frontiers | Frontiers in Oncology

TYPE Mini Review
PUBLISHED 14 February 2023
DOI 10.3389/fonc.2023.1090757

OPEN ACCESS

EDITED BY
Elena Lastraioli,
University of Florence, Italy

REVIEWED BY
Shiva Prasad Kollur,
Amrita Vishwa Vidyapeetham, India
Eswari Dodagatta-Marri,
University of California, San Francisco, United States

*CORRESPONDENCE
Fanming Kong
kongfanming08@163.com

SPECIALTY SECTION
This article was submitted to Cancer Genetics, a section of the journal Frontiers in Oncology

RECEIVED 07 December 2022
ACCEPTED 27 January 2023
PUBLISHED 14 February 2023

CITATION
Zhao L, Wang N, Zhang D, Jia Y and Kong F (2023) A comprehensive overview of the relationship between RET gene and tumor occurrence.
Front. Oncol. 13:1090757.
doi: 10.3389/fonc.2023.1090757

A comprehensive overview of the relationship between RET gene and tumor occurrence

Lu Zhao[1,2], Na Wang[1,2], Dou Zhang[1,2], Yingjie Jia[1,2] and Fanming Kong[1,2]*

[1]Department of Oncology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China, [2]National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, China

RET gene plays significant roles in the nervous system and many other tissues. Rearranged during transfection (RET) mutation is related to cell proliferation, invasion, and migration. Many invasive tumors (e.g., non-small cell lung cancer, thyroid cancer, and breast cancer) were found to have changes in RET. Recently, great efforts have been made against RET. Selpercatinib and pralsetinib, with encouraging efficacy, intracranial activity, and tolerability, were approved by the Food and Drug Administration (FDA) in 2020. The development of acquired resistance is inevitable, and a deeper exploration should be conducted. This article systematically reviewed RET gene and its biology as well as the oncogenic role in multiple cancers. Moreover, we also summarized recent advances in the treatment of RET and the mechanism of drug resistance.

KEYWORDS

RET, thyroid cancer, lung cancer, breast cancer, targeted therapy

Introduction

Precision therapy changed the prospect of solid tumors. The intervention of aberrant tyrosine kinase has become the optimal target. Rearranged during transfection (RET) was first identified in 1985 in the transfection of NIH3T3 (1). RET gene has been confirmed to have a great role in the development of the kidney and nervous systems (2). The mechanism of RET aberrant activation was different from that of other receptor tyrosine kinases, which need both additional glial cell-derived neurotrophic factor (GDNF) family receptor-α (GFRα) and co-receptors (GFα1/2/3/4). The tripartite complex form (GDNF ligand+GFRα complex+RET kinase) stimulated RET by autophosphorylation and then triggered RAS, MAPK, ERK, PI3K, and AKT signaling pathways to promote tumor cell proliferation, migration, and differentiation (1, 3–5).

Many treatment advances have been made in recent years. Multikinase inhibitors including sunitinib, vandetanib, regorafenib, and alectinib were approved by the Food and Drug Administration (FDA) (6–10). However, their response rates were lower when compared with those of ALK or ROS1, and the off-target toxicity limited the application (11). Selective RET inhibitors LOXO-292 (selpercatinib) and BLU-667 (pralsetinib), which

were approved by the FDA in 2020 with good clinical benefits and low incidence of serious adverse events, were more ideal (12, 13). It is worth mentioning that the two drugs have a strong intracerebral activity, which is in line with the carcinogenicity of RET. However, recent publications reported the novel acquired resistance to selpercatinib and pralsetinib (14). Second-generation RET inhibitors such as BOS172738, TPX-0046, TAS0953/HM06, and LOX-18228 are currently in clinical trials (15). Moreover, platinum-containing chemotherapy or immune-checkpoint inhibitors (ICIs) were also explored to increase the chances of drug resistance patients.

This article systematically reviewed RET gene and its biology as well as the oncogenic role in multiple cancers. Moreover, we also summarized recent advances in the treatment of RET and the mechanisms of drug resistance. Finally, we analyzed the opportunities and challenges and, then, gave proposals for this portion of patients to maximize their survival time in the future.

