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DRUG EVALUATION

Selpercatinib in the treatment of thyroid cancer

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ABSTRACT

Selpercatinib, a highly selective RET inhibitor, represents a major advancement for RET-driven thyroid cancers, including medullary thyroid cancer (MTC) and radioiodine-refractory differentiated thyroid cancer (DTC). Clinical trials, such as LIBRETTO-001 and LIBRETTO-531, demonstrate its superior efficacy, safety, and tolerability compared to the less specific multikinase inhibitors, with overall response rates exceeding 84% in treatment-naïve RET-mutant MTC and 95% in RET fusion-positive DTC. Real-world studies further confirm its long-term benefits in diverse populations. With approvals from the U.S. FDA and EMA, selpercatinib is recommended as a first-line therapy for advanced RET-mutant MTC and as a second-line option for RAIR DTC. This review explores the molecular underpinnings of thyroid cancer, highlights the therapeutic landscape, and delves into the clinical performance of selpercatinib.

PLAIN LANGUAGE SUMMARY

What is thyroid cancer?

Thyroid cancer is one of the ninth most common cancers worldwide, with subtypes such as differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC). More than 90% of cases have good outcomes, but advanced stages may require additional therapies, especially when specific genetic alterations like RET mutations drive the cancer.

What is selpercatinib?

Selpercatinib is a targeted therapy designed to inhibit RET, a protein involved in the growth of some thyroid cancers. Unlike older drugs that target multiple pathways, selpercatinib focuses specifically on RET, reducing side effects while maintaining effectiveness.

How effective is it?

In clinical trials, selpercatinib showed excellent results, with response rates of 84–95% in RET-driven thyroid cancers. It significantly delayed cancer progression and may improve survival, with better tolerability compared to previous treatments. Real-world studies confirmed these findings, showing sustained benefits even in patients with complex cases.

Who can benefit?

Selpercatinib is approved for patients with advanced RET-mutant MTC as a first-line treatment and for RET fusion-positive DTC after other therapies. However, access may vary by region due to reimbursement policies.

Why does it matter?

Selpercatinib highlights the importance of precision medicine – using treatments tailored to the specific genetic features of a cancer. This approach improves outcomes and quality of life, marking a step forward in the fight against thyroid cancer.

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Selpercatinib; thyroid cancer; RET inhibitors; medullary thyroid cancer; papillary thyroid cancer; targeted therapy; safety profile; clinical efficacy

1. Introduction

With more than 820,000 estimated new cases in 2022, thyroid cancer represents the seventh most frequent malignancy worldwide [1]. Thyroid cancers are broadly categorized into differentiated thyroid cancers (DTC, approximately 95% of cases), medullary thyroid cancer (MTC, 4%), and anaplastic thyroid cancer (ATC, 1%) [2]. Among DTC, the papillary subtype is predominant, though other variants, such as follicular, oncocytic, high-grade, and poorly differentiated subtypes, are also observed.

Thyroid cancers, excluding the highly aggressive ATC, typically have an excellent prognosis, with 5-year survival rates exceeding 95% for most subtypes [3]. This favorable clinical outcome significantly influences therapeutic strategies, especially the selection of systemic treatments where long-term safety profiles are a key consideration. Surgery remains the cornerstone of curative treatment for both MTC and DTC. In DTC, additional therapies, such as radioactive iodine (RAI) and thyrotropin suppression, are employed for intermediate- and high-risk patients. For patients with metastatic disease, treatment approaches often prioritize observation over immediate systemic therapy, unless significant disease progression is evident. Local treatments,

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Article highlights

- Thyroid cancer is molecularly heterogeneous, with RET alterations playing a central role in medullary thyroid cancer (MTC) and a subset of differentiated thyroid cancers (DTC).
- RET mutations occur in over 50% of sporadic MTCs and in nearly all hereditary MTCs, making RET a key therapeutic target in this subtype.
- Multikinase inhibitors (vandetanib, cabozantinib) improved progression-free survival in MTC but are limited by frequent off-target toxicities and treatment discontinuations.
- Selpercatinib is a highly selective RET inhibitor with potent activity against common RET mutations and fusions, including the RET M918T and gatekeeper V804M mutations.
- In the LIBRETTO-001 trial, selpercatinib achieved objective response rates > 80% in RET-mutant MTC and > 90% in RET-fusion positive DTC, with prolonged progression-free survival.
- The phase III LIBRETTO-531 trial confirmed selpercatinib's superiority over vandetanib/cabozantinib in treatment-naïve RET-mutant MTC, with a 72% reduction in progression risk.
- Selpercatinib demonstrates a favorable safety profile, with fewer severe adverse events and treatment discontinuations compared to multikinase inhibitors.
- Resistance to selpercatinib may involve RET solvent-front mutations or bypass signaling via RAS or FGFR fusions, highlighting the need for next-generation RET inhibitors or combination strategies.
- Real-world studies confirm selpercatinib's efficacy and tolerability across various clinical contexts, including hereditary MTC and neoadjuvant settings.
- Selpercatinib is now approved as first-line therapy for RET-driven thyroid cancers in the US and EU. Several second-generation RET inhibitors are being developed.

including surgery, external beam radiotherapy, and interventional radiology, are appropriate for addressing oligoprogressive or symptomatic lesions [4].

