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The Emerging Role of RET Alteration in Solid Tumors: From Pathogenesis to Targeted Therapies

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Abstract:

The study investigates the emerging role of RET (rearranged during transfection) alterations in solid tumors, focusing on their pathogenesis and implications for targeted therapies. Ret alterations have been proven to be critical oncogenic factors in various types of solid tumors, most notably PTC and NSCLC. These alterations cause continuous activity of RET signaling pathways, contributing to tumor proliferation and progression. A comprehensive review of recent literature was conducted to elucidate the mechanisms by which RET alterations promote oncogenesis across different tumor types. The efficacy of targeted therapies, specifically RET- selective TKIs such as selpercatinib and pralsetinib, was also evaluated through clinical trial data. In conclusion, RET alterations represent a promising target for precision oncology in solid tumors. Continued research is essential to fully understand the genomic landscape of RET-positive cancers and to optimize therapeutic approaches. The findings support the integration of RET testing in clinical practice to facilitate the development of personalized treatment plans for affected patients.

Keywords: RET alterations, Solid tumors, Targeted therapy, Tyrosine kinase inhibitors, Precision medicine.

Introduction

RET is a receptor tyrosine kinase that is essential for the growth, differentiation, and survival of cells and is involved in embryonic development. The RET signaling pathway is constitutively activated by RET changes, which include gene fusions, point mutations, and amplifications (three functional domains). This promotes carcinogenesis and aids in the development of the neuroendocrine, sympathetic nervous, and genitourinary systems. Numerous malignancies and developmental problems are associated with RET mutations (1-3).

The growth of the sympathetic nervous, GU and neuroendocrine systems during embryonic life is influenced by RET. RET's transforming potential was originally reported in 1985. One of the

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earliest oncogenes found in solid tumors. This was particularly true for papillary thyroid carcinomas (PTCs) including RET fusions. In 30%-70% of invasive breast malignancies (particularly those with ER+ and HER2+ fractions) and 50%-65% of pancreatic ductal adenocarcinomas, the RET protein is overexpressed (17, 18).

The efficacy of RET mutation detection techniques varies. For germline mutations, Sanger sequencing is the gold standard; for somatic mutations, qPCR and digital PCR are preferable. The analysis provided by next-generation sequencing (NGS) is more thorough (4-6).

Point mutations are widespread in medullary thyroid cancer and other solid tumors, while RET fusions, such as KIF5B-RET and CCDC6-RET, are common in papillary thyroid cancer and non-small cell lung cancer (7-9).

RET mutations are variations in the RET gene's DNA sequence. These changes may be: Mutations in Germlines are inherited and found in every human cell. In MEN2, germline mutations are pathognomonic and are categorized as familial medullary thyroid cancer (FMTC), MEN2A, and MEN2B. The M918T mutation and classical cysteine mutations are associated with multiple endocrine neoplasia types 2A (MEN2A) and 2B (MEN2B) (10).

Somatic mutations are acquired changes that occur in specific cells during a lifetime. These are unique to tumor cells and are not inherited. In sporadic MTC, somatic RET mutations are linked to more aggressive tumor characteristics and a poorer prognosis (11, 12).

RET rearrangements are chromosomal structural modifications that align the RET gene with another gene to form a fusion gene. This may result in the atypical protein that promotes cancer growth. Recurrent epithelial-mesenchymal transitions (RETs) are frequently observed in a subset of thyroid malignancies (ten percent to twenty percent of PTCs; RETs are less common in anaplastic, follicular, and medullary thyroid carcinomas) and lung cancers (non-small cell lung cancer). Patients with RET-rearranged NSCLC are younger (≤60 years old), and have poorly differentiated tumors, minimal to no smoking history, low tumor mutational burden, low PD-L1 expression, and poor response to immunotherapies. Also present in several cancers, such as esophageal cancer, cholangiocarcinoma, head and neck cancer, bladder carcinoma, chronic myeloproliferative neoplasms, mesothelioma, atypical lung carcinoid tumor, low-grade glioma KRAS wild-type pancreatic ductal adenocarcinoma, it and gastric adenocarcinoma (13, 14).

The term "RET amplification" describes a rise in the RET gene's copy quantity inside the cell. The RET protein may be overproduced as a result, which may encourage the growth and survival of cancer cells. Numerous tumors have been shown to have RET amplifications, including non-small cell lung cancer (NSCLC) and thyroid cancers such as medullary thyroid carcinoma (MTC), papillary thyroid carcinoma (PTC), and anaplastic thyroid cancer. RET copy number amplifications and gains are more frequent in NSCLC than RET rearrangements. Glioblastoma, colorectal adenocarcinoma, gastric cancer, prostate cancer, breast cancer, urothelial carcinoma and hepatobiliary cancers are among other conditions that have RET amplifications (15, 16).

Overexpression of RET is connected to prostate cancer that is moderately to poorly differentiated, as well as node metastases and nerve invasion in pancreatic cancer. Shorter median progression-free survival (mPFS) and overall survival (OS) are correlated with high RET expression in renal clear cell carcinoma (19- 21).

The identification of genetic changes responsible for carcinogenesis has transformed the management of cancer by facilitating the creation of tailored treatments. Rearranged during transfection (RET) gene modifications are one type of these changes that have become important in the pathophysiology of many types of solid tumors. In this overview, we explore the growing significance of RET modification in solid tumors, covering everything from its molecular underpinnings to the creation of tailored treatments (5, 22).

Molecular Mechanisms & Pathogenic Role of RET Alteration in Solid Tumors:

Chromosome 10q11.2 contains the RET oncogene, which genes for a receptor tyrosine kinase with three domains: intracellular, transmembrane, and extracellular. Activation necessitates a complex involving glial cell-derived neurotropic factor and a co-receptor (23-25). RET mutations activate carcinogenic signaling pathways, such as the MAPK and PI3K/AKT pathways, resulting in uncontrolled cell proliferation, survival, and metastasis. In addition to their function in tumor launch and development, RET mutations have been associated with resistance to conventional therapies, underscoring the significance of targeting the RET pathway in cancer treatment (Fig.1) (26, 27, 191).

There are two ways that RET mutations might cause oncogenesis: constitutive kinase activation from tyrosine kinase domain mutations or constitutive dimerization and activation from extracellular domain mutations. Chromosome rearrangements and germline or spontaneous mutations can potentially activate RET, resulting in ligand-independent phosphorylation and tumor development (28–30).

The two most prevalent RET gene fusions in cancer are 3' kinase fusions and 5' kinase fusions,