Function and biology of RET

RET gene was first identified in 1985 from the transfection of NIH3T3 (16). It was located in chromosome 10 (10q11.2) and contained 21 exons, its full length was 60 kb, and it was the receptor for GDNF (17). In addition to GDNF, this family also included artemin (ARTN), neurturin (NRTN), and persephin (PSPN). RET gene was required for the development of the brain and nervous systems, thyroid and lung tissues, and others (18). Unlike other RTKs, RET gene was not bound directly to the ligands. Instead, the RET ligands first bind to the GFRα receptor. The GFL–GFRα complex then mediated RET homodimerization, which lead to autophosphorylation and then activated the proliferation pathways such as MAPK, PI3K, JAK-STAT, PKA, and PKC (19, 20).

PI3K-AKT-mTOR and RAS-RAF-MEK-ERK were the major ways of cell survival, proliferation, migration, and differentiation (21). Three general mechanisms of aberrant RET activation will trigger the above pathways: in-frame RET fusions, targeted mutation, and aberrant overexpression (22, 23). However, the different sites lead to a different degree of tyrosine kinase transformation. Three main ways were included: sudden changes of codons in the extracellular region result in the transform of cysteine residues, codon mutations in the transmembrane region cause two receptor proteins to draw nearby non-covalent bond, and ATP binds to its site easily made by codon mutations in the intracellular regions (24–26). Among them, RET point mutation frequently occurred in multiple endocrine neoplasias and medullary thyroid carcinoma (27). However, RET fusion has been commonly reported in papillary thyroid and non-small cell lung cancers (14, 28).

RET gene and tumor occurrence

RET expression in lung cancer

Lung cancer is the most prevalent malignant tumor in the world with a poor survival rate and faster progression. Non-small cell lung cancer (NSCLC) accounted for 80% to 85% (29, 30). For patients who are not eligible for targeted therapy, platinum-based chemotherapy is the standard treatment. However, their survival time is less than 12 months. RET fusion was discovered in approximately 1%–2% of NSCLC (31). KIF5B was the most common type in RET fusion, and 47 other partners have been identified so far (7, 32). The clinical and pathological features of RET fusion NSCLC patients differ from those caused by other oncogenes. RET fusion NSCLC patients correlated with adenocarcinoma histology, never-smoking status, younger age, more advanced stage disease, and potentially higher chemo-sensitivity (pemetrexed-based regimens) (33, 34). It is of high concern that RET fusion NSCLC patients are more likely to have brain metastases, and the incidence is up to 27% (35, 36). Therefore, developing novel agents with blood–brain barrier (BBB) permeability is necessary. Multikinase inhibitors (MKIs) showed inferior activity in RET-NSCLC, compared with EGFR or ALK. The off-target toxicity and suboptimal intracerebral activity also limited its application in clinical. ICIs in driver gene mutation tumors are controversial. The present studies reported disappointing efficacy with ICI monotherapy in this portion of patients. However, ICI-based combination therapy may bring hope in the future (37, 38). Thus, chemotherapy remained a reasonable choice until RET-selective tyrosine kinase inhibitors (TKIs) emerged.

RET expression in thyroid cancer

Thyroid cancer only accounts for 3%–4% of all human cancers commonly caused by ionization radiation (39). Nevertheless, it is prevalent in endocrine neoplasia with the highest increase in the past two decades. Thyroid cancer is categorized into four different types [papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), anaplastic thyroid cancer (ATC), and medullary thyroid cancer (MTC)]. RET mutations were most commonly found in PTC and MTC (40). Indeed, the activation mechanisms were different in the two types. Chromosomal rearrangements were found in PTC, and somatic mutations lead to MTC (41).

PTC accounts for 85% of thyroid cancer and is the first human cancer associated with RET fusion. RET/PTC chimeric protein formed dimers that are required for oncogenic activation, which activated the RAS/MAPK/ERK pathway to promote proliferation and migration. An assay that targeted 244 cancer-related genes detected RET fusion in 4.35% PTC. Subsequently, in The Cancer Genome Atlas (TCGA) study, which enrolled 500 PTC patients, 6.8% had RET fusion. The high-frequency forms were CCDC6-RET (RET/PTC1) and NCOA4-RET (RET/PTC3), which were the consequences of double-stranded breaks caused by ionizing radiation (42). RET fusion has been reported more commonly in pediatrics and dose-dependently with irradiation. The Chernobyl accident remained an example that activated the MAPK pathways by chromosomal rearrangement. Approximately 58% aged <10 years old patients harbored RET fusion, and 50% of PTC patients who were exposed to high radiation doses (>0.5 Gy) had RET fusion (41, 43). Regrettably, the relationship between RET rearrangement and the prognosis of PTC is still controversial. Some studies confirmed that RET/PTC is a more aggressive phenotype combined with advanced-stage disease. On the contrary, other trials hold that there was no significant correlation between RET/PTC and tumor aggressiveness (14, 39, 44).