The decision to initiate systemic treatment relies on several factors. For MTC, systemic therapy is generally considered for cases with symptomatic, unresectable metastatic disease or significant tumor burden that cannot be controlled by local means. Additional criteria for systemic therapy include tumors larger than 1–2 cm exhibiting at least a 20% increase in size over one year and rapidly doubling calcitonin levels, particularly when the doubling time is less than 6 months. In DTC, systemic therapy is considered only in cases refractory to RAI, with growing or symptomatic lesions unsuitable for local treatments [5]. The primary systemic options for both MTC and RAI-refractory DTC are tyrosine kinase inhibitors (TKIs), with either broad-spectrum multikinase inhibitors or highly selective agents targeting specific molecular alterations. Chemotherapy remains of limited utility due to its low efficacy in this setting.

Given the prolonged survival expected in these cancers, systemic therapies must not only demonstrate efficacy but also maintain a favorable safety profile to ensure a good quality of life. This necessity underscores the importance of developing targeted therapies, which offer high selectivity with potentially fewer off-target effects compared to traditional multikinase inhibitors. Selpercatinib, a highly selective RET kinase inhibitor, exemplifies this new paradigm in the management of RET-altered thyroid cancers [6].

2. Overview of the field

2.1. Molecular breakdown of thyroid cancer

Thyroid cancer is notable for having one of the lowest mutation densities among human malignancies [7]. Despite this, its molecular landscape is diverse and varies considerably depending on the subtype. DTC are predominantly driven by mutually exclusive genetic alterations affecting effectors of the mitogen-activated protein kinase (MAPK) signaling pathway. These include BRAFV600E mutations (approximately 60%), RAS mutations (around 15%), and rearrangements involving BRAF, RET, NTRK, or ALK (collectively 12%) [8]. The remaining 13% of DTCs often exhibit copy number alterations without an identifiable oncogenic driver [9].

MTC stands out for its strong genetic predisposition. Inherited germline mutations in the RET (rearranged during transfection) proto-oncogene account for approximately 25% of cases and are the hallmark of multiple endocrine neoplasia type 2 (MEN 2) syndromes [10]. Furthermore, somatic RET mutations – most notably the M918T mutation – are present in over half of sporadic metastatic MTC cases (Figure 1) [11]. These RET mutations play a central role in both familial and sporadic MTC, making RET the primary oncogenic driver in this subtype and contributing significantly to the clinical aggressiveness and progression of the disease. RET encodes a transmembrane receptor with an intracellular tyrosine kinase domain that binds glial-derived neurotrophic factor (GDNF) ligands. Pathogenic RET alterations lead to constitutive activation of its kinase function, triggering the recruitment of specific adaptor proteins that initiate downstream signaling cascades. These cascades, including the MAPK, PI3K, and JAK-STAT pathways, drive cellular processes such as angiogenesis, invasion, proliferation and cell survival [12]. In addition to RET, RAS mutations represent another significant driver in sporadic MTC but are associated with a more favorable prognosis compared to RET alterations [13].

The high prevalence of RET alterations, particularly in MTC, establishes it as a prime therapeutic target. Historically, patients with RET-driven thyroid cancers were treated with multikinase inhibitors, which were able to inhibit RET among several kinases. While effective, these agents lacked specificity and were associated with significant off-target toxicities. Recent advancements have led to the development of selective RET inhibitors, offering enhanced efficacy and safety profiles. This review will focus primarily on systemic treatment options for MTC, given the predominance of RET alterations in this subtype, and will highlight the transformative impact of these targeted therapies.

2.2. Multikinase inhibitors (non-RET-specific RET inhibitors)

Several systemic treatments target RET with varying degrees of specificity (Table 1). The first-generation multikinase inhibitors (MKIs) vandetanib and cabozantinib were the first agents developed to target RET alongside angiogenesis pathways

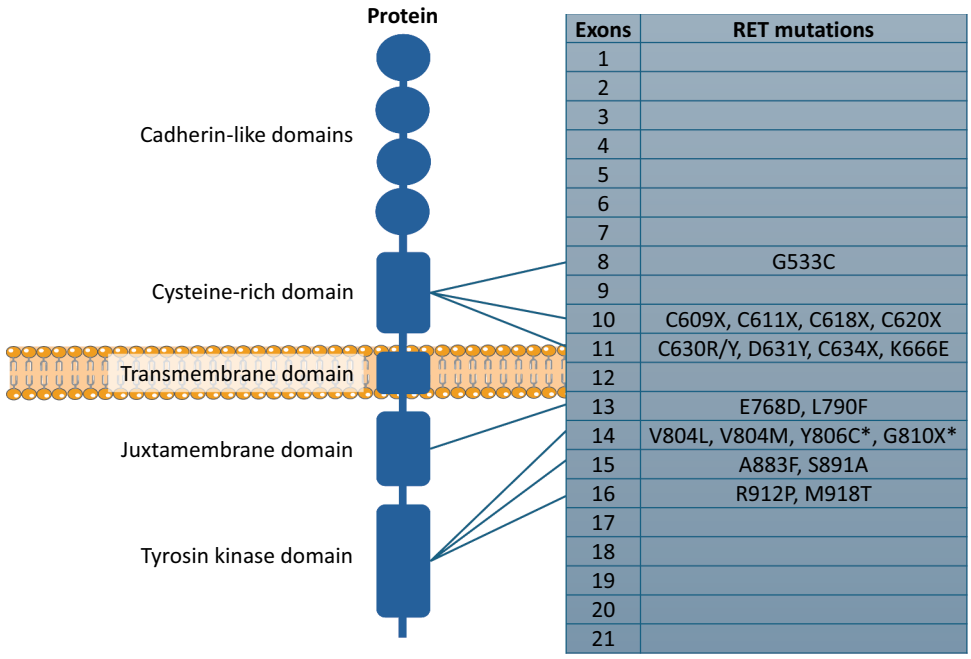

Figure 1. Schematic representation of the RET protein and its most common mutations (resistance-associated mutations are indicated with an asterisk*).