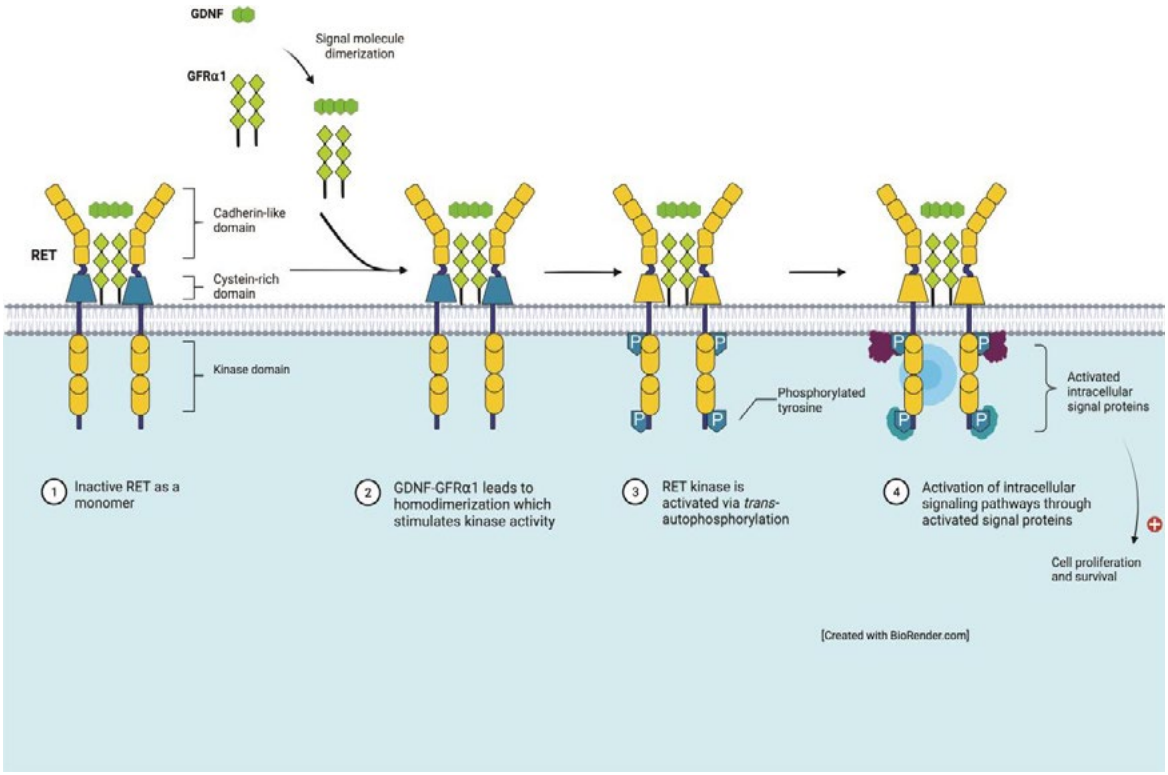

Fig 1. Subtitle: GDNF: glial cell-line-derived neurotrophic factor, GFRα1: GDNF family receptor alpha1, RET: Rearranged during Transfection.

both of which preserve the kinase domain. These fusions increase carcinogenic activity by activating kinases and triggering signal transduction via pathways like PI3K/AKT and MAPK. Increased kinase expression, ligand-independent activation, and modified intracellular localization represent a number of the mechanisms. KIF5B-RET fusion is caused by a pericentric inversion of chromosome 10, which is one of the structural abnormalities that drive RET fusions, along with translocations and inversions (31-33).

A hybrid gene that generates a fusion protein is produced when the RET gene fuses with another gene, a process known as RET fusion. This fusion protein may exhibit aberrant behavior that encourages the growth of cancer. it appears in 1-2% of lung carcinomas and 5-10% of spontaneous PTCs, mainly in NSCLC with adenocarcinoma histology. KIF5B and CCDC6 in NSCLC and CCDC6, PRKAR1A, NCOA4, GOLGA5, TRIM24, TRIM33, KTN1, and RFG9 in PTC are examples of common fusion partners (31, 34).

RET fusions trigger many receptor tyrosine kinases (RTKs) and downstream signaling cascades, as well as ligand-independent dimerization of fusion proteins. Because RET fusions can be targeted by particular treatments, patients with these genetic abnormalities may have a new avenue for treatment. Poorly differentiated tumors and a poorer prognosis for non-small cell lung cancer (NSCLC) are associated with RET fusion genes (27, 32, 35).

By activating the MAPK and PI3K pathways, RET fusions show transformative potential in preclinical models and are linked to poorer overall survival (OS) in several malignancies. MTC and NSCLC, two RET-driven malignancies, exhibit reduced PD-L1 expression and a low tumor-mutational load. In NSCLC, RET fusion is an independent risk factor for brain metastases (22, 32, 36).

Chromosome rearrangements that result in fusion genes with the RET kinase domain and gain-of-function mutations in its extracellular and cytoplasmic domains are the primary mechanism by which RET is activated in cancer. Cancer is also associated with increased expression of wild-type RET. Although introns 7 and 10 can also be involved, RET rearrangements usually involve intron 11, which results in fusions with the cytoplasmic part of RET. More than 35 genes can fuse with RET to produce dimerization domains that improve RET activation and expression. These rearrangements are thought to be driven by the repair of DNA double-strand breaks, which are frequently brought on by ionizing radiation and genotoxic substances (5, 22, 27, 32).

Standard Methods for Detection:

Common Techniques for Identification When available, universal screening for RET alterations

should be taken into consideration. Patients with thyroid carcinoma, NSCLC, and tumors identified with RET fusions histology are included in this category. The US FDA has approved selective-RET treatments, or they are being tested in countries without approval (37).

The ESMO guidelines state that FISH or RT-PCR may utilized in malignancies in which RET mutations or fusions are quite prevalent. It is recommended to use NGS in malignancies like NSCLC where RET fusions are uncommon. This allows for histocyte-agnostic screening (4).

Due to comparatively large percentages of false positives (about 62%) and false negatives (approximately 46%) in specimens that were previously evaluated using RT-PCR, IHC is not a safe technique to detect RET rearrangement. When combined, FISH and PCR are a useful toolkit. PCR is not enough, for finding new fusions. On the other hand, NGS, particularly those utilizing hybrid DNA/RNA-based systems, offers the benefit of being able to identify new fusions, identify the gene partner, and effectively detect somatic mutations in addition to gene fusions (38).

Since IHC could be utilized for measuring RET protein overexpression, scientists have looked into the diagnostic method of RET IHC as a possible detecting tool for oncogenic RET changes, especially RET fusions. RET IHC is rarely used in clinical practice, nonetheless, because immunostaining methods and antibodies are still not well standardized (4, 39).

The specificity and sensitivity of IHC are 82% and 87% respectively, with cytoplasmic staining involved by ≥1% of tumor cells. The RET IHC sensitivity varies depending on the fusion partner; for example, KIF5B has a 100% sensitivity, while RET rearrangements involving the NCOA4 fusion partner only have a 50% sensitivity (39). The tracheal epithelium (40), adrenal glands (41), parafollicular C cells (4), and colorectal tissue are among the normal cells in which wild-type RET expression may be found by IHC (42).

Additionally, a study showed that even without evidence of RET fusions, RET expression can increase in NSCLC (43). Thus, as a stand-alone test, RET IHC may be deceptive, and as a screening tool for RET changes, alternative diagnostic tests typically perform better than IHC. To clinically screen for carcinogenic RET mutations, RET IHC is not advised due to these difficulties (4, 44).

Before the widespread availability of DNA-based NGS, FISH was a more popular alternative technique for RET rearrangement detection. When analyzing 100 non-overlapping nuclei, break apart FISH is generally regarded as positive if at least 10% to 15% of tumor cells show a rearrangement pattern with two signals surrounding the RET gene separated (4, 39).

FISH has significant drawbacks despite its benefits, which include fast turnaround times and single-cell resolution. Firstly, information about unusual the inclusion of the RET kinase domain or breakpoints in the RET fusion cannot be obtained by FISH analysis due to its lack of spatial resolution. To determine whether the RET rearrangement is harmful and, hence, warrants intervention, these datapoints are essential. Secondly, the fusion partner involved determines how accurate FISH is. Break-apart FISH has a 100% sensitivity for KIF5B and CCDC6 intrachromosomal rearrangements, but a 67% sensitivity for NCOA4 rearrangements (39, 45). These are most likely caused by the proximity of RET and NCOA4 on chromosome 10, which can produce a more modest splitting pattern, which is probably the cause of these discrepancies (46).

FISH is also relatively expensive, requires technical expertise for interpretation, and is typically only available in larger centers and reference laboratories (47). NSCLC has the highest sensitivity when taking tumor primary into account (100%), the second is thyroid cancer (88%), and then other tumors (75%). These variations are probably caused by the varying frequencies of fusions like NCOA4-RET (39).

Sanger sequencing based on DNA PCR Assays, provides an accurate way to identify recognized single-nucleotide alterations in cases where their relative allelic frequency exceeds 15%. It is only useful in MEN2A and FMTC, and it still serves as a confirming test because it cannot identify gene mutations with low VAFs, gene rearrangements or partial deletions. Hot-spot mutations at VAFs as low as 1% can be reliably detected using quantitative PCR on DNA. However, a major factor limiting the tests' capacity to detect fusions and less common oncogenic mutations that don't occur in hot regions is the limited number of primers that are utilized with this technique. Although in practical practice, NGS-based tests are better at identifying RET-activating mutations, quantitative PCR is still a good substitute in cases where NGS is not easily accessible (4).