In contrast to PTC, MTC is a rare type (2%–4%) of thyroid cancer. Radiation exposure is not associated with RET fusion in MTC compared to PTC (45). MTC included five subtypes, but MEN2A and MEN2B are the most common. The current research indicated that MEN2A is related to the RET-C634 mutation (46). Mulligan analyzed 118 unrelated families and found that the RET-C634 mutation occurred in 95% of MEN2A families (47). In agreement with their earlier study, they did not detect the RET-C634 mutation in MEN2B families. Instead, MEN2B always shared the RET-M918T mutation with a 95% detection rate. It was first detected in 1994 by a separate study that detected the mutation in 34 unrelated MEN2B patients (48). Moreover, many studies have confirmed that RET mutations in MEN2A and MEN2B were reliable biomarkers for the identification of highly aggressive MTC.

RET expression in breast cancer

Breast cancer (BC) is the most common cancer in women, with approximately 1.7 million people diagnosed every year, and RET alteration occurrence is approximately 1.2% (49). RET amplification is the most common, followed by RET fusion. Most RET mutations in BC appear after drug resistance, and CCDC6-RET and NCOA4-RET occur frequently (50). RET is actionable in ER^+ BC. Gattelli identified that RET activation promoted proliferation and migration in ER^+ BC patients (8). Plaza-Menacho showed that RET modulates the sensitivity of ER^+ BC to endocrine therapy and that activated RET promotes estrogen-independent activation of ERa, which suggested an interference between RET and the ERa pathway in endocrine-resistant BC (51). After that, Isacke also determined that RET signaling was hyperactivated in aromatase-resistant ER^+ BC (52). Although RET expression was related to ER in luminal BC, it lacked prognostic significance as an independent biomarker. In addition to ER^+ BC, RET was also actionable in HER2-enriched and triple-negative BC patients who failed targeted therapy (53). A recent study showed that trastuzumab resistance was associated with the activation of the RET–HER2 signaling axis (54).

RET expression in other tumors

RET mutations also occurred in other tumors. For example, G533C was confirmed to increase proliferation and migration in colon cancer (55). In pancreatic cancer, RET led to lymphatic invasion and was upregulated in ductal adenocarcinoma (56). In kidney cancer, RET was confirmed to predict survival and the high expression results in a shorter survival time. In prostate cancer, moderately to poorly differentiated tumors displayed overexpression of RET (57). In summary, RET was increasingly recognized as an oncogene and a potential target in multiple tumors.

RET kinase inhibitors

Non-selective MKI

Multi-targeted drugs are being used in RET mutation cancers in the early stage. For example, type I inhibitors such as vandetanib and lenvatinib were confirmed to bind to the ATP in an active conformation of RET kinase. Famous type II inhibitors such as cabozantinib and sorafenib can bind to the ATP in an inactive conformation. However, the clinical benefits (lower overall response rate (ORR) and shorter progression-free survival (PFS)) and significant off-target toxicities limited their application. A phase II clinical trial (NCT01639508) reported that cabozantinib had not reached the endpoints with 28% ORR, 5.5 months median PFS (mPFS), and 9.9 months median overall survival (mOS) (7). Similarly, a phase III clinical trial (NCT00704730) in MTC harboring RET-M918T showed that OS was 6.6 months (58). Also, lenvatinib (NCT01877083) in RET fusion NSCLC yielded a relatively low response (ORR = 16%, mPFS = 7.3 months) (59). Subsequently, a clinical study by Carlomagno identified that vandetanib may not yield clinical efficacy. The ORR was 18%, mPFS was 4.5 months, and mOS was 11.6 months in RET fusion NSCLC (6). After that, randomized, phase III, registrational trials confirmed that cabozantinib and vandetanib in patients with advanced MTC were also unspectacular, the ORR was 28% and 45%, and mPFS was 7.2 and 11.2 months, respectively, and uncontrollable adverse events frequently occurred (60). To sum up all the above studies, MKIs were not outstanding agents for RET mutation patients.

RET selective TKI

BLU-667 (pralsetinib) and LOXO-292 (selpercatinib) were two highly selective RET inhibitors with good efficacy and tolerable adverse effects. Currently, the clinical data of the two drugs have been recently released. The ensuing drug resistance has become a new challenge. Other RET inhibitors such as BOS172738, GSK3352589, and GSK3179106 are currently undergoing phase I clinical trials.