Table 1. Biochemical potency of multikinase inhibitors and RET inhibitors against RET mutants and VEGFR2 [14].

	Biochemical IC50 (nM)				
Compound	RET wild type	RET V804M	RET M918T	CCD6-RET	VEGFR2
Cabozantinib	11	162	8	34	2
Vandetanib	4	726	7	20	4
Selpercatinib	0.4	0.8	0.7	–	100

(non-RET-specific RET inhibitors). Both have been evaluated in phase III trials for the treatment of MTC.

The ZETA trial evaluated vandetanib in 331 patients with locally advanced inoperable (5%) or metastatic (95%) MTC. Notably, tumor progression per RECIST criteria was not required for inclusion [15]. In the vandetanib group, median progression-free survival (PFS) was not reached but was estimated at 30.5 months, compared to 19.3 months in the placebo group. The objective response rate (ORR) was 45%. However, no significant difference in overall survival was observed between the groups. A post-hoc analysis demonstrated significant efficacy for PFS in patients with progressive disease at baseline (21.4 months with vandetanib vs. 8.4 months with placebo) [16]. Grade 3–4 adverse events (AEs) occurred in 50% of patients, including diarrhea, hypertension, and QT interval prolongation. Treatment modifications were common, with dose reductions required in one-third of patients and treatment discontinuation due to toxicity in 12%.

The EXAM trial evaluated cabozantinib in 330 patients with inoperable locally advanced or metastatic progressive MTC within 14 months per RECIST criteria [17,18]. Cabozantinib improved PFS (11.2 months vs. 4 months with placebo), with an ORR of 27% and a median response duration of 14 months. Similar to vandetanib, there was no significant impact on overall survival. Grade 3–4 adverse events were more frequent, reported in 75% of patients, including diarrhea, hand-foot syndrome, hypertension, constipation, vomiting, and mucositis. Dose reductions were required in 80% of patients, and 20% discontinued treatment due to toxicity.

Although direct comparisons of vandetanib and cabozantinib are challenging due to differences in patient populations across trials, a recent meta-analysis integrating data from phase I – III studies and real-world retrospective series highlights the tolerability profiles of these agents. Treatment discontinuation due to intolerance was reported in 39% of vandetanib-treated patients and 66% of those treated with cabozantinib [19]. These findings underscore the need for more selective therapies with improved safety profiles, particularly in patients requiring prolonged treatment.

2.3. RET-specific inhibitors

This article will extensively review selpercatinib. We will first briefly outline other RET-specific inhibitors currently in development or use.

Pralsetinib (BLU-667), developed by Blueprint Medicines, is a selective RET inhibitor designed for RET fusion-positive non-small cell lung carcinoma (NSCLC) and RET-altered thyroid cancers. The ARROW trial, a multi-cohort, open-label, registrational phase I/II study, assessed pralsetinib's safety and efficacy in adult patients with RET-altered solid tumors, including RET-mutant MTC (122 patients) and RET fusion-positive DTC (20 patients) [20]. The overall response rates (ORR) were 71% in

Table 2. Comparison of efficacy, safety, and regulatory approval between selpercatinib [23] and pralsetinib [18].

	Selpercatinib	Pralsetinib
ORR	69.4%	77.4%
12 m-PFS	91.3%	84.7%
12 m-OS	ND	94.0%
Discontinuation due to AE	4.7%	5.7%
Dose reduction due to AE	38.9%	52.6%
FDA approval	RET-fusion positive metastatic NSCLC RET-fusion positive DTC	RET-mutated MTC RET-fusion positive metastatic NSCLC RET-fusion positive DTC RET-fusion positive solid cancer

treatment-naive RET-mutant MTC, 60% in patients previously treated with cabozantinib or vandetanib (or both), and 89% in RET fusion-positive thyroid cancer. Median duration of response (DoR) and PFS were 25.8 months in previously treated RET-mutant MTC and not reached in treatment-naive patients. In RET fusion-positive thyroid cancer, the median DoR and PFS were 23.6 and 25.4 months, respectively [21]. The most common grade 3–4 AEs were hypertension (17%), neutropenia (13%), lymphopenia (12%), and anemia (10%). Serious treatment-related adverse events (TRAEs) occurred in 15% of patients, with pneumonitis being the most frequent. Discontinuation due to TRAEs was low (4%). However, in June 2023, Genentech (Roche Group) voluntarily withdrew the US indication for RET-mutant MTC, citing challenges in obtaining full approval following the drug's accelerated approval in December 2020. Pralsetinib is now developed by Rigel [22]. A comparison of efficacy, safety, and regulatory approval between selpercatinib and pralsetinib is provided in Table 2.

Zeteletinib (BOS172738) is another selective RET inhibitor that targets RET fusion proteins and resistant RET-active site mutations with high potency [24]. In the NCT03780517 phase I study, zeteletinib demonstrated broad anti-tumor activity, with a global ORR of 33% ($n = 18/54$) and 44% ($n = 7/16$, including one complete response) in MTC [25]. The most common TEAEs were creatinine phosphokinase increase (54%), dyspnea (34%), facial edema (25%), AST elevation, anemia (25%), neutropenia, diarrhea (22% each), fatigue (21%), and constipation (20%).

SY5007, investigated in a phase I/II trial for RET-altered advanced solid tumors in China (NCT05278364), showed promising early results [26]. In 50 evaluable patients, primarily with RET-fusion NSCLC and a few with RET-mutant MTC, the ORR was 62%, and the disease control rate (DCR) was 94%. Grade ≥ 3 TRAEs occurred in 37% of patients, including hypertension (15%), diarrhea (5%), and elevated ALT (3%).