Advances in DNA sequencing techniques have made it easier to discover RET mutations in a variety of tumor types using DNA-based NGS. RET mutations and rearrangements can be detected simultaneously using targeted DNA-based NGS if there is adequate Intron inclusion and exonic coverage of RET fusion. A variety of gene panels with varying RET mutation detection rates are clinically accessible to identify canonical RET changes. However, in certain instances of rearrangements of unknown significance (i.e., non-canonical RET rearrangements), only RNA sequencing was able

to confirm the presence or absence of oncogenic RET fusion transcripts. This was the case when comparing the performance of MSK IMPACT (hybrid capture DNA-based NGS panel) to RNA-based NGS as a reference standard (MSK-Fusion) in detecting RET fusions. DNA-based NGS is also capable of detecting somatic mutations at low VAFs because of its great sensitivity (39).

Regardless of the underlying DNA-level processes, functionally definite RET fusion transcripts can be identified using RNA-based NGS. RNA-based testing is frequently regarded as the gold standard technique for RET fusion identification and is a crucial confirmatory assay in many clinical contexts (38).

There are generally two methods for incorporating RNA sequencing into clinical workflow. For a more conclusive and useful evaluation, RNA testing can be carried out on a subset of individuals with RET rearrangements of uncertain importance in processes that include screening by DNA-based sequencing. The best way to detect RET fusion is a DNA-sequencing test, and in advance along DNA-sequencing, RNA-sequencing could be done. But its not always necessary to be done. Quality control of preanalytical settings is essential to guarantee the correctness of results since formalin fixation and tissue block preservation are linked to considerable RNA degradation (48).

As another way to assess monitoring, diagnosis, and prognosis in several cancers, cfDNA offers a viable substitute for invasive biopsies. A non-invasive method of detecting RET changes is plasma-based circulating free DNA (cfDNA), which is an alternative to tissue-based DNA sequencing. However, cfDNA testing's diagnostic yield depends on the DNA turnover rates and tumor load at the moment of liquid biopsy; progressive or metastatic diseases have higher sensitivity than those with localized or stable diseases (39, 49).

The poor specificity of DNA-based sequencing and varying sensitivity are still problems for cfDNA-based liquid biopsy testing. But with longitudinal testing, cfDNA can capture tumor heterogeneity and treatment response dynamics, offering a useful platform to identify how clonal and subclonal mutations impact tumor growth. Therefore, when assessing therapy resistance mechanisms and investigating logical combination therapies, prospective cfDNA testing can offer important insights (50).

Targeted Therapies for RET-Altered Solid Tumors

Lung cancer

In 2012, they were identified as non-small-cell lung cancer (NSCLC) (53, 54). They account for only 1% to 2% of all non-small cell lung cancers (NSCLCs), with an estimated 10,000 new cases occurring every year worldwide. In NSCLC, KIF5B and CCDC6 are the most frequently occurring partner genes of RET fusions (55–57).

RET fusion-positive NSCLC have the following clinical characteristics: adenocarcinoma histology, poorly differentiated tumors, equal incidence in both sexes, younger patient (approximately 60 y), and little to no tobacco exposure (58, 59). Furthermore, in terms of the dissemination to the CNS, The attitude of NSCLC with RET alteration is intermediate to that of patients with ALK-positive and ROS1 positive (60).

Chemotherapy

Although chemotherapy has a low effect, RET-positive NSCLC seems to be susceptible to regimens which include pemetrexed, according to findings from retrospective investigations (61-64).

Immunotherapy

Immunotherapy data in patients with RET fusion-positive NSCLC is derived from retrospective research rather than prospective investigations. It is debatable if this treatment is beneficial for this population (65).

Multi-targeted agent

Cabozantinib

The multi-TKI targets not just RET but also VEGFR2, AXL, c-KIT, FLT3 and MET (66). It's interesting to note that the number of lines treated before, previous VEGF inhibitors, and gene partners all had a detrimental impact on cabozantinib's effectiveness (tumors containing CCDC6-RET or ERC1-RET showed no responses). In NSCLC, KIF5B-RET fusions had shorter mPFS than those with CCDC6-RET fusions, which is an unusual consequence for cabozantinib (67).

Increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), hypothyroidism, diarrhea, palmar-plantar erythrodysesthesia, and skin hypopigmentation were the most frequent treatment-related adverse events (AEs) of any grade (79). While not required by its approval, periodic evaluation of electrolytes, calcium, and TSH should be part of safety monitoring during treatment (e.g., monthly at the beginning) (100).

Vandetanib

is an EGFR, VEGFR-2/3 and RET inhibitor (68). It is taken 300 mg per day. The three most frequent adverse events were rash acneiform, diarrhea, and hypertension (101). Start with 200 mg per day for people with mild renal impairment (creatinine clearance 30 to 50

mL/min). When the creatinine clearance is less than 30 milliliters per minute, use is not advised. Electrocardiograms (ECGs) and blood levels of potassium, calcium, magnesium, and TSH should be taken at 2–4 weeks and 8–12 weeks after beginning medication, and then every three months after that, as required by the REMS program. More regular monitoring may be necessary for those who have diarrhea (102).

Lenvatinib

This is a multi-TKI of platelet-derived growth factor receptor alpha (PDGFRα), fibroblast growth factor receptor (FGFR1-4), VEGFR1-3, RET, and KIT (69). CCDC6-RET and KIF5B-RET fusions produced similar responses; headache, diarrhea, decreased appetite, nausea, vomiting, proteinuria and Hypertension were the most frequent adverse events (70).

Ponatinib

is a RET and BCR-ABL inhibitor (71). The most frequent adverse events were dry skin, nausea, diarrhea, constipation, abdominal pain, and skin rash (103). Trials of several multi-TKIs in RET-positive NSCLC have shown that these medications have moderate activity but substantial toxicity, which is probably related to the inhibition of non-RET targets, particularly VEGFR-2.

Other Multi-TKIs

alectinib, sunitinib, sorafenib, nindetanib and regorafenib have very low function and little evidence available. Clinical information on these multi-TKIs from retrospective research and clinical trials (62, 72-77). All VEGF-targeted antiangiogenic MKIs (aaMKI) have the same side effects, which include muscle wasting, delayed wound healing, myelosuppression, arterial thromboembolism, hypertension, kidney toxicity, bleeding, hepatotoxicity, cardiotoxicity and hand-foot skin reaction. The higher dosage needed for derivatives of vitamin D and thyroid hormone can also result from aaMKIs in patients with hypothyroidism following thyroidectomy or decreased parathyroid function (104).

Arterial thromboembolic events during the last 6 to 12 months, encasement of major arteries by tumor, untreated hemorrhagic brain metastases current bleeding and major surgery within 28 days are all considered relative contraindications to aaMKIs. Because tracheoesophageal fistulas have been reported after external beam radiation therapy (EBRT) to the neck, we also attempt to limit the use of strong antiangiogenic medicines in these patients (104).

In conclusion, MKI for RET-altered advanced NSCLC was linked to both significant TRAEs and low efficacy outcomes. Although the non-selective inhibition of the RET-RTK is most likely the cause of these outcomes, patient selection may also play a role, as nearly all of the patients in the preceding trials had received prior treatment (75, 76). Therefore, in this context, none of these medications were approved by the US Food and Drug Administration (FDA) (78).

In some situations, multitargeted RET inhibitors such as sunitinib, alectinib, vandetanib, and cabozantinib may be helpful substitutes for selpercatinib and pralsetinib. They are substantially less effective than selective RET inhibitors, although the FDA has approved them for various applications (79, 80).

Selective RET Inhibitors (RET-Is)

Praseltinib

(Original name: BLU-667) is a powerful and selective RET-TKI. It has been proven to inhibit RET in vitro with a potency that is at least ten times greater than that of other multi-TKIs that do not target VEGFR2. Additionally, pralsetinib showed the same strong action against the V804R/L and the CCDC6-RET fusion, which may provide resistance to the multi-TKIs (81). it has demonstrated activity against KIF5B–RETV804L Ba/F3 and KIF5B–RET Ba/F3 allograft tumors in preclinical models (82).

Pralsetinib was tested in patients with RET-positive NSCLCs and other solid tumors as part of the global phase I/II investigation ARROW (83). hyponatremia and hypertension had occurred at 600 mg daily dose during Phase I Bayesian. Safety and pharmacokinetics data indicated 400 mg once daily as the recommended dose.