Selpercatinib is an oral RET inhibitor designed to overcome the weaknesses of MKIs. The *in vitro* and *in vivo* studies revealed that selpercatinib can inhibit wild and altered RET, meanwhile holding back KDR/VEGFR2 activity. LIBRETTO-001, a global phase I/II trial, demonstrated that selpercatinib had the perfect outcomes in RET fusion NSCLC patients with a 68% ORR. The ORR of the brain metastases patients also reached 91%. The median diagnostic odds ratio (mDOR) was 20.3 months, and mPFS was up to 18.4 months (13). After that, LIBRETTO-321 was performed to evaluate the efficacy and safety of selpercatinib in Chinese patients. Consistent with the previous conclusions, the ORR was 61.1%, and 90% of the patients remained in continuous remission after 6 months (28). As for RET-mutant MTC, LIBRETTO-001 showed a 56% ORR, and the ORR was similar regardless of whether MKI has been used before (61). Therefore, the FDA accelerated the approval of selpercatinib for RET mutation NSCLC and MTC patients in 2020. Currently, LIBRETTO-121 and LIBRETTO-431 are ongoing to confirm the effectiveness of selpercatinib in other tumors.

Same as selpercatinib, pralsetinib is also an ATP-competitive inhibitor that selectively inhibits RET. ARROW was a single-arm phase I/II trial that demonstrated that 90% of PTC and MTC have radiographic tumor reduction with pralsetinib. The ORR

was 60% (disease control rate (DCR) 100%) *vs.* 63% (DCR 94%) in RET fusion NSCLC and RET mutation MTC. Nine patients with brain metastases showed an intracranial response rate of 56% in MTC (12). Remarkably, pralsetinib can be widely used regardless of RET fusion partner (62). Based on these data, pralsetinib was granted by the FDA in 2020 for RET mutation NSCLC and MTC. Subsequently, China's State Food and Drug Administration [National Medical Products Administration (NMPA)] also approved pralsetinib for Chinese patients in March 2021. Other ongoing clinical trials such as NCT04222972, NCT04222972, and NCT04760288 were aimed to assess the application of pralsetinib in other tumors.

Other therapy

ICIs have become the keystone in cancer treatment and are considered a salvage treatment for patients with actionable driver alterations after targeted therapies. Building on previous experience that ICI monotherapy was unsatisfactory, combination therapy has been increasingly applied in RET mutation cancers. A clinical trial showed that bevacizumab+carboplatin+pemetrexed can highly prolong the survival time of RET fusion NSCLC patients. The mPFS was 6.6 months *vs.* 5.7 months (63). Subsequently, Guisier also determined the effectiveness of ICIs-based combination therapy for RET mutation cancers in a real-world setting. Among 107 patients, only nine had RET translocation. Before ICIs, they had received at least one line of treatment. The results showed the mPFS was 7.6 months, the median DOR was 4.7 months, and the ORR was 38% (64). A multicenter retrospective study reported a high DCR (60%) in RET mutation patients who failed targeted therapy, with a conclusion that was in line with that of another trial (ORR = 58%, mPFS = 5.4 months, mOS = 19 months) (65). Based on the above data, the therapeutic value of ICIs in patients with RET mutation has become clear. After targeted therapy, ICIs or in combination with chemotherapy will bring new vitality to this portion of patients.

Given that those RET selective inhibitors were recognized recently, the majority of patients are still being treated with chemotherapy. Platinum-doublet chemotherapy is the standard regimen in RET mutation NSCLC patients (66). A multicenter retrospective study showed that 65 RET fusion NSCLC patients used platinum-based chemotherapy as the first-line treatment, the ORR was 51%, and the mPFS was 7.8 months. Another global trial also showed optimistic results (mPFS = 6.6 *vs.* 7.8 months, OS = 23.6 *vs.* 24.8 months) in RET mutation NSCLC and MTC patients (67, 68).

The mechanistic pathway of drug resistance

According to the present data, both instinct and acquired resistance of RET TKIs exist. Understanding the mechanistic pathway of targeted agents is imperative to prolong remissions due to the drugs. On-target and off-target resistance were included to explain the underlying mechanisms of drug resistance.

