years, often associated with no symptoms in most cases.[4]

The progression of thyroid cancer was based on a well-defined tumor progression model. Approximately about 85% of patients with DTC have an excellent prognosis followed by treatment, and between 15% and 10% of tumors will mutate into more aggressive variants which may lead to clinical manifestations and mortality.[5]

Approximately 1.1 million new cases of thyroid cancer are projected to occur worldwide in 2025. An estimated 91,000 deaths due to thyroid cancer are expected globally in 2025. About 65% of new cases are anticipated in individuals under 55 years old, while nearly 83% of deaths are expected in those aged 55 years and above. Thyroid cancer is more common in women than in men. High Human Development Index (HDI) countries report significantly higher incidence rates compared to low HDI countries, although mortality rates are relatively similar across regions. These projections underscore the growing global burden of thyroid cancer, with significant regional and demographic variations. (Fig 1)

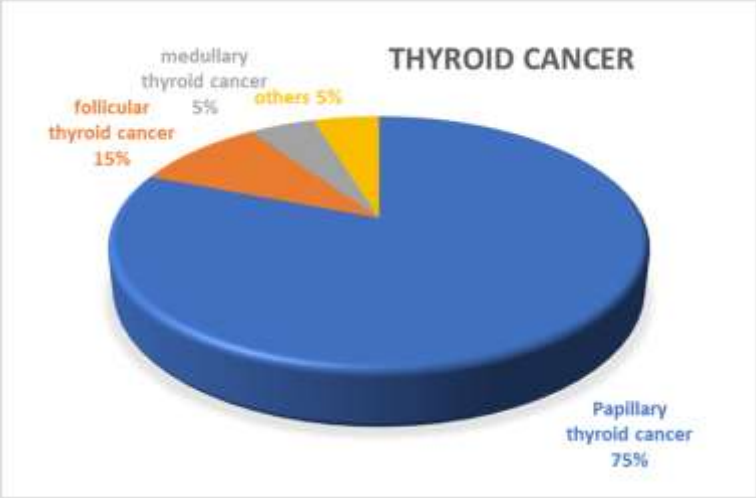

Figure 1. Epidemiological data of thyroid cancer as on 2025

1. TYPES OF THYROID CANCER:

A study found increased incidence in rates of differentiated thyroid cancer of all sizes in both men and women based on SEER data (surveillance epidemiology and end results) [6]. Among all the types of thyroid cancer Papillary Thyroid Cancer, Follicular Thyroid Cancer, and Medullary Thyroid Cancer were most prevalent.[6]