EP0031 demonstrated greater potency than first-generation RET inhibitors against common RET fusions and on-target resistant mutations, including V804 gatekeeper and RET G810 solvent-front mutations, while showing enhanced brain penetration. In the KL590586/A400 trial, EP0031 yielded an ORR of 60% and a DCR of 94% among 90 evaluable patients, including those previously treated with selective RET inhibitors [27]. Grade 3 TRAEs included anemia and elevated ALT/AST (23.9%), with low rates of dose interruptions (6.4%) and discontinuations (2.8%). Phase I/II trials are ongoing in China, the US, and Europe (NCT05443126).

HS-10365, a potent selective RET inhibitor, has been evaluated in a phase I study (NCT05207787) [28,29]. Preliminary results from 30 RET fusion-positive NSCLC patients demonstrated a 70% ORR. Common TRAEs included cytopenia, liver toxicity, and prolonged QT intervals.

Vepafestinib (TAS0953/HM06) is a next-generation selective RET inhibitor with potential activity against solvent front mutations. It is currently undergoing evaluation in the biomarker-driven phase I/II MARGARET trial in the US and Japan for patients with RET-altered solid tumors progressing on prior therapies (NCT04683250).

LOXO-260 is a next-generation selective RET inhibitor developed to target resistance mechanisms, including solvent front and gatekeeper mutations. It was evaluated in a phase I clinical trial for patients with RET fusion-positive NSCLC, RET fusion-positive thyroid cancers, and RET-mutant MTC [30], but development has been discontinued.

3. Introduction to the compound

Selpercatinib (formerly LOXO-292) is a highly selective, ATP-competitive small molecule RET inhibitor orally bio-available, which have shown strong inhibitory activity against the "gatekeeper" mutation at RET codon 804, in contrast to vandetanib or cabozantinib. Its powerful anti-RET activity, high selectivity, and central nervous system coverage were preclinically confirmed using RET-dependent tumor models both in vitro and in vivo.

4. Pharmacology

RET is a receptor tyrosine kinase crucial for the proper development of the kidneys and nervous system during embryogenesis. It comprises 3 main domains: extracellular, transmembrane, and intracellular [31,32]. Chromosomal alterations in the RET gene can lead to fusions between dimerization domains at the 5′ end and the tyrosine kinase domain at the 3′ end, creating fusion proteins like KIF5B-RET and CCDC6-RET. These proteins drive downstream signaling via autophosphorylation [33].

Selpercatinib is a highly selective kinase inhibitor targeting activated RET proteins, including those with CCDC6-RET,

KIF5B-RET, RET V804M, and RET M918T mutations [14]. IC50 ranging from 0.9 to 67.8 nanomolar (nM), varying by genotype, including both wild-type RET and its mutated forms. It also inhibits vascular endothelial growth factor receptors (VEGFR1–3) and fibroblast growth factor receptors (FGFR1–4), albeit with reduced potency compared to RET [34]. Preclinical studies have demonstrated its high specificity, with biochemical IC50 values of 0.4 nM for RET wild-type, 0.7 nM for RET M918T, 0.8 nM for RET V804M, and 100 nM for VEGFR2 [35].

The pharmacokinetics of selpercatinib were extensively evaluated in patients with advanced or metastatic solid tumors receiving 160 mg twice daily [36]. Selpercatinib exhibits dose-proportional increases in area under the curve (AUC) and maximum plasma concentration (Cmax), achieving steady-state within approximately 7 days. The median accumulation ratio is 3.4. The drug is well-absorbed, with a bioavailability of 73% for the capsule form (ranging from 60% to 82%). It has a large volume of distribution (Vss/F) of 203 L and demonstrates high plasma protein binding (96%).

Metabolism primarily occurs via CYP3A4, resulting in a half-life of approximately 32 hours. Despite its extended half-life, twice-daily (BID) administration was chosen to maintain stable plasma concentrations while avoiding excessive peak levels. This approach helps optimize tolerability, as higher drug concentrations are associated with an increased risk of adverse events, including QT interval prolongation, which is concentration-dependent [23]. Peak plasma concentrations are typically reached 2 hours after oral administration. Excretion is predominantly through feces (69%, with 14% as unchanged drug) and to a lesser extent through urine (24%, with 12% as unchanged drug). Selpercatinib's clearance rate is 6 L/hour. Importantly, the tablet and capsule formulations are bioequivalent, providing flexibility in administration without compromising efficacy. Selpercatinib's pharmacokinetic profile highlights its favorable absorption, distribution, metabolism, and excretion (ADME) characteristics, ensuring consistent therapeutic drug levels. These properties, combined with its potent and selective inhibition of RET, contribute to its clinical efficacy and manageable safety profile.

5. Clinical efficacy

The efficacy of selpercatinib was initially established in the LIBRETTO-001 trial, a pivotal phase I/II, single-arm, open-label study conducted in patients with RET-altered solid tumors [37]. Among the 837 enrolled patients, 324 had RET-mutant MTC – 152 of whom had been previously treated with multikinase inhibitors and 143 were cabozantinib/vandetanib-naïve – and 66 had RET fusion-positive differentiated thyroid cancer (DTC), including 41 previously treated and 24 treatment-naïve patients [38]. For patients with RET-mutant MTC, the ORR was 84.5% in the treatment-naïve cohort and 79.5% in those previously treated with MKIs, with efficacy observed across all mutation types. The median PFS was not reached in treatment-naïve patients and was 41.4 months in the pretreated cohort. Median OS was also not reached in the treatment-naïve group and reached 64.3 months for pretreated patients. In RET fusion-positive DTC, the ORR was 95.8% in treatment-naïve patients and 85.4% in previously treated patients. Median PFS was not reached in the treatment-naïve group but was 27.4 months for pretreated patients. Median OS was not reached in either group.