On-target mechanism of drug resistance

There was an acquired resistance inside the target kinase, which was continuously activated by kinase inhibitors. Gatekeeper mutations and solvent front mutations are two common types in MKI and TKI (15). The construction of the *in vitro* model confirmed that RET V840 gatekeeper mutations mediated drug resistance in the following two ways: lead the spatial conflict between leucine and methionine side chains and the 4-bromo-2-fluorophenyl group and increase the adenosine triphosphate affinity (22). A recent study showed that a novel RET inhibitor, SYHA1815, can overcome this resistance, which may be a new direction for drug development (69). However, Gly-810 is representative of solvent front mutation, which is located at the solvent front of the ATP binding pocket (70). Solomon reported that RET G810R, G810S, and G810C mutations occurred in three NSCLC cases with RET fusion after selpercatinib (71). Of note, their study also described that RET V840 gatekeeper mutation and G810 solvent front mutation could be present at the same time. Therefore, more clinical studies need to explore whether RET-selective TKI was able to prevent gatekeeper mutation.

Off-target mechanism of drug resistance

Off-target resistance activates different intracellular pathways that bypass the kinase-mediated signal. MET, EGFR, BRAF, and RAS were all reported in recent trials, of which MET was common as a recurring and potential type of resistance of selpercatinib and pralsetinib (72). A retrospective clinical trial analyzed 20 RET fusion NSCLC patients who were resistant to selpercatinib and pralsetinib, and they found 15% MET amplification and 10% G810C/S mutation. EGFR would activate downstream pathways and disrupt the combination of kinase inhibitors to restore fusion signaling complexes, which promote proliferation and hide RET inhibitors (73, 74). RAS and BRAF mutations were reported in two and one KIF5B-RET fusion NSCLC patients, respectively, who received selpercatinib, yet more experimental validation is still needed.

Next-generation RET inhibitors

While not overwhelmingly dominant, RET resistance mutations are recurrent in patients treated with selpercatinib or pralsetinib. For these patients, novel RET inhibitors harboring potency against the resistance mutations are needed. Next-generation RET inhibitors including BOS172738, TPX-0046, TAS0953/HM06, and LOX-18228 were designed to solve the above problems. BOS172738 could overcome RET-G810 resistance and showed good activity in patients with RET fusion tumors (55). A phase I clinical trial showed good efficacy and safety with 33% ORR. TPX-0046 presents perfect benefits *in vitro* and *in vivo* RET fusion cancers. It can overcome RET-G810 resistance. A phase I/II clinical trial (NCT04161391) is ongoing to evaluate the efficacy and safety of TPX-0046 in advanced cancers harboring RET mutants (15). HM06, another selective RET inhibitor, circumvents RET-V804X gatekeeper mutation and RET-G810X resistance mutations. This drug is currently in phase I/II clinical trials (NCT04683250) in a patient

with RET mutation (75). Lastly, LOX-18228 can inhibit RET-V804X and RET-G810X mutations, which have a promising use after first-generation RET inhibitors. LOX-18228 is now entering phase I clinical trials.

Summary and prospects

RET proto-oncogene was identified more than 30 years ago, and the rearrangement and mutation of RET have been reported in a variety of cancers, including thyroid cancer, non-small cell lung cancer, and breast cancer. Currently, targeted therapy and immune checkpoint inhibitors brought new life to this portion of patients. Multiple kinase inhibitors easily generate toxicity because of the off-target effects. Most of them were not authorized by the FDA (76–80). Immune checkpoint inhibitors as the post-line treatment option were sensible for driver gene mutation patients (38, 63, 81, 82). The highly selective RET inhibitors such as selpercatinib and pralsetinib provided considerable benefit in both MTC and NSCLC patients and were authorized for the first-line treatment (83, 84). However, like other inhibitors, on-target or bypass resistance of RET-TKI will become more common. Several novel RET inhibitors, which cover not only the drug-resistant site but also other RTKs that can activate parallel signaling pathways, are at an early stage (26, 85). Of note, further research still needs to explore the broader coverage of potential resistance mechanisms, and combination therapies to optimally pathways are also important.

Author contributions

LZ and FK contribute equally to this article. All authors contributed to the article and approved the submitted version.