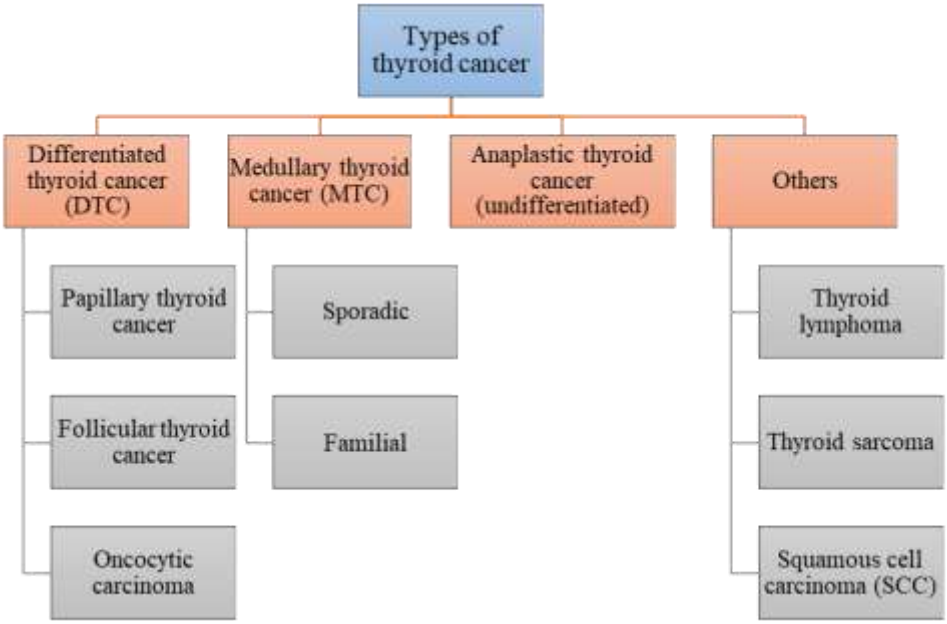

Figure 2. Types of Thyroid Cancers

2.1. PAPILLARY THYROID CANCER:

Classified based on their histological data, Papillary thyroid cancer (PTC) is most common and least aggressive type of cancer, mostly seen in the age group of 20 to 60, women (75%) comprised the majority of cases. 27% survived more than ten years after diagnosis.[7]

The size of typical papillary carcinoma often averages 2–3 cm, although lesions may be quite larger or commonly subcentimeter in size. The lesions are white, extensive sclerosis resembles a scar, and cyst formation may also appear.[7]

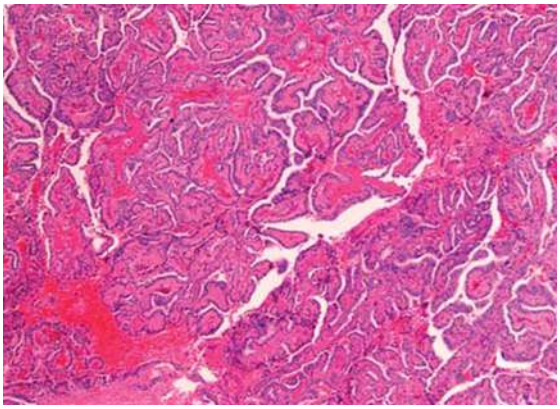

Figure 3. Histological appearance of Papillary thyroid carcinoma [7]

Although PTCs grow slowly in situ, metastasis often occurs in practice and are validated by post-operative pathological diagnoses. The common types of metastases in PTC include

- capsular invasion, which occurs in ~21–58% of cases
- extrathyroidal extension (ETE), occurs in ~11–48% of cases
- lymph node metastasis (LNM), occurs in ~14–64% of cases
- lymphatic vessel invasion (LVI), occurs in ~18–60% of cases
- Distant metastasis (DM) occurs in ~2.4% of all cases, with lung metastasis accounting for 49.1% of DM cases,
- bone metastasis accounts for 24% of DM cases
- Brain metastasis accounts for 18% of DM cases. [8]

2.2. FOLLICULAR THYROID CANCER:

Follicular thyroid cancer (FTC), second most common type of thyroid cancer, originates from the thyroid follicular cells, it has a prevalence of 10 to 15%, and FTC has capacity to invade blood vessels and metastasize distant organs.[9]

It affects older individuals between 40 and 60, approximately 20% have developed distant metastasis, whereas only 5 to 10% have developed lymph node metastasis.[9]

The cytopathology report shows malignancy, ultrasound (US) findings of high suspicion, tumor size ≥30mm, tumor volume doubling rate ≥1.0/year, and follicular neoplasms.[10]

distinguishing between FTC and FA (follicular adenoma) was difficult, factors like distant metastasis, tumor size, age, vascular invasion, histological subtype, and TERT promoter mutation, are essential for prognostic prediction and precise management of patients with FTC.[10]

FTC growth patterns that are solid, trabecular, or insular react favorably to radioactive iodine and may have a worse prognosis. Some FTCs have less well-differentiated sections that coexist, which makes it difficult to distinguish among FTC and poorly differentiated FTC (PDTC).[11]

Histological characteristics of angio-invasive and minimally invasive follicular thyroid carcinoma:

- solid and microfollicular neoplasm growth patterns encased in a thick capsule
- capsular invasion
- (c and d) invasion of vascular involvement. [11]

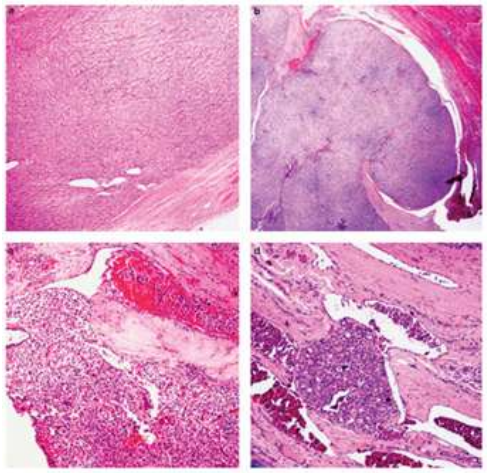

Figure 4. Histological appearance of Follicular Thyroid Cancer [11]