ORR as determined by safety and BIRC were the main goals in phase II of the experiment. Particularly in the individuals who had already received treatment, pralsetinib showed strong activity: the mPFS was 17.1 months, the mDoR was not reached, and the ORR was 61%. Crucially, the reactions were independent of ICI, previous multi-TKIs, and/or the RET fusion partner. The mDoR was mPFS were 9 months, and ORR was 70% among patients who had never received treatment (84, 85).

Pralsetinib exhibits intracranial action in tumor driven by CCDC6-RET or KIF5B-RET fusions, according to preclinical study findings (84). The IC-ORR was 56% among patients with demonstrable CNS illness and 51% among individuals with CNS metastases (62). Treatment-naïve and pretreated patients did not significantly differ in terms of toxicity. Treatment discontinuation was 7% in all cases. There was one pneumonia-related treatment-related death (85).

The ARROW experiment was further updated at the of ESMO 2022, with a median 16-month follow-up. The efficacy population, which included

RET + NSCLC (1:1 previously pretreated and treatment naïve), was enrolled at the data cutoff. As with previous data cuts, the ORR was 77.6% for patients who had never received systemic treatment and 63.1% for patients who had previously received platinum treatment. Pre-treated patients had a median overall survival of 44.3 months, while treatment-naïve patients did not. Among grade ≥3 adverse events (AEs), anemia, hypertension, reduced neutrophil count, pneumonia, and neutropenia were the most frequent (≥10%). As a result of treatment-related adverse events, 10% of patients stopped using pralsetinib (86).

The starting dosage for adults is 400 mg once daily, without food. Due to adverse reactions or possible drug interactions, dose modifications can be required. It is recommended to assess liver biochemistry tests before starting pralsetinib and every two weeks after starting it. Monitor every month after the first three months if liver tests stay stable (105).

Pralsetinib was given accelerated clearance by the FDA on September 4, 2020, for RET NSCLCs, regardless of previous treatment . EMA authorized pralsetinib on December 13, 2020, RET altered NSCLCs who had not received any previous RET inhibitor treatment (87).

The IC-ORR was 83% among patients with CNS target lesions, according to real-world data from the EAP of pralsetinib. Incidence of AEs was 39% with a G > 3 and occurred in 83.6% of the patients. Thrombocytopenia, oral mucositis, and neutropenia were the most prevalent G3 or greater AES. 42% of adverse events resulted in a dose reduction, and 12% led to treatment discontinuation. There were two documented treatment-related deaths: one from typhlitis and one from sepsis (88).

AcceleRET Lung was a worldwide trial that compared standard chemotherapy +/- pembrolizumab to first-line pralsetinib in patients who had not yet received treatment for RET + advanced non-small cell lung cancers. Patients randomly assigned to the control group were allowed to switch to pralsetinib as their condition progressed. PFS was the main endpoint, and it was evaluated with BIRC (89).

Selpercatinib

(previously LOXO-292) is a selective RET-TKI. Selpercatinib inhibits several point mutations, RET V804M, and RET fusions according to preclinical research. selpercatinib is demonstrated invivo, to suppress the proliferation of patient-derived xenografts, such as a patient-derived RET fusion-positive xenograft implanted orthotopically into the brain, and RET-altered human cancer cell lines. Two patients have also been described as receiving the first evidence of selpercatinib's activity: one MTC with RET (M918T) mutation who was not responding to cabozantinib, vandetanib or sorafenib, and another RET-altered NSCLC was advancing on alectinib, erlotinib, chemotherapy and nivolumab (90–92).

Libretto-001 has been a worldwide experiment that tested selpercatinib in individuals with solid tumors that had an activating RET change. Patients received seven doses throughout the phase I portion; DLTs were not reported. 160 mg twice dose day was determined to be the recommended for phase II (91). ORR via BIRC was the phase II part's main endpoint. The ORR, mDoR, and mPFS of the patients who had previously received treatment were 64%, 17.5 months, and 16.5 months, respectively. The ORR was 85%, and the mDoR and mPFS for the treatment-naive patients could not be estimated (92).

Libretto-001 was analyzed subgroup-wise among baseline CNS metastasis patients. Of that patients, 56% had previously undergone brain radiation treatment. IC-ORR for patients with CNS target lesions has been reported at 82%, but IC-mDoR couldn't be estimated. IC-mPFS was 13.7 months overall (93). Additionally, one EMLA4-RET-altered NSCLC that developed leptomeningeal carcinomatosis and advanced to agerafenib was shown to benefit from selpercatinib, achieving a PR with an indeterminate duration of response following 10.8 months (94).

The Libretto-001 has been updated to include all patients who were enrolled before the cutoff point for data and had a six-month follow-up. About 40 months was the median follow-up period. Patients who pre-received treatments, had an ORR of 61.5%, mDoR of 31.6 months, mPFS of 26.2 months and OS of 47.6 months. In patients who had never received treatment, the mDoR was 20.3 months, the ORR was 82.6%, the mPFS was 22 months and the OS was not estimable. In CNS metastasis patients, an IC-ORR and IC-mDoR were 84.6% and 9.36 months, respectively (95-97).

Based on the efficacy, safety, and tolerability of selpercatinib in patients with metastatic RET fusion-positive NSCLC, the LIBRETTO-432 trial demonstrates the benefits of adjuvant selpercatinib in patients with earlier stages (IB-IIIA) of RET fusion-positive NSCLC following definitive radiotherapy or surgery. Targeting treatment during the surveillance period after completing curative therapies and applicable adjuvant chemotherapy is expected to improve outcomes for patients with stage IB-IIIA RET fusion-positive NSCLC (192).

The most frequent adverse events (AEs) in terms of safety were weariness, skin rash, elevated ALT, elevated AST, dry mouth, edema, and diarrhea. Increases in ALT, AST, and hypertension were the most frequent G-≥3 adverse events, and the rate was 42%. Drug cessation was caused by 11% of adverse events, while dose reductions were caused by 48.9% of them (95, 96).

The starting dose is 160 mg twice daily among patients ≥50 kg and 120 mg twice daily for individuals under 50 kg. It's crucial to refrain from using gastric acid-lowering drugs at the same time as selpercatinib because this can lower plasma levels. Selpercatinib should be taken with food if that is not feasible. It must be administered two hours before the acid-reducing drug, or two or ten hours following a H2 receptor antagonist or locally acting antiacid, if the patient is taking any of these medications. It may be essential to lower the dose to address unpleasant reactions. Tests for LFT biochemistry must be performed before starting selpercatinib and every two weeks after starting it. Monitor every month after the first three months if liver tests stay stable. Before starting and at regular intervals following, measure the QT interval, electrolytes, and TSH (106, 107).

Among treatment-naive patients with advanced RET fusion-positive NSCLC (including unresectable stage IIIB, IIIC, and IV), the Libretto 431 (NCT04194944) compared conventional therapies (chemotherapy +/- pembrolizumab at the investigator's discretion) to first-line selpercatinib. In the selpercatinib group, mDoRs were longer (11.5 vs 24.2 months), and the experimental arm had higher responses (ORR 84% vs. 65%). In comparison to the control treatment, selpercatinib increased the median PFS. The overall survival rate data were not yet mature. Selpercatinib also improved the TTP impacting the CNS. Increases in alanine aminotransferase, aspartate aminotransferase, and hypertension were the most common grade ≥3 events with selpercatinib (98).

Selpercatinib was approved by the FDA on September 21, 2022, for adult patients with RET fusion positive NSCLCs, regardless of their previous treatment regimens. The European Medicines Agency (EMA) authorized selpercatinib on September 29, 2022, for advanced non-small cell lung cancers in people who had not received RET inhibitor treatment before (98). Using the RET inhibitor selpercatinib instead of immunotherapy and/or chemotherapy in the front-line scenario is recommended, but pralsetinib is a suitable substitute (albeit one with less evidence than selpercatinib). On the other hand, using these agents in the subsequent-line setting is equally permissible. Patients with locally progressed RET-positive non-small cell lung cancer are also eligible to receive selpercatinib (98, 99).