Funding

This work is supported by the National Key Research and Development (R&D) plan (2018YFC1707400), the National Natural Science Foundation of China (No. 81403220), and the Tianjin Health and Family Planning-High Level Talent Selection and Training Project.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1090757/full#supplementary-material

References

1. Regua AT, Najjar M, Lo HW. RET signaling pathway and RET inhibitors in human cancer. *Front Oncol* (2022) 12:932353. doi: 10.3389/fonc.2022.932353

2. Olmedo ME, Cervera R, Cabezon-Gutierrez L, Lage Y, de la Fuente EC, Rueda AG, et al. New horizons for uncommon mutations in non-small cell lung cancer: BRAF, KRAS, RET, MET, NTRK, HER2. *World J Clin Oncol* (2022) 13:276–86. doi: 10.5306/wjco.v13.i4.276

3. Li W, Guo L, Liu Y, Dong L, Yang L, Chen L, et al. Potential unreliability of uncommon ALK, ROS1, and RET genomic breakpoints in predicting the efficacy of targeted therapy in NSCLC. *J Thorac Oncol* (2021) 16:404–18. doi: 10.1016/j.jtho.2020.10.156

4. Subbiah V, Yang D, Velcheti V, Drilon A, Meric-Bernstam F, et al. State-of-the-Art strategies for targeting RET-dependent cancers. *J Clin Oncol* (2020) 38:1209–21. doi: 10.1200/JCO.19.02551

5. Takahashi M, Kawai K, Asai N. Roles of the RET proto-oncogene in cancer and development. *Jma J* (2020) 3:175–81. doi: 10.31662/jmaj.2020-0021

6. Yoh K, Seto T, Satouchi M, Nishio M, Yamamoto N, Murakami H, et al. Final survival results for the LURET phase II study of vandetanib in previously treated patients with RET-rearranged advanced non-small cell lung cancer. *Lung Cancer* (2021) 155:40–5. doi: 10.1016/j.lungcan.2021.03.002

7. Zheng Q, Fang W, Huang Y, Gan J, Zhang L, et al. Identification of a novel KIF5B-RET, ABHD17C-RET double-fusion variant in lung adenocarcinoma and response to cabozantinib. *J Thorac Oncol* (2020) 15:e132–e3. doi: 10.1016/j.jtho.2019.12.114

8. Mehta M, Griffith J, Panneerselvam J, Babu A, Mani J, Herman T, et al. Regorafenib sensitizes human breast cancer cells to radiation by inhibiting multiple kinases and inducing DNA damage. *Int J Radiat Biol* (2021) 97:1109–20. doi: 10.1080/09553002.2020.1730012

9. Tian Z, Niu X, Yao W. Receptor tyrosine kinases in osteosarcoma treatment: Which is the key target? *Front Oncol* (2020) 10:1642. doi: 10.3389/fonc.2020.01642

10. Hida T, Velcheti V, Reckamp KL, Nokihara H, Sachdev P, Kubota T, et al. A phase 2 study of lenvatinib in patients with RET fusion-positive lung adenocarcinoma. *Lung Cancer* (2019) 138:124–30. doi: 10.1016/j.lungcan.2019.09.011

11. Thein KZ, Velcheti V, Mooers BHM, Wu J, Subbiah V, et al. Precision therapy for RET-altered cancers with RET inhibitors. *Trends Cancer* (2021) 7:1074–88. doi: 10.1016/j.trecan.2021.07.003

12. Subbiah V, Cassier PA, Siena S, Garralda E, Paz-Ares L, Garrido P, et al. Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. *Nat Med* (2022) 28:1640–5. doi: 10.1038/s41591-022-01931-y

13. Drilon A, Subbiah V, Gautschi O, Tomasini P, Braud FD, Solomon BJ, et al. Selpercatinib in patients with RET fusion-positive non-Small-Cell lung cancer: Updated safety and efficacy from the registrational LIBRETTO-001 phase I/II trial. *J Clin Oncol* (2023) 41(2):385–94. doi: 10.1200/JCO.22.00393

14. Rosen EY, Won HH, Zheng Y, Cocco E, Selcuklu D, Gong Y, et al. The evolution of RET inhibitor resistance in RET-driven lung and thyroid cancers. *Nat Commun* (2022) 13:1450. doi: 10.1038/s41467-022-28848-x

15. Repetto M, Crimini E, Ascione L, Bielo LB, Belli C, Curigliano G, et al. The return of RET GateKeeper mutations? an in-silico exploratory analysis of potential resistance mechanisms to novel RET macrocyclic inhibitor TPX-0046. *Invest New Drugs* (2022) 40:1133–6. doi: 10.1007/s10637-022-01259-x

16. Myrand SP. A novel oncogenic RET fusion variant in NSCLC: RELCH-RET. *J Thorac Oncol* (2021) 16:e95. doi: 10.1016/j.jtho.2020.12.018

17. Kim J, Bradford D, Larkins E, Pai-Scherf LH, Chatterjee S, Mishra-Kalyani PS, et al. FDA Approval summary: Pralsetinib for the treatment of lung and thyroid cancers with RET gene mutations or fusions. *Clin Cancer