2.3. MEDULLARY THYROID CANCER:

Medullary thyroid cancer (MTC) is relatively rare, and occurs about 1 to 2% of all types of thyroid cancer. Associated with a high rate of mortality and low incidence, 75% of MTCs are sporadic, 25% are hereditary, either familial or occurring in association with multiple endocrine neoplasia type 2 (MEN 2) syndrome secondary to a germline mutation in the RET (Rearranged during transfection) proto-oncogene.[12]

MEN 2A, also known as Sipple syndrome, affects 60% of MEN, while MEN 2B, also designated as Wagenmann-Froboese syndrome, occurs in MTC. MEN 2A is recognized by the association of MTC with a variable occurrence of pheochromocytoma, which is present in approximately 50 percent of cases, and mild or late-onset primary hyperparathyroidism, which is present in roughly 20% of cases; 15–20% of cases can be linked to cutaneous lichen amyloidosis and Hirschsprung's disease.[13]

In MEN 2B, MTC is associated with pheochromocytoma in 50% of cases, along with mucosal neuromas, intestinal ganglio neuromatosis, corneal nerve hypertrophy, and a characteristic marfanoid habitus.[13]

MTC might result in morbidity and mortality in certain aggressive cases and may induce early metastasis. Approximately 5 to 10% of patients with sporadic MTC existing with metastases in the bones, brain, skin, and liver.[13]

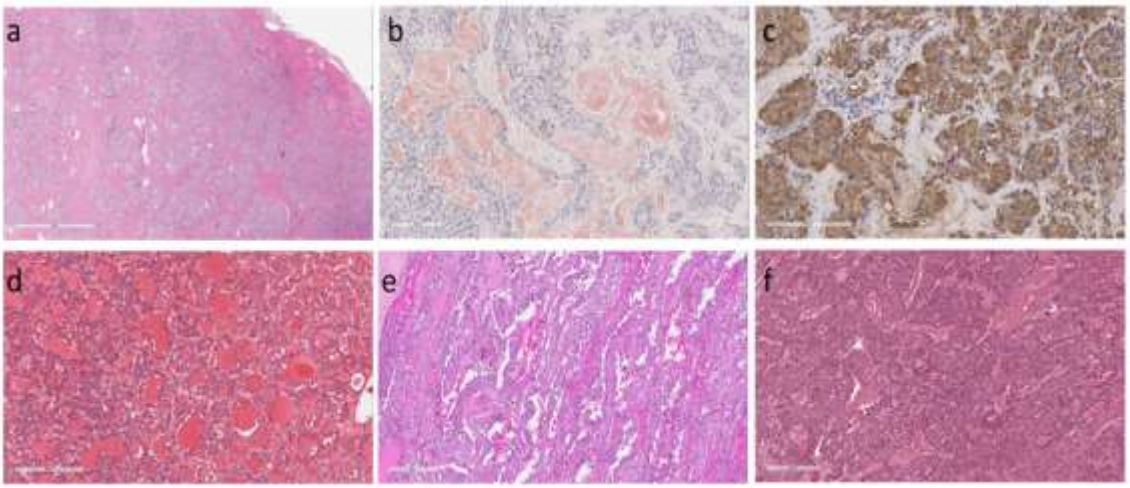

Figure 5. Histological appearance of medullary thyroid carcinoma.[14]

a. The amyloid can be recognized by its intense staining with Congo red

b. It also exhibits apple green birefringence with polarized light (not seen)

c. Tumor cells stain for calcitonin as well as for chromogranin A and carcinoembryonic antigen (not seen)

d. The diagnosis can be missed when a medullary thyroid carcinoma has a follicular architecture,

e. Pseudopapillary patterns

f. Oncocytic, which may be misclassified as follicular cell-derived lesions.[14]