The LIBRETTO-531 trial, a phase III, randomized, multicenter study, directly compared selpercatinib with standard treatments for RET-mutated MTC [6]. This trial enrolled 291 patients with metastatic or locally advanced, treatment-naïve RET-mutant MTC, who had experienced disease progression within 14 months before enrollment. Patients were randomized 2:1 to receive selpercatinib or investigator-selected cabozantinib/vandetanib. Selpercatinib demonstrated superior efficacy, with an ORR of 69.4% (including 11.9% complete responses) compared to 38.8% in the control group. Median PFS was not reached in the selpercatinib arm but was 16.8 months in the control arm, representing a 72% reduction in disease progression risk (HR 0.28; 95% CI 0.16–0.48; $p < 0.001$). This benefit was consistent across all prespecified subgroups, regardless of the type of RET alteration.

Despite these robust results, resistance to selective RET inhibitors can arise. A molecular analysis of 46 MTC patients treated predominantly with treated with selective RET inhibitors (mainly selpercatinib) aimed to identify resistance mechanisms in post-treatment samples [39]. "On-target" resistance mutations, observed in 25% of cases, involved changes in the solvent front domain (p.G810) or the hinge region domain (p.Y806C), which disrupted selpercatinib binding. "Bypass" resistance mechanisms were more common (75%) and included mutations in RAS genes as well as fusions involving FGFR and ALK. These findings underscore a key distinction in resistance patterns: while on-target mutations may be overcome by next-generation RET inhibitors such as LOXO-260, bypass alterations likely necessitate combination approaches targeting parallel signaling pathways. Furthermore, histological analyses comparing initial thyroidectomy samples, pre-treatment, and post-treatment samples revealed progressive tumor aggressiveness. The mean Ki-67 index increased from 7% at baseline to 17% pre-treatment and 40% post-treatment, with some cases displaying more aggressive poorly differentiated histology after therapy.

A broader genomic study of RET-driven cancers treated with selpercatinib confirmed that acquired resistance is frequently mediated by MAPK pathway reactivation through diverse routes [40]. These included both secondary RET mutations and selection of preexisting RET-wildtype subclones driven by alternative mitogenic pathways. Multiple concurrent resistance mechanisms were often present within the same patient, highlighting the polyclonal nature of therapeutic escape and the need for molecular re-characterization at progression to inform rational salvage strategies.

6. Real-world evidence

Real-world data provide valuable insights into the efficacy and safety of treatments in broader and more diverse patient populations. A retrospective study using de-identified U.S. databases evaluated selpercatinib outcomes in patients with advanced or metastatic non-small cell lung cancer or thyroid cancer [41]. Among the 24 thyroid cancer patients included, the median time to treatment discontinuation or death was not reached.

Medication adherence was notably high, with a median medication possession ratio (MPR) of 0.98, and 77.3% of patients demonstrated good adherence (MPR ≥0.80). These findings align with results from clinical trials, despite the real-world cohort including frailer patients, characterized by higher rates of comorbidities and Eastern Cooperative Oncology Group (ECOG) performance statuses ≥ 2.

Real-world studies also shed light on outcomes in specific patient subgroups. For instance, a retrospective analysis conducted at MD Anderson Cancer Center assessed selective RET inhibitors in 23 patients with hereditary MTC [42]. Among these, 13 were treated with selpercatinib and 10 with pralsetinib. The ORR was 78%, with the median PFS not reached and a median OS of 51 months. Safety outcomes were favorable, with grade ≥ 3 adverse events reported in only 22% of patients, addressing initial concerns regarding the side effect profile in patients with germline RET mutations. Pediatric patients with multiple endocrine neoplasia type 2 (MEN2) and advanced MTC demonstrated similarly promising outcomes in another study [43].

Beyond the metastatic setting, selective RET inhibitors are increasingly being explored in neoadjuvant contexts. The first documented case of neoadjuvant selpercatinib treatment was reported in 2021, followed by a case series of four patients with locoregionally advanced RET-mutated MTC [44,45]. Neoadjuvant therapy over 4–6 months enabled surgical resection while reducing morbidity scores. These encouraging results have prompted the initiation of a clinical trial evaluating neoadjuvant selpercatinib for RET-altered MTC (NCT04759911).

The growing body of real-world evidence underscores the efficacy and safety of selpercatinib across various clinical settings, complementing its robust performance in clinical trials. These findings highlight the potential of selpercatinib not only in metastatic disease but also in earlier and more complex treatment scenarios.

7. Safety and tolerability

The specificity of selpercatinib for RET kinases minimizes off-target effects, contributing to its favorable tolerability profile. The most frequently observed severe adverse events (grade 3 or 4) include elevated blood pressure (21–42%), increased alanine aminotransferase (ALT) levels (11–26%), elevated aspartate aminotransferase (AST) levels (9–24%), hyponatremia (8%), and gastrointestinal issues such as diarrhea (6–26%) [6,37]. Common side effects reported in ≥ 20% of patients include dry mouth (32%), diarrhea, constipation, nausea, abdominal discomfort, skin rashes, hypertension, headaches, fatigue, and peripheral edema. Serious adverse effects include hypertension (18%) and prolonged QT interval (4%). Allergic reactions occurred in approximately 4–5% of patients. In the LIBRETTO-531 trial, selpercatinib had a more favorable toxicity profile than cabozantinib/vandetanib, with fewer dose reductions (39% vs. 77%) and treatment discontinuations (4.8% vs. 27%) [6].