Thyroid cancer

PTC commonly exhibits RET rearrangements

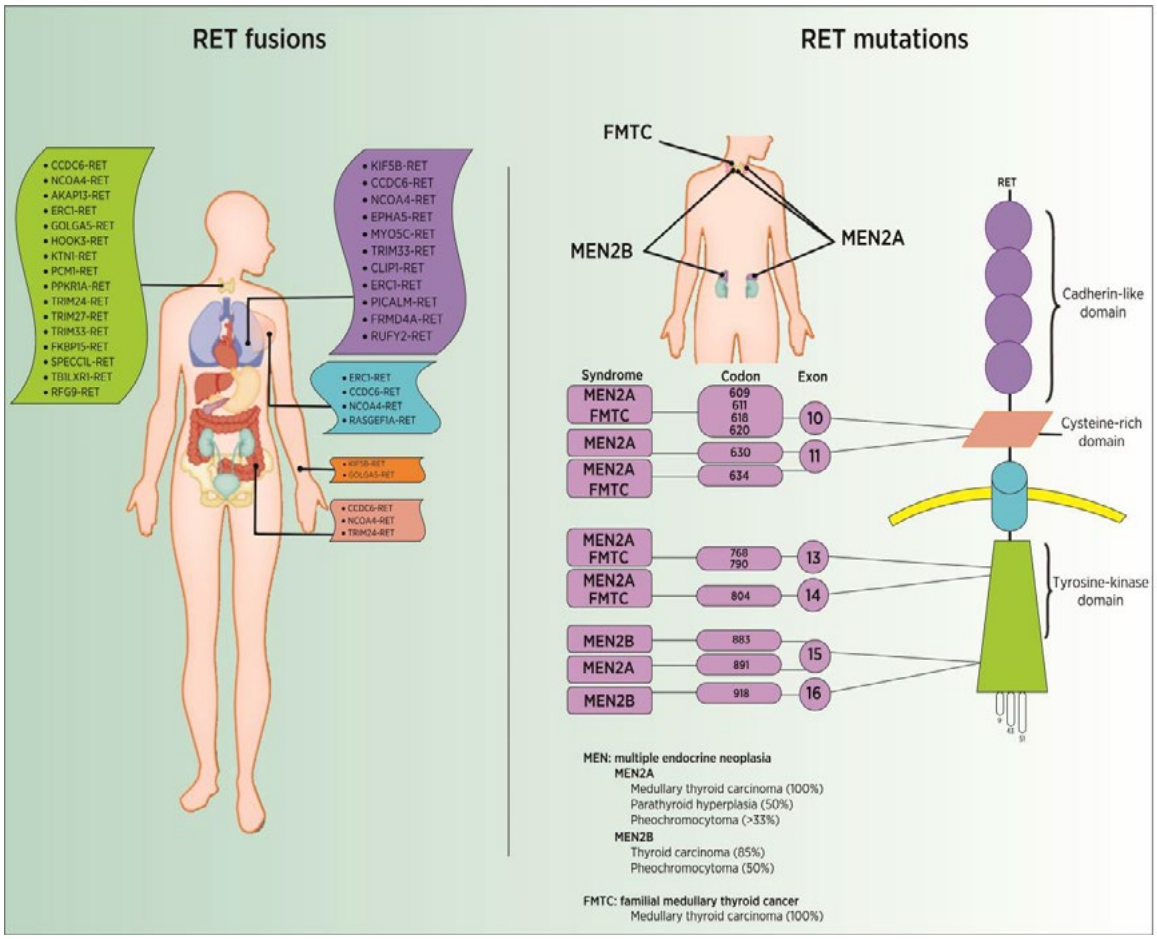

Fig 2. RET gene mutations and fusions in solid tumors

(Fig. 3), particularly in individuals who have previously been exposed to ionizing radiation. In post-Chernobyl PTC, 50% to 90% of children exhibit RET rearrangements because their follicular cells are prone to genetic alterations because of their high rate of proliferation. In a large PTC cohort, the Cancer Genome Atlas consortium recently discovered RET fusions for about 6.8% , however, other studies indicate that the incidence of rearrangements varies greatly (2.6%–70%) (108-111). The two most common RET fusion partners in PTC (>90% of cases) are CCDC6 and NCOA4, the latter of which is typically linked to a larger size of the tumor, higher stage at presentation, and aggressive behavior (112).

The autosomal dominant multi-tumor syndrome known as MEN2 is further classified as familial MTC, MEN2B, and MEN2A, which accounts for over 90% of cases (114). The bulk of the most prevalent variations are located in important residues in the extracellular and kinase domains, with extracellular domain mutations more commonly observed in MEN2A and FMTC (Fig. 2), even though about half of the 200 RET variants that have been identified in MEN2 are known to be harmful (115). Molecular testing can detect germline RET mutations, a pathognomonic feature of MEN2, in 98% to 100% of cases (113).

Missense mutations impact the cysteine-rich domain in the extracellular area by substituting alternative amino acids for the cysteine (C609, C611, C618, C620, C630, and C634). (116, 117)

The most prevalent substitution seen in MEN2A patients is an On exon 11 there may be a mutation that involves C634 which is the most prevalent substitution in MEN2A(about 85%). Each of the different cysteine residues (C611, C609, C620, C630, and C618) had an equal number of mutations in FMTC (118). MEN2B syndrome is pathognomonic for mutations in the kinase domain, 95% of them have M918T on exon 16 and the additional 2-3% have A883F on exon 15 (119). Compared to other RET mutations, the M918T mutation causes enhanced aggression by changing the RET receptor's catalytic core, which increases Receptor activation and ATP binding independent of receptor dimerization (120, 121).

In MEN2A and FMTC, tyrosine kinase domain mutations have also been reported (V804M and V804L in exon 14, and L790F and E768D in exon 13). These mutations are typically linked to a later onset of illness or more indolent disease.FMTC is also considered a clinical variation of MEN2A with reduced penetrance due to the shared mutational signatures between these two disorders in the extracellular and kinase domains. Desmoplastic melanoma (20%), melanoma (6.6%), colorectal cancer (3.6%–6.9%), cutaneous SCC (10%), Anaplastic thyroid carcinoma (4.3%), ureter urothelial carcinoma, and breast cancer and paraganglioma, are among the various thyroid cancers that also include somatic RET mutations (122).

MTC, or medullary thyroid cancer has been more common during the past years, and it accounts for 1–5% of cases (25% inherited and 75% sporadic). MTC is responsible for over 14% of all thyroid cancer-related deaths, despite its modest frequency (123).

MTC can run in families and is derived from parafollicular C cells. It may occur sporadic or linked to one of the two forms of MEN2 syndromes. Roughly 50% of sporadic MTCs and over 95% of hereditary MTCs have RET mutations. Other Solid Tumors Affected by RET Of all differentiated thyroid cancers, 80–85% are papillary thyroid cancers. About 20–40% of sporadic cases of papillary thyroid cancer have been reported to feature RET fusions, in which RET fusions following radioiodine exposure have higher rates (124, 125).

The most common genetic changes in MTC are RET-activating mutations. Germline gain-of-function mutations in the RET proto-oncogene cause around 25% of MTCs to be inherited and are associated with types 2A and 2B (128). Almost all individuals with MEN2A have MTC, along with a variety of additional symptoms including primary hyperparathyroidism, pheochromocytoma, and in rare cases, Hirschsprung disease and cutaneous lichen amyloidosis. In terms of MTC's penetrance and aggressiveness, as well as the presence of other related disorders, the genotype influences the syndrome's phenotypic presentation (131).

However, MTC is quite aggressive and frequently manifests in infancy in these patients (131). M918T, in exon 16 which is a germline RET mutation and replaces a methionine with a threonine inside RET kinase domain is nearly the only cause of MEN2B (126, 133-137).

Double mutations which involve V804M and A883F mutations (on exon 15) are present in less than 5% of MEN2B syndrome individuals (128,132). Apart from MTC, MEN2B syndrome is characterized by skeletal abnormalities like a marfanoid body habitus, pheochromocytoma, widespread ganglioneuromas of the aerodigestive tract, and ophthalmologic abnormalities (128, 131).