2. RET MUTATION IN PTC AND MTC:

PTC is often characterized by RET chromosomal rearrangement, or point mutation of RAS or B-RAF proto-oncogenes, which can trigger the activation of mitogen-activated protein kinase (MAPK) cascade. BRAF is responsible for the

regulation of cell proliferation, differentiation, and programmed cell death. Mutations of the B-RAF, RAS, or RET genes may lead to the advancement of carcinoma, which is observed in approximately 70% of PTC instances.[15]

RET is located on chromosomal band 10q 11.2 and encodes receptor kinase involved in many signaling pathways, which plays a key role in the development of parathyroids, urogenital system, and neural crest including the brain, sympathetic and parasympathetic ganglia, adrenal medulla, enteric ganglia, and thyroid C cells. [16]

RET-PTC and MTC-related carcinogenesis is caused by chromosomal rearrangements in which the C terminal of the RET kinase domain is linked to the N terminal domains of an unrelated gene. A minimum of eleven unique genes situated on different chromosomes (intrachromosomal rearrangements) have been demonstrated to rearrange with the RET gene.[17]

RET/PTC rearrangements that have been observed and vary according to the different genetic fusion patterns; fact, these mutations are exclusively found in the rearrangements of RET/PTC1 and RET/PTC3, which are apparently the most prevalent, accounting for more than 90% of all rearrangements.

A paracentric, intrachromosomal inversion of chromosome 10q results in the RET/PTC1 and RET/PTC3 oncogenes, in which RET is fused to the activating genes NCOA4 (also referred to as ELE1 or RFG) and CCDC6 (also referred as H4). [18]

RET/PTC1 rearrangement was found to be associated with the classical variant of PTC, where the RET/PTC3 rearrangement appeared to be more commonly present in solid variant PTC tumors.[19]