Long-term safety data from the LIBRETTO-001 trial reinforced these findings. In a post-hoc analysis of patient-reported outcomes (PROs) across multiple cancer types – non-small cell lung cancer (NSCLC), medullary thyroid cancer (MTC), non-medullary thyroid cancer (TC), and tumor-agnostic RET-altered cancers – patients reported significant improvements in health-related quality of life [46]. Approximately 75% (NSCLC), 81% (MTC), 75% (TC), and 40% (tumor-agnostic) of patients achieved stable or improved QLQ-C30 scores over 2–3 years of selpercatinib treatment. The median time to first improvement ranged from 2.0 to 19.4 months, and the duration of improvement lasted 1.9 to 28.2 months. Among MTC patients, diarrhea prevalence dropped from 80.8% at baseline to 35.6% at three years, demonstrating an improvement in gastrointestinal tolerability

A separate analysis using the FDA Adverse Event Reporting System database identified 1,007 selpercatinib-related adverse events, revealing three newly associated significant AEs: dysphagia, pericardial effusion, and hemiparesis [47]. Regional variations were noted, with hepatic function abnormalities reported more frequently in Asia, particularly at doses exceeding 160 mg. Hypersensitivity reactions were also more common in Asian populations and among patients weighing less than 50 kg. These findings emphasize the need for ongoing vigilance regarding newly identified adverse events.

Specific recommendations are available for the prevention and management of selpercatinib-associated toxicities, including cutaneous toxicities, edema, hypertension, hepatotoxicity, and QT prolongation, allowing for personalized strategies to optimize patient outcomes [48].

Overall, selpercatinib's safety profile represents a key advantage, with most adverse events being mild, manageable, and less frequent than those observed with nonspecific RET inhibitors. Its tolerability, combined with lower off-target toxicity, makes selpercatinib an attractive option for long-term therapy in RET-altered cancers.

8. Regulatory affairs

These findings, demonstrating superior progression-free survival, response rate, and tolerance, have recently led to the approval and reimbursement of selpercatinib as a first-line treatment for advanced RET-mutated medullary thyroid cancer and RET-fusion positive differentiated thyroid cancer.

In May 2020, the U.S. Food and Drug Administration (FDA) granted selpercatinib accelerated approval based on data from the LIBRETTO-001 trial, which suggested exceptional efficacy and safety [49]. More recently, the phase III LIBRETTO-531 trial solidified selpercatinib's position as the first-line treatment of choice for advanced RET-mutant MTC, leading to full regulatory approval and reimbursement [50]. Similarly, the European Medicines Agency (EMA) approved in December 2020 selpercatinib for advanced RET-mutant MTC and RET-fusion positive differentiated thyroid cancer [51]. However, reimbursement remains a hurdle in some regions, such as France, where the drug is reimbursed for RET-mutant MTC but not yet for RET-fusion positive differentiated thyroid cancer.

While pralsetinib, another selective RET inhibitor, initially gained accelerated FDA approval for RET-mutant MTC, its

approval was voluntarily withdrawn in 2023 due to the lack of confirmatory phase III trial data needed for full regulatory approval. Similarly, pralsetinib has not secured EMA approval for RET-altered DTC. Note however, that pralsetinib retains its indication in the US for RET-fusion positive metastatic NSCLC and RET-fusion positive differentiated thyroid cancer. The conditional approval in the EU was withdraw in October 2024. These challenges highlight the importance of generating robust phase III data to sustain regulatory approvals.

Selpercatinib's remarkable efficacy in RET-driven cancers, including response rates of up to 95.8% in treatment-naïve RET fusion-positive DTC and 84.5% in treatment-naïve RET-mutant MTC, posed challenges from a regulatory and ethical perspective about conducting randomized trials against standard chemotherapy or less effective treatments. The lack of equipoise (the ethical basis of randomized trials) in such comparisons, particularly given the superior safety profile of selpercatinib compared to multikinase inhibitors, underscored the importance of adopting innovative regulatory pathways for precision therapies targeting rare molecular alterations

9. Conclusion

Selpercatinib represents a significant advancement in the treatment of RET-driven thyroid cancers. As a highly selective RET inhibitor, it addresses gaps in care by providing improved efficacy, better tolerability, and durable outcomes for patients with advanced disease. Data from clinical trials and real-world studies confirm its important role in this therapeutic landscape, positioning selpercatinib as a key option in the management of RET-altered cancers. This progress highlights the growing importance of precision medicine in oncology and the potential of targeted therapies to improve patient outcomes in specific molecular subgroups.