Unlike MTC, PTC has occasionally been found to be caused by RET fusions rather than mutations, particularly in children and after radiation exposure. Five to ten percent of PTCs have RET fusions, which most frequently involve RET with NCOA4-RET or coiled-coil domain containing 6 (CCDC6-RET) after a DNA double-strand break defective repaired (127–129). There are two possible ways that RET fusions increase the activation of downstream signaling

pathways: either the widespread expression of the upstream partner gene that causes expression of RET in cells by aberrant transcription and where typically, it isn't, or The dimerization domain contributed by the partner gene causes ligand-independent dimerization and RET kinase activation(4, 33, 127).

Chemotherapy and immunotherapy

Chemotherapy for RET-positive thyroid cancer, particularly in MTC and other cancers of the thyroid with RET alterations, has evolved significantly with the introduction of targeted therapies. Traditional chemotherapy generally targets rapidly dividing cells indiscriminately, which can cause a broad range of adverse effects.

Immunotherapy in RET-positive medullary thyroid cancer (MTC) is an emerging area of research, particularly as advancements in understanding tumor biology and immune mechanisms continue to evolve.

Multi-TKIs

Advanced radioiodine-refractory differentiated thyroid carcinomas (RR-DTCs), particularly the ones that have RET mutations, can be treated with lentvatinib, cabozantinib, and sorafenib. While overall survival (OS; 21.1 vs. 26.6 months) did not significantly increase in the EXAM trial, cabozantinib compared to placebo have been improved mPFS (4.0 vs. 11.2 months) and ORR (0% vs 28%). According to a retrospective review of the data from this trial, the presence of M918T mutation was correlated with improvements in ORR (2%vs. 34%), PFS (5.8 vs. 14.2 months), and OS (20.2 vs. 44.3 months) when compared to others (138, 139).

Biochemical tests have demonstrated the effectiveness of both cabozantinib and vandetanib against M918T (121, 140). The ZETA trial showed that vandetanib improved ORR statistically significantly (45% vs. 13%; P < 0.001) and lengthened the mPFS when compared to a placebo (30.5 vs. 19.3 months; P ¼ 0.001). Because there was not enough biological data available for this study, several of the patients in this clinical trial had unknown RET mutational status. However, the M918T mutation was once more linked to a higher ORR in the subgroup analysis when compared to the group that did not have this change (54.5% vs. 30.9%) (141).

Phase II clinical trials in thyroid malignancies have also evaluated lenvatinib, sunitinib, sorafenib, motesanib, and dovitinib which also are MKIs that have an anti-RET effect (142–146). mPFS and ORR varied from 5.4 to 17.9 months and 2% to 36%, respectively, in the world's demographic, irrespective of RET modification. Although post hoc RET subgroup analyses were performed in some of these studies, There was no discernible association between these patient groups and the response of the tumor (142, 143, 146).

The ORR for 33 RET-positive tumors in the motesanib study, which had the greatest number of RET-positive patients, was 0%, but it was 8% for 13 other tumors that were RET wild-type tumors. Finally, vandetanib and cabozantinib appear to provide superior outcomes in certain cancers of the thyroid with RET-positive; nevertheless, prospective trials with RET-positive chosen patients are required to confirm this concept. Notably, these medications have side effects that are comparable to those shown in NSCLC trials and are not insignificant. Vandetanib and cabozantinib had treatment discontinuation rates of 12% and 16%, respectively. Adverse effects necessitated a dose decrease for 35% and 79% of patients, respectively (146).

Selective RET Inhibitors (RET-Is)

Selpercatinib and pralsetinib, two medications with strong and specific anti-RET action, have been developed to address some of the limitations of MKIs (Table 1) (147-150). patients receiving RET-selective inhibitor therapy have been known to develop mutations

Table 1. Clinical trials of selpercatinib and pralsetinib in lung and thyroid cancer.

Selective RET inhibitor	Study name	Number		Follow-up (monthes)	ORR (%)	mPFS (months)	mOS (months)
Selpercatinib	LIBRETTO-531	T=291	S=193	12	69.4	NE	-
	phase3(Thyroid)		C=98	12	38.8	16.8	-
	LIBERTTO-431	T=261	S=159	17.9	84	24.8	NE
	phase3(Lung)		C=102	12.7	63	11.2	NE
	LIBERTTO-001	T=316	P=247	40	61.5	26.2	47.6
			N=69	40	82.6	22	NE
Pralsetinib	ARROW	T=145	PM=61	25.4	55.7	25.8	-
	(Thyroid)		NM=62	25.4	77.4	NE	-
			PTh=22	25.4	0.4	25.4	-
	ARROW	T=233	P=158	16	63.1	16.4	44.3
	(Lung)		N=75	16	77.6	12.6	NE

in codon 810 that result in selpercatinib resistance (152). For advanced or metastatic MTC and other thyroid tumors with a change (mutation or fusion) in the RET gene, the FDA has licensed selpercatinib (153).

Comparing sepercatinib to vandetanib or cabozantinib, the former lowers the probability of disease progression. Additionally, it works well for patients who have already received vandetanib and/or cabozantinib treatment. For instance: Among 291 patients with advanced, metastatic or progressive MTC with RET-mutation who were never treated with a kinase inhibitor, LIBRETTO-531 was a randomized open-label trial compared each of vandetanib or cabozantinib with selpercatinib. The median progression-free survival in the active comparator group was 16.8 months (151).

Selpercatinib had a higher 12-month progression-free survival (PFS) rate (86.8%) than either cabozantinib or vandetanib (65.7%). 57.5 and 34.7 percent, respectively, had partial responses, whereas 11.9 and 4 percent, respectively, had complete responses. The selpercatinib group saw fewer grade 3 or higher adverse events (76.3 versus 52.8 %), and fewer patients stopped taking the medication because of side effects (26.8 versus 4.7 %). At 12 months, the selpercatinib group's treatment failure-free survival rate was 86.2%, while the control groups were 62.1 %. Overall survival seemed to benefit the selpercatinib as well, despite the modest number of mortality events that were documented.

The overall response rate (ORR) for selpercatinib in the open-label LIBRETTO-001 study was 69 and 73 percent, respectively, in 143 patients with advanced MTC that all of them were RET-mutant and had either received treatment with vandetanib or cabozantinib or not (154). CR was seen in 9% of patients who had previously undergone treatment with an aaMKI., while 11 percent of treatment-naive patients reported it; 60 and 61 percent, however, reported PR respectively. The 12-month rates of PFS were 82 and 92 percent, respectively, but mPFS have not yet been attained.

Selpercatinib can result in quick palliation for patients experiencing symptoms of the condition, such as diarrhea or ectopic Cushing syndrome (156). Another trial is assessing selpercatinib before thyroidectomy in patients with nodal metastases or locally advanced primary tumors because of the drug's ability to rapidly decrease tumors (151). pralsetinib is approved by the FDA for the treatment of RET fusion-positive thyroid tumors that have advanced disease. A failure to finish the trial required to meet postmarketing conditions led the firm to voluntarily withdraw the FDA-approved preliminary indication for RET-mutant MTC in July 2023. No new safety or efficacy information led to the indication's withdrawal (151).

The open-label ARROW trial used pralsetinib to treat 122 patients with RET-mutant MTC. Patients who had previously received cabozantinib and/or vandetanib had an overall response rate of 60%, whereas those who had never received treatment had a response rate of 71%. The complete and partial response rates were 1.8 and 58 percent, respectively, among the 55 patients who previously had been treated with cabozantinib or vandetanib (154, 155).

Overall response rates were comparable in an updated study with two further years of follow-up (77.4 % in treatment naïve patients and 55.7 % in previously treated patients with vandetanib or cabozantinib) (155).

RET in other solid tumors

Other cancers that are associated with RET fusions include pancreatic acinar cell carcinoma (PACC), in 7.5% of cases which frequently conflicts with BRAF fusions. Less than 1% of colorectal carcinomas (CRC) include RET Fusions; these tumors are more common in older individuals, right-sided, RAS/BRAF wild-type, and MSI-high tumors, and they are linked to a poor prognosis (51).

In some instances, NCOA4-RET fusion serves as a resistance mechanism in breast tumors that are HER2-negative. Salivary gland cancers are uncommon and diverse, with some subtypes, such as intraductal carcinoma and mammary analogue secretory carcinomas (MASCs), containing RET fusions, including TRIM27-RET, ETV6-RET, NCOA4-RET, and KIAA1217-RET. A sporadic condition that involves many gene partners and is not associated with MEN 2 syndrome is pheochromocytoma (52).

Resistance mechanisms of RETtargeted therapy

Growing applications of cell-free DNA analysis and next-generation sequencing during tumor growth have improved our knowledge of potential resistance pathways and guided potential solutions. To date, two primary mechanisms have been identified for resistance to selective RET inhibitors: activation of alternate signaling pathways that allow RET inhibition to be bypassed and on-target mutations that degrade drug binding (150, 155). Non-gatekeeper mutations and Solvent-front mutations are acquired RET kinase domain mutations, which both disrupt the binding of the drug and provide resistance to selective RET inhibitors (150, 155, 156).

Several TKIs have been licensed for the treatment of advanced MTC, as previously mentioned, and have demonstrated significant efficacy; nevertheless, resistance to these TKIs has also developed. acquired and intrinsic resistance to RET-targeted TKIs, both, have been found in clinical practice, while the underlying mechanisms are still mostly unclear.

Table 2. New second generation RET inhibitors against resistance mutations

Drugs / Mutations	TPX-0046	BOS-172738	TAS0953/HM06	LOXO-260	EP0031/A400
G810C	+	–	+	+	+
G810R	+	–	+	+	+
G810S	+	–	+	+	+
V804L	–	+	+	+	+
V804M	–	+	+	+	+

Insufficient oncogenic RET kinase inhibition is at least partially responsible for the poor ORR that hinders the effectiveness of MKIs like Cabozantinib and Vandetanib. Many MTC patients (35–79%) who were using Vandetanib or Cabozantinib needed to have their dosages reduced because to the incidence of off-target adverse events. Therefore, it is challenging to use these MKIs to achieve the right drug concentrations for RET inhibition (127).

Even though the introduction of Selpercatinib and Pralsetinib, has significantly enhanced the out come for these patients who were resistant to MKI, demonstrating improved efficacy, less toxicity profile and significantly improved ORR (96,107,149), more than 30% of patients do not experience a partial response (PR) to these medications, and some patients experience rapid tumor recurrence or progression following an initial response to TKIs, which may indicate the presence of acquired and primary resistance. According to these findings, the field of RET resistance is complicated, and to overcome it, it is essential to comprehend the physiopathology of the several processes involved (157).

Understanding how RET inhibitors attach to RET kinase is essential before looking at how RET inhibitors cause resistance. To prevent kinase activity, TKIs totally or partially bind to the RET kinase domain's nucleotide-binding pocket. Additionally, depending on the activation loop's spatial orientation, kinases can take on an inactive or active form. It is referred to as "DFG-out" indicates that the aspartate-phenylalanine-glycine (DFG) motif at the N-terminal is flipped-out, while "DFG-in" indicates that it is in the activation loop. TKIs are divided into three categories: type I, type II, and type III. Each kind has a different mode of action. Type II inhibitors, such as sunitinib, work by competing with ATP for binding to the ATP binding site, preventing the kinase from adopting its active conformation. Type I TKIs, such as sorafenib, is only accessible in the DFG-out conformation, and stabilize the inactive kinase by indirectly competing with ATP by taking up residence in the ATP-binding site's nearby hydrophobic pocket (158). Type III TKIs, such as Vandetanib, function by covalently attaching to cysteines at particular, variable kinase sites to stop them from activating (159).

Notably, selective RET inhibitors and MKIs have distinct RET binding mechanisms. To get to the back cleft without passing through the gate, sepercatinib attaches itself to the front cleft and wraps around it., whereas MKIs enter the drug-binding pockets through the gate and take up residence in the front and back clefts (147).

Intrinsic resistance mechanisms

Alterations in RET that interact One mechanism of main resistance to MKIs have been identified as coexisting RET change. M918T is the most common mutation in MTC, that impacts on kinase's C-lobe. Patients with RET mutations may require a larger dose of Vandetanib, Cabozantinib, and Lenvatinib, as their half maximum inhibitory concentrations (IC50s) for RET M918T kinase were found to be many times that of the wild-type RET kinase (160). Intrinsic mechanisms of resistance have occasionally been defined as additional abnormalities, like RET V804L/M intrinsic gatekeeper mutations or other changes that normally function as acquired resistance mechanisms (90, 150, 158, 161).

Bypass signaling

Driver oncogenes such as mutation in EGFR and RAS, and amplification of the MET have been shown to co-occur in RET-altered tumors in clinical settings (50, 125), and preclinical studies have also detected acquired mutations of these driver oncogenes (162). The above driver genes may co-occur and circumvent the RET proto-oncogene requirements, reducing the effectiveness of RET-targeted TKIs. However, it hasn't been found in MTC. Since in vitro research has demonstrated how AKT2 amplification contributes to carcinogenesis and because serine/threonine kinases encoded by the AKT gene family phosphorylate downstream protein effectors like mTOR, It has been believed that AKT2 amplification contributes to both acquired and de novo resistance to targeted therapies like Vandetanib for MKIs, which persistently activate RET. However, the NCT01582191 trial (phase 1) showed longer PFS and greater ORR when Everolimus was added to Vandetanib in RET-driven malignancies suggesting that the inclusion of Everolimus and other mTOR inhibitors might be able to break through this resistance(161, 163-165).

According to a prior trial, patients with RET fusion-positive and MET amplification-positive non-small cell lung cancer (NSCLC) reacted to the combination of MET/ALK/ROS1-targeted TKI Crizotinib and Selpercatinib, whereas those who were resistant to Selpercatinib (166).

Tumor immune infiltration and microenvironment

The various biological components that make up the tumor microenvironment (TME) include vasculature, fibroblasts, extracellular matrix, tumor cells, immune cells, and a range of associated chemokines and cytokines (168). First, TME stressors and autophagy can impact EGFR-TKI resistance, and EGFR-TKIs may be more effective if CD4+ and CD8+ T cells are present in the TME (169). Second, TME can influence the tumor's responsiveness to certain TKIs. However, it is unknown and has not yet been shown how TME affects the efficacy of RET inhibitors (170).

NK cells, tumor-associated macrophages, myeloid-derived suppressor cells, TIL, and other immune cell subsets infiltrate TME locally. The many cell types and distributions comprise the intricate immunological features of TME (171). Tregs that suppress the immune system, which is associated with a poor prognosis and are very prevalent in TME (172, 173), are distinguished by their CD4+ CD25+ FOXP3+. Tregs are now using a variety of techniques to minimize early resistance to RET inhibitors, including downregulating MHCI or inhibiting FOXP3 through the utilization of RET inhibitors to counteract this immunosuppressive impact. One such strategy is the use of CXC chemokine receptor 4 (CXCR4) inhibitors (174).

CXCR4, a G-protein-coupled receptor that is triggered by C-X-C pattern chemokine ligand 12 (CXCL12), is one of the primary regulators of Tregs. Encouraging tumor growth and drawing in stromal and immune cells, it contributes significantly to TME. Thyroid cells that express RET or RET-positive MTC exhibit significant levels of CXCR4 expression, as do endothelial cells and Tregs (175, 176, 179). As a result, preclinical research shows that RET-mutant cell lines treated with Vandetanib exhibit downregulated CXCR4 expression (175, 177) and plans to combine CXCR4 inhibitors with traditional treatments are being developed for solid and hematologic tumors (176). The only CXCR4 inhibitor currently authorized for use in patients with multiple myeloma or non-Hodgkin's lymphoma is AMD3100 (Plerixafor or Mozobil) (178).

Acquired resistance mechanism

Secondary RET alteration

Gatekeeper mutations' emergence MKIs's Acquired resistance to Lenvatinib, Cabozantinb, or Vandetanib is usually the result of RET V804L/M/E. Both sunitinib and ponatinib continue to exhibit limited efficacy against V804M. However, considerable non-RET kinase activity explains the clinical response observed in 75% of patients who were treated with Vandetanib and had V804 mutation (90, 150, 158, 161). Other areas of acquired RET mutations include solvent front G810A/S mutations, RET Y806C mutations, and RET S904F activation loop mutations. The three RER mutation types mentioned above provide resistance to Vandetanib, whereas the S904F mutation is susceptible to Nintedanib, and the G810A/S mutation is susceptible to Ponatinib and Lenvatinib. A different mutation, RET I788N, is responsive to Ponatinib but resistant to AD80, Vandetanib, and Cabozantinib (58, 149, 150, 161, 180). Almost none of these mutations have been identified as germline changes. Secondary RET mutation is another significant acquired resistance mechanism for selective RET inhibitors (90, 150, 158, 161).

Bypass signaling

An escape strategy that frequently occurs across oncogenic drivers is the activation of alternative pathways linked to cell proliferation. When driver oncogenes are found in RETpositive tumors, they may circumvent the RET proto-oncogene's requirements and result in both acquired and primary resistance to RET-targeted TKIs. MKI resistance in RET-rearranged cells has been linked to the co-activation of the MAPK/ERK pathway. Trametinib, a particular MEK inhibitor with strong RET-blocking

activity, must be added to AD80 in this case to eradicate the resistant cells (149, 150, 181).

According to preclinical research, this pathway was downregulated when EGFR inhibitors Gefitinib or Cetuximab were added to MKI therapy. This prevented the phosphorylation of AKT and ERK (170). MET or EGFR inhibitors can overcome other bypass mechanisms, such as MET amplification in colorectal cancer or the acquisition of MET D1228V in NSCLC (161). Within the phase III EXAM trial, 21% of patients had changes in the genes CDK4, CCND2, CDK6, CCND1, CDKN2C or CDKN2A/B. The cyclin D-dependent kinases CDK4 and CDK6 may be activated as a result of these changes. It is yet unknown how CDK4/6 inhibitors affect cancers with RET mutations (128).

A further resistance mechanism to selective RET inhibitors is an acquired NTRK3 fusion, which has been reported in RET fusion-positive lung cancer treated with sepercatinib. Larotrectinib or Entrectinib, two NTRK selective inhibitors, may be a good strategy in this situation (167). Additionally, there have been reports of KRAS amplification and BRAF and ROS1 mutations of uncertain significance (77, 83).

In addition to the secondary RET mutation, Rosen's study revealed that another significant mechanism of resistance to Selpercatinib was bypass signaling, as evidenced by emergent MAPK activating changes comparable to those causing primary resistance. According to a polyclonal resistance theory, a complicated polyclonal resistance pattern to sepercatinib treatment may develop, as evidenced by the variety of Mechanisms of primary or acquired resistance induced by MAPK that were also seen throughout specific patients (Fig.3) (183).

New drug era

RET inhibitors of the second generation: The development of many next-generation RET inhibitors is part of the ongoing search for new medication for the treatment of malignancies with RET alterations. There is a new and powerful RET inhibitor TPX-0046 that works against 18 altrations of RET, which include solvent-front alterations in G810R and G810S that cause acquired resistance to pralsetinib and selpercatinib (68).

Its usage in patients with RET V804 gatekeeper mutations is restricted, because it does not block these mutations. In vitro, TPX-0046 exhibits strong inhibitory effect against SRC kinase while sparing VEGFR-2. On RET-driven xenograft tumor models, this medication demonstrated strong in vivo anti-tumor action (184). SWORD1trial (phase I/II) is presently under progress to verify its effectiveness and assess its safety in humans. Initial findings in 21 patients with advanced MTC or NSCLC and RET-alteration revealed that 4/5 of those who were

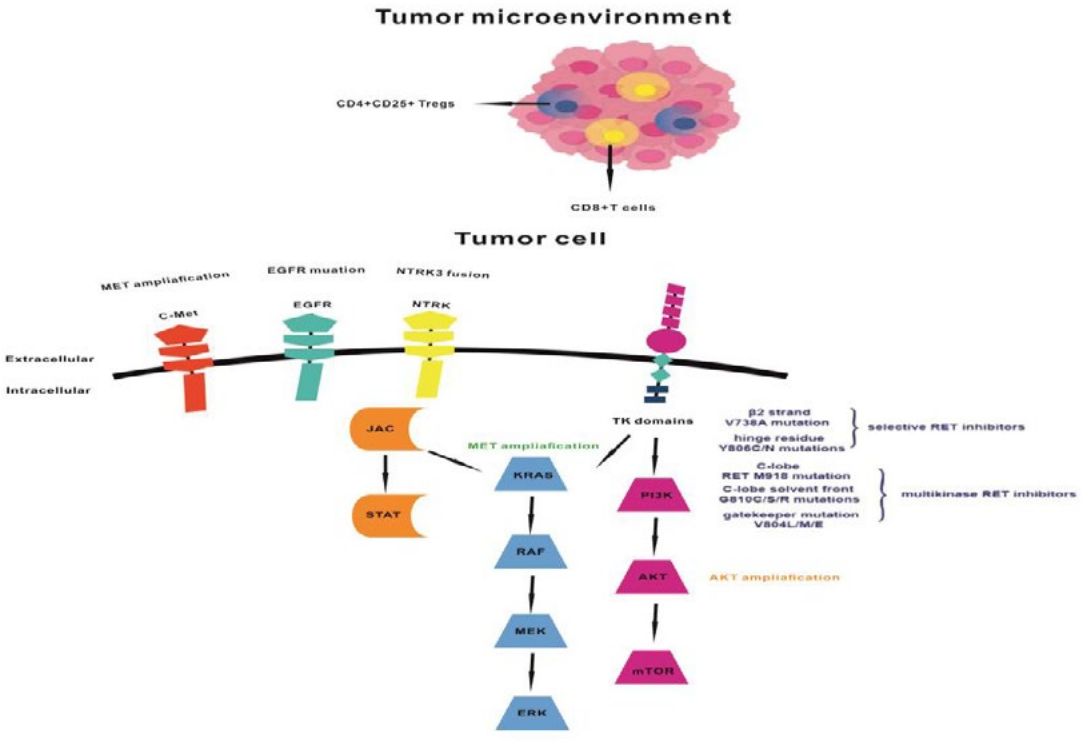

Fig3. Both primary and acquired resistance mechanisms to RET inhibitors.

TKI naïve (−3 to −42%) and 3/9 of those who were TKI pretreated (−17 to −44%) experienced tumor regression, with an acceptable toxicity profile (185).

The other second-generation RET inhibitor, BOS-172738, is presently being studied in a phase I trial. It was created with strong selectivity against VEGFR-2, nanomolar efficacy against RET, such as V804 M/L mutations, and Kd values ≤ 1 nM. Its strong anti-tumor efficacy and strong and specific RET inhibition were validated in vivo (186).

A new ATP-competitive and highly selective RET inhibitor, TAS0953/HM06 exhibits strong in vitro suppression of both G810R/S and RETV804M/L mutations in addition to RET-wildtype. It is insensitive to solvent front mutations because of its distinct binding mechanism to RET. In xenograft tumor models made from mice resistant to selpercatinib and pralsetinib, it showed substantial anticancer activity in vivo, indicating a good therapeutic promise (187). Additionally, data from animal models indicate that TAS0953/HM06 has higher suppression of brain xenograft tumors, increased survival in mice with intracranial metastases, and more effective CNS penetration than selpercatinib (188).

Highly selective RET inhibitor, LOXO-260 is made to be active for solvent-front and RET gatekeeper mutations while still exhibiting strong inhibition against other typical RET changes. In NSCLC or thyroid cancer patients that have RET altration or who have already taken a RET inhibitor, it is presently being studied in a phase I trial (NCT05241834) (189). Another powerful next-generation selective RET inhibitor, EP0031/A400, has improved effectiveness over selpercatinib against known resistance mutations, such as G810R/S/C and RET V804M/L, and has blood-brain barrier penetration. In 87 patients with RET-altered tumors, including 10 MTCs, the ongoing phase 1 basket trial's preliminary data (NCT05443126) indicate a 64% ORR, high tolerability, few adverse events, and no dose-limiting toxicities (190).

Other next-generation selective RET inhibitors are also being studied in advanced RET-altered tumors, including thyroid cancer. However, since bypass RAS mutations account for amount of acquired resistance to first-generation RET inhibitors and for which there is presently no specific targeted therapy, more research is necessary to address the shortcomings of the available treatments. Patients who have these acquired RAS mutations may have hope as several trials exploring the use of pan-RAF inhibitors in solid tumors are now in progress (Table 2) (191).

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