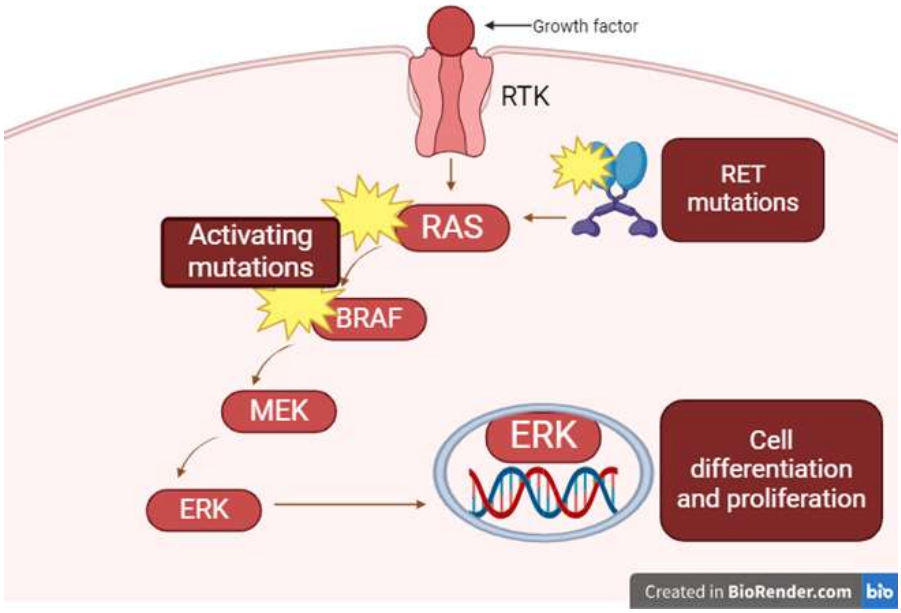

Figure 6. Scheme of cell signaling in thyroid cancer pathogenesis

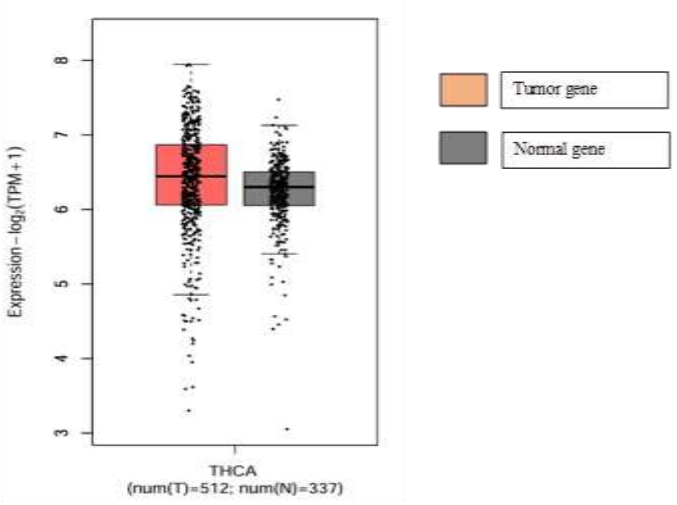

Figure 7. Gene expression profile of RET in normal and tumor gene [box plot using Gepia2 software] in thyroid tumor cells

3. CLINICAL TRIAL DATA:

The clinical development of selpercatinib for RET mutant thyroid cancer has been marked by significant progress through multiple trial phases:

LIBRETTO-001 (Phase I/II): This registrational single-arm, open-label clinical trial, conducted by Eli Lilly and Company (US), took place from May 2017 to June 2019. The study evaluated the efficacy of selpercatinib in RET mutant variant thyroid cancer (ClinicalTrials.gov identifier: NCT03157128). The results demonstrated a remarkable response rate, with nearly 70% of patients exhibiting significant clinical benefits. Follow-up over three years further validated the drug's potent and durable efficacy in RET-driven thyroid cancer.

LIBRETTO-531 (Phase III): In this trial, selpercatinib was compared with other multikinase inhibitors to assess failure-free survival rates. The study confirmed selpercatinib's consistent safety profile and superior efficacy, solidifying its position as a targeted therapy for RET mutant thyroid cancers. .[20]

Following the success of the Phase III trials, the US Food and Drug Administration (FDA) approved selpercatinib for the treatment of RET mutant thyroid cancers on **27th September 2024**. .[21]

4. SELPERCARTINIB:

In the era of precision medicine and genetic testing, the molecular profile of the tumor helps to make therapeutic decisions. Rearranged during transfection (RET) mutations are present in sporadic variants, approximately 20 to 30% of PTC, and 70 % of MTC.[22]

As per global observatory data 2023, around 586,202 (3%) of thyroid cancers reported worldwide.[23]

Drugs like vandetanib, regorafenib, and cabozantinib (Multikinase inhibitors) were known to block RET receptors and thus employed in thyroid cancer treatment, but failed due to nonspecific target interactions, as well as failure to respond to radioactive iodine treatment, so in recent years highly selective RET inhibitors like Selpercartinib and pralsetinib have been developed.[24]

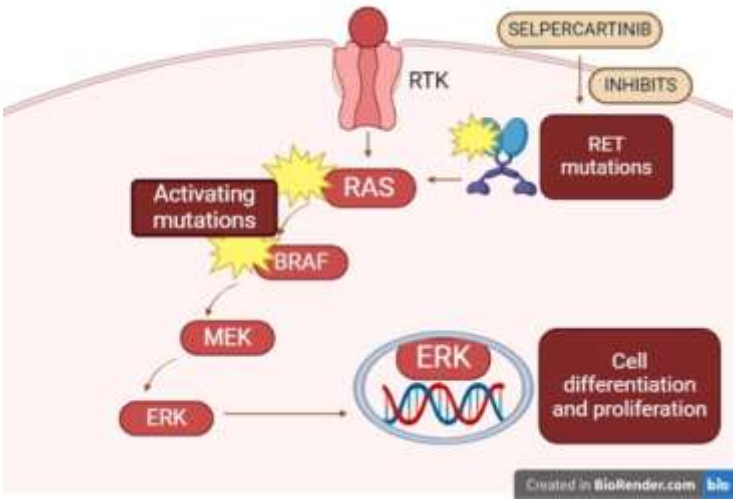

Figure 8. Mechanism of action of Selpercartinib

RETEVMO (Selpercartinib) was introduced by the USFDA, on September 27, 2024, for the treatment of RET MTC and RET PTC in adults and pediatric patients age 2 and above. [25]