Author contribution

Thibault Gauduchon and Romain Varnier: investigation, data curation, writing – original draft. Philippe A Cassier: conceptualization, writing – review and editing.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Filho AM, Laversanne M, Ferlay J, et al. The GLOBOCAN 2022 cancer estimates: data sources, methods, and a snapshot of the cancer burden worldwide. Int J Cancer. 2024;156(7):1336–1346. doi: 10.1002/ijc.35278
2. Boucai L, Zafereo M, Cabanillas ME. Thyroid cancer: a review. JAMA. 2024;331(5):425–435. doi: 10.1001/jama.2023.26348

• **Review of thyroid cancer treatments.**

3. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48. doi: 10.3322/caac.21763
4. Porcelli T, Sessa F, Luongo C, et al. Local ablative therapy of oligoprogressive TKI-treated thyroid cancer. J Endocrinol Invest. 2019;42(8):871–879. doi: 10.1007/s40618-019-1001-x
5. Filetti S, Durante C, Hartl DM, et al. ESMO clinical practice guideline update on the use of systemic therapy in advanced thyroid cancer. Ann Oncol. 2022;33(7):674–684. doi: 10.1016/j.annonc.2022.04.009
6. Hadoux J, Elisei R, Brose MS, et al. Phase 3 trial of selpercatinib in advanced RET-mutant medullary thyroid cancer. N Engl J Med. 2023;389(20):1851–1861. doi: 10.1056/NEJMoa2309719

•• **Results of the LIBRETTO-531 trial.**

7. Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature. 2013;499(7457):214–218. doi: 10.1038/nature12213
8. Fagin JA, Wells SA, Longo DL. Biologic and clinical perspectives on thyroid cancer. N Engl J Med. 2016;375(11):1054–1067. doi: 10.1056/NEJMra1501993
9. Agrawal N, Akbani R, Aksoy BA, et al. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014;159(3):676–690. doi: 10.1016/j.cell.2014.09.050
10. Mulligan LM, Kwok JBJ, Healey CS, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature. 1993;363(6428):458–460. doi: 10.1038/363458a0
11. Elisei R, Cosci B, Romei C, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. J Clin Endocrinol Metab. 2008;93(3):682–687. doi: 10.1210/jc.2007-1714
12. Cerrato A, Falco VD, Santoro M. Molecular genetics of medullary thyroid carcinoma: the quest for novel therapeutic targets. J Mol Endocrinol. 2009;43(4):143–155. doi: 10.1677/JME-09-0024
13. Ciampi R, Romei C, Ramone T, et al. Genetic landscape of somatic mutations in a large cohort of sporadic medullary thyroid carcinomas studied by next-generation targeted sequencing. iScience. 2019;20:324–336. doi: 10.1016/j.isci.2019.09.030
14. Subbiah V, Velcheti V, Tuch BB, et al. Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol Off J Eur Soc Med Oncol. 2018;29(8):1869–1876. doi: 10.1093/annonc/mdy137
15. Wells SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30(2):134–141. doi: 10.1200/JCO.2011.35.5040