Available as tablets (40 mg, 80 mg, 120 mg, 160 mg) and capsules (40 mg, 80 mg), the recommended dosage for adult and adolescent patients 12 years of age or older, is based on weight

- Less than 50 kg - 120 mg orally twice daily
- 50 kg or greater - 160 mg orally twice daily

the recommended dosage for Pediatric patients 2 to less than 12 years of age, is based on body surface area

- 0.33 to 0.65 m^2: 40 mg orally three times daily
- 0.66 to 1.08 m^2: 80 mg orally twice daily
- 1.09 to 1.52 m^2: 120 mg orally twice daily
- ≥1.53 m^2: 160 mg orally twice daily. [26]

Prior to starting RETEVMO, ALT and AST levels should be checked every two weeks for the first three months of treatment, and subsequently monthly for patients with uncontrolled hypertension.

Selpercartinib often leads to edema, diarrhea, exhaustion, dry mouth, hypertension, abdominal pain, and headache in adults with solid tumors. In children with solid tumors, the common side effects include musculoskeletal discomfort, diarrhea, headache, nausea, vomiting, pyrexia, and bleeding.[27]

Grade 3 or 4 cancers shows decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium in adults. QT prolongation, bleeding problems, decreased calcium, decreased haemoglobin, and decreased neutrophil in pediatric patients.[28]

Table 1. Physiochemical properties of Selpercartinib

PARAMETER	DESCRIPTION
Molecular weight	525.613 g/mol
CAS number	2152628-33-4
Drug status	Approved, investigational
Brand name	Retevmo, Retesvmo
Water solubility	>1mg/ml
Indication	NSCLC, RET MTC, RET PTC
Drug Bank Accession Number	DB15685[29]
appearance	White amorphous powder

Selpercartinib (Fig 10) has molecular formula $C_{29}H_{31}N_7O_3$, chemically called as 6-(2-hydroxy-2-methylpropoxy)-4-[6-[6-[(6-methoxypyridin-3-yl) methyl]-3,6- diazabicyclo [3.1.1] heptan-3- yl] pyridin-3-yl] pyrazolo [1,5-a] pyridine-3-carbonitrile. (Table 1)[30]

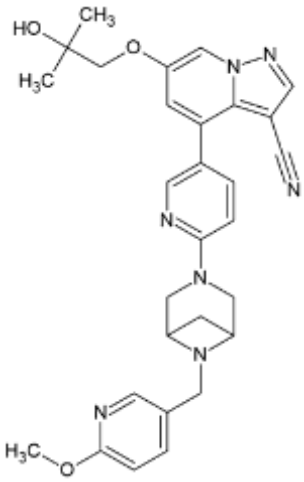

Figure 9. Structure of Selpercartinib

5. REPORTED ANALYTICAL METHODS OF SELPERCARTINB:

Several analytical methods have been developed and validated for the analysis of Selpercatinib. These methods are crucial for ensuring the quality, safety, and efficacy of the drug, as well as for monitoring its stability and pharmacokinetics

Paka Ramya *et al.,* developed an RP-HPLC method using a Hypersil ODS C18 column (250 X k4.6 mm, 5 µm) with a mobile phase consisting of 0.2% trifluoroacetic acid (pH 6.5) and acetonitrile in a ratio of 70:30 (v/v). The flow rate was set at 1 ml/min. The retention time for selpercatinib was determined to be 3.012 min. The detection wavelength was 248 nm. the method was linear, accurate, precise, robust, and cost-effective. [31]

Srinivasa Rao Katta *et al.,* developed an LC – MS method for the characterisation of degradation products, the analytes were resolved on ZORBAX Eclipse C18 (250 mm) stationary phase that was maintained employing 0.5 M sodium perchlorate at pH 5.4, methanol and acetonitrile in 50:20:30 (v/v) pumped at isocratic flow, at rate of 0.8 mL/min, the detection wavelength was 241 nm. They confirmed the presence of four degradation products based on fragmentation patterns, this method can be applied for effective quantification of impurities and degradation products (DPs) of Selpercartinib.[32]

Bheemi Reddy Divya *et al.,* performed the chromatographic resolution of selpercatinib and its impurities, along with DPs, which was effectively attained on a Zorbax C18 (250 mm × 4.6 mm, 5 µm) column using aqueous ammonium acetate and methanol in the composition of 70:30 (v/v) at pH 4.5 with 0.1% formic acid as the mobile phase, pumped isocratically at a flow rate of 0.9 mL/min and detected at 226 nm wavelength. the five degradation products (DPs) formed in different stress conditions of selpercatinib were characterized by liquid chromatography-tandem mass spectrometry (LC-MS/MS). [33]

Quin Wang *et at.,* isolated an unknown acid-forced degradation impurity of selpercatinib, designated sel-1, and purified using semi-preparative liquid chromatography (semi-prep LC) using 2mM phosphoric acid solution (contains 0.4% triethylamine adjusted to pH 2.4 with phosphoric acid) in acetonitrile 90:10 (v/v) ratio as mobile phase, flow rate was set as 1mL/min. The detection wavelength was 235nm. The purified set 1 showed high chromatographic purity of 99.1%, MTT assay revealed that set 1 exhibited significant anti-tumour activity against HepaRG and MKN-1 cell lines, with stronger. [34]

Sundararajan Raja *et al.,* developed a novel, specific, and precise RP-HPLC method for the quantification of selpercatinib in pure and its pharmaceutical dosage form. The separation was accomplished on the Zorbax C18 column (150 x

4.6 mm) with a 5µ particle size. 0.1% orthophosphoric acid and acetonitrile, 60:40 (v/v) were used as an optimized mobile phase at a flow rate of 1mL/min. The wavelength selected was 220nm. The retention time for selpercatinib was 2.653 min. the developed method was validated as per ICH Q2 (R1) guideline.[35]

Rahul Godje *et al.,* used QbD (quality by design) approach-based HPLC method development using methanol and 0.1% acetic acid 80:20 (v/v) as mobile phase. Kromasil C18 liquid chromatographic column, the flow rate was found to be 0.7 mL/min. The detection wavelength was 220nm. The retention time of selpercatinib was 3.20 minutes. The assay was found to be 99.01% for selpercatinib. And validated as per ICH Q2(R1) guideline.[36]

Rahime Senturka et al. used liquid chromatography-tandem mass spectrometry (LC MS/MS) to develop a bioanalytical method for estimating selpercatinib and pralsetinib in mouse plasma and partially in eight mouse tissue homogenates. Using an internal standard (erlotinib), the samples were prepared by protein precipitation with acetonitrile. Using methanol and ammonium hydroxide, the chromatographic gradient elution was carried out on an ethylene bridged octadecyl silica C18 column. By using positive electrospray ionization, analytes were found. The assay was validated utilizing a linear concentration range of 2–2000 ng/ml for both inhibitors. Both the within-day and between-day precision values. Additionally, the accuracy data acquired was within a reasonable range. Under every condition examined, both analytes were stable, and no discernible matrix effects or extraction losses were detected.[37]

Mohamed Attwa *et al.,* developed a highly specific, sensitive, fast liquid chromatography tandem mass spectrometry (LC-MS/MS) method for quantifying Selpercartinib (SLP) in human liver microsomes (HLMs) and it can be applied to the evaluation of metabolic stability of (SLP). The FDA's bioanalytical methodology validation requirements (linearity, selectivity, matrix effect, accuracy, precision, carryover, and extraction recovery) were followed in the validation of the LC-MS/MS method. employing a 0.4 mL/min flow rate with a mobile phase of 55% acetonitrile and an aqueous phase of 45%, 0.1% 10 mM ammonium formate in water. Using a positive ESI source in multiple reaction monitoring (MRM) mode for mass spectrometric analysis and analyte ion estimation, SLP was detected using a triple quadrupole detector (TQD). The IS-normalized matrix effect and extraction recovery were acceptable according to the FDA guidelines for the bioanalysis of SLP.[38]

Brigatinib, oratinib, prasetinib, and Selpercartinib were all simultaneously quantified in human K2-EDTA plasma by Judith Gulikers et al. The method involved chromatographic separation using a HyPURITY C18 analytical column with gradient elution using ammonium acetate in water and methanol, both of which were acidified with 0.1% formic acid. An electrospray ionization interface on a triple quad mass spectrometer was used for detection and quantification. The technique was verified and offers a quick and easy way to measure four medications using a single assay in clinical settings. [39]

Wataru Suzuki et al. devised a high-performance liquid chromatography (HPLC) method for assessing selpercatinib levels in the blood to aid in therapeutic drug monitoring (TDM) in clinical practice. Acetonitrile was used to precipitate the proteins. Acetonitrile was used to precipitate the proteins, and HPLC-UV was used to separate the internal standard (gefitinib) and selpercatinib. Using a Capcell Pak C18 MG II guard column (10

mm × 4.0 mm) and a Capcell Pak C18 MG II reversed-phase column (250 mm × 4.6 mm i.d.), chromatographic separation was accomplished. Acetonitrile in ratio of 70:30 (v/v) and 0.5% KH2PO4 (pH 4.5) are combined to form the mobile phase, which is pumped at a rate of 1.0 mL/min. At 240 nm, UV detection was carried out. This study develops a straightforward and accurate technique for measuring selpercatinib in human plasma for medicinal purposes (Table 2). [40]

Table 2. Reported analytical methods for the estimation of Selpercartinib

Sr. no	Sample	Techniques	Mobile Phase	Detection wavelength	Column	Flowrate
1	Selpercartinib	RP - HPLC	Trifluoroacetic acid and acetonitrile (70:30 v/v)	248nm	Hypersil ODS C18 column	1 ml/min
2	Selpercartinib	LC/MS	0.5 M Sodium perchlorate at pH 5.4, methanol and acetonitrile (50:20:30 v/v)	241 nm	ZORBAX Eclipse	0.8 mL/min
3	Selpercartinib	LC/MS/MS	Ammonium acetate and methanol (70:30 v/v)	226 nm	Zorbax C18 column	0.9 mL/min
4	Selpercartinib	Prep-LC, HRMS, NMR	2 mM Orthophosphoric acid in acetonitrile (90:10) as mobile phase A and acetonitrile as mobile phase B.	235 nm	Agilent 5 HC-C 18	1 ml/min
5	Selpercartinib	HPLC	0.1% Ortho phosphoric acid and Acetonitrile (60:40 v/v)	220 nm	Zorbax C18 column	1ml/min
6	Selpercartinib	RP - HPLC	Methanol and 0.1% acetic acid (80:20 v/v)	220 nm	Kromasil C18	0.7 mL/min
7	Selpercartinib	LC/MS/MS	50% Methanol/ 49.9% water/ 0.1% formic acid (v/v/v)	Mass detector (TQD)	UPLC BEH C18 column	600 µl/min
8	Selpercartinib	LC-MS/MS	Organic part (55% ACN) and an aqueous part [45% aqueous solution (0.1% 10 mM ammonium formate in H_2O)	Mass detector (TQD)	Luna 3 m PFP	0.4ml/ml
9	Selpercartinib	HPLC-MS/MS	Mobile phase A - 2 mM ammonium acetate in water (+0.1% formic acid). Mobile phase B - 2 mM ammonium acetate in methanol	Mass detector (TQD)	HyPURITY C18	500µl/min
10	Selpercartinib	HPLC	0.5% KH_2PO_4 (pH 4.5) and acetonitrile (70:30 v/v),	240 nm	Capcell Pak C18	1 ml/min

6. CONCLUSION:

This review highlights the critical role of selpercatinib in the treatment of RET-altered cancers, emphasizing its efficacy in clinical trials and its potential to significantly improve patient outcomes for those with specific genetic mutations. The review also covers the currently available analytical methods used for the quantification of selpercatinib in bulk, pharmaceutical dosage forms, and biological samples. Methods such as High-Performance

Liquid Chromatography (HPLC), Liquid Chromatography–Tandem Mass Spectrometry (LC-MS/MS), High-Resolution Mass Spectrometry (HRMS), and Nuclear Magnetic Resonance (NMR) have been developed and validated for this purpose.

This overview of analytical techniques will be valuable for advancing the development of novel methods aimed at the estimation of selpercatinib in various matrices, thereby supporting improved monitoring and therapeutic outcomes in clinical settings.

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