16. Kreissl MC, Bastholt L, Elisei R, et al. Efficacy and safety of vandetanib in progressive and symptomatic medullary thyroid cancer: Post hoc analysis from the ZETA trial. J Clin Oncol Off J Am Soc Clin Oncol. 2020;38(24):2773–2781. doi: 10.1200/JCO.19.02790
17. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(29):3639–3646. doi: 10.1200/JCO.2012.48.4659
18. Schlumberger M, Elisei R, Müller S, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol Off J Eur Soc Med Oncol. 2017;28(11):2813–2819. doi: 10.1093/annonc/mdx479
19. Efstathiadou ZA, Tsentidis C, Bargiota A, et al. Benefits and limitations of TKIs in patients with medullary thyroid cancer: a systematic review and meta-analysis. Eur Thyroid J. 2021;10(2):125–139. doi: 10.1159/000509457
20. Subbiah V, Hu MI, Wirth LJ, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. Lancet Diabetes Endocrinol. 2021;9(8):491–501. doi: 10.1016/S2213-8587(21)00120-0
21. Subbiah V, Hu MI, Mansfield AS, et al. Pralsetinib in patients with advanced/metastatic rearranged during transfection (RET)-altered thyroid cancer: updated efficacy and safety data from the ARROW study. Thyroid®. 2024;34(1):26–40. doi: 10.1089/thy.2023.0363
• **Results of the ARROW trial.**
22. "Rigel pharmaceuticals acquires U.S. Rights to GAVRETO®. 2024. Available from: https://www.rigel.com/investors/news-events/press-releases/detail/379/rigel-pharmaceuticals-acquires-u-s-rights-to-gavreto
23. U.S. Food and Drug Administration. Selpercatinib multi-disciplinary review and evaluation. 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213246Orig1s000TOC.cfm
24. Keegan M, Wilcoxen K, Ho PT. Abstract 2199: BOS172738: a novel highly potent and selective RET kinase inhibitor in phase 1 clinical development. Cancer Res. 2019;79(13_Supplement):2199. doi:10.1158/1538-7445.AM2019-2199
25. Schoffski P, Cho BC, Italiano A, et al. BOS172738, a highly potent and selective RET inhibitor, for the treatment of RET-altered tumors including RET-fusion+ NSCLC and RET-mutant MTC: phase 1 study results. J Clin Oncol. 2021;39(15_suppl):3008–3008. doi: 10.1200/JCO.2021.39.15_suppl.3008
26. Zhou C, Li W, Zhang Y, et al. A first-in-human phase I, dose-escalation and dose-expansion study of SY-5007, a highly potent and selective RET inhibitor, in Chinese patients with advanced RET positive solid tumors. J Clin Oncol. 2023;41(16_suppl):9111–9111. doi: 10.1200/JCO.2023.41.16_suppl.9111
27. Zhou Q, Wu Y-L, Zheng X, et al. A phase I study of KL590586, a next-generation selective RET inhibitor, in patients with RET-altered solid tumors. J Clin Oncol. 2023;41(16_suppl):3007–3007. doi: 10.1200/JCO.2023.41.16_suppl.3007
28. Lu S, Wang Q, Wu L, et al. Abstract CT201: HS-10365, a highly potent and selective RET tyrosine kinase inhibitor, demonstrates robust activity in RET fusion positive NSCLC patients. Cancer Res. 2023;83(8_Supplement):CT201. doi: 10.1158/1538-7445.AM2023-CT201
29. Miyazaki I, Ishida K, Kato M, et al. Abstract P06–02: discovery of TAS0953/HM06, a novel next generation RET-specific inhibitor capable of inhibiting RET solvent front mutations. Mol Cancer Ther. 2021;20(12_Supplement):06–02. doi: 10.1158/1535-7163.TARG-21-P06-02
30. Pennell NA, Wirth LJ, Gainor JF, et al. A first-in-human phase 1 study of the next-generation RET inhibitor, LOXO-260, in RET inhibitor refractory patients with RET-altered cancers (trial in progress). J Clin Oncol. 2022;40(16_suppl):TPS8595–TPS8595. doi: 10.1200/JCO.2022.40.16_suppl.TPS8595
31. Subbiah V, Yang D, Velcheti V, et al. State-of-the-art strategies for targeting RET-dependent cancers. J Clin Oncol. 2020;38(11):1209–1221. doi: 10.1200/JCO.19.02551
32. Li AY, McCusker MG, Russo A, et al. RET fusions in solid tumors. Cancer Treat Rev. 2019;81:101911. doi: 10.1016/j.ctrv.2019.101911
33. FDA approves selpercatinib for lung and thyroid cancers with RET gene mutations or fusions. FDA. 2024.
34. Kooijman JJ, van Riel WE, Dylus J, et al. Comparative kinase and cancer cell panel profiling of kinase inhibitors approved for clinical use from 2018 to 2020. Front Oncol. 2022;12:953013. doi: 10.3389/fonc.2022.953013
35. Seoane J, Capdevila J. The right compound for the right target: tackling RET. Ann Oncol. 2018;29(8):1623–1625. doi: 10.1093/annonc/mdy188
36. Markham AS. Selpercatinib: first approval. Drugs. 2020;80(11):1119–1124. doi:10.1007/s40265-020-01343-7
37. Wirth LJ, Sherman E, Robinson B, et al. Efficacy of selpercatinib in RET-altered thyroid cancers. N Engl J Med. 2020;383(9):825–835. doi: 10.1056/NEJMoa2005651
38. Wirth LJ, Brose MS, Subbiah V, et al. Durability of response with selpercatinib in patients with RET-activated thyroid cancer: long-term safety and efficacy from LIBRETTO-001. J Clin Oncol. 2024;42(27):3187–3195. doi: 10.1200/JCO.23.02503
•• **Results of the LIBRETTO-001 trial.**
39. Hadoux J, Al Ghuzlan A, Lamartina L, et al. Patterns of treatment failure after selective rearranged during transfection (RET) inhibitors in patients with metastatic medullary thyroid carcinoma. JCO Precis Oncol. 2023;7(7):e2300053. doi: 10.1200/PO.23.00053
•• **Analysis of resistance mutations.**
40. Rosen EY, Won HH, Zheng Y, et al. The evolution of RET inhibitor resistance in RET-driven lung and thyroid cancers. Nat Commun. 2022;13(1):1450. doi: 10.1038/s41467-022-28848-x
•• **Analysis of resistance mutations.**
41. Liao C-Y, Gonzalez-Ferrer C, Whipple S, et al. Real-world outcomes of selective RET inhibitor selpercatinib in the United States: descriptive, retrospective findings from two databases. Cancers (Basel). 2024;16(22):3835. doi: 10.3390/cancers16223835
42. Hamidi S, Yedururi S, Hu MI, et al. Efficacy and safety of selective RET inhibitors in patients with advanced hereditary medullary thyroid carcinoma. Thyroid®. 2025;35(1):6–17. doi: 10.1089/thy.2024.0495
43. Shankar A, Kurzawinski T, Ross E, et al. Treatment outcome with a selective RET tyrosine kinase inhibitor selpercatinib in children with multiple endocrine neoplasia type 2 and advanced medullary thyroid carcinoma. Eur J Cancer Oxf Engl. 1990;158:38–46. doi: 10.1016/j.ejca.2021.09.012
44. Jozaghi Y, Zafereo M, Williams MD, et al. Neoadjuvant selpercatinib for advanced medullary thyroid cancer. Head Neck. 2021;43(1):E7–E12. doi: 10.1002/hed.26527
45. Contrera KJ, Gule-Monroe MK, Hu MI, et al. Neoadjuvant selective RET inhibitor for medullary thyroid cancer: a case series. Thyroid®. 2023;33(1):129–132. doi: 10.1089/thy.2022.0506
46. Raez LE, Kang H, Ohe Y, et al. Patient-reported outcomes with selpercatinib treatment in patients with RET-driven cancers in the phase I/II LIBRETTO-001 trial. ESMO Open. 2024;9(5):103444. doi: 10.1016/j.esmoop.2024.103444
47. Qian J, Zhang S, Jiang C. Adverse event profiles of selpercatinib: a real-world pharmacovigilance analysis based on FAERS database. BMC Cancer. 2024;24(1):1486. doi:10.1186/s12885-024-13250-1
48. Nardo M, Gouda MA, Nelson BE, et al. Strategies for mitigating adverse events related to selective RET inhibitors in patients with RET-altered cancers. Cell Rep Med. 2023;4(12):101332. doi: 10.1016/j.xcrm.2023.101332
49. FDA approves selpercatinib for lung and thyroid cancers with RET gene mutations or fusions. FDA. 2020.
50. FDA approves selpercatinib for medullary thyroid cancer with a RET mutation. FDA. 2024.
51. Retsevmo | European Medicines Agency (EMA). 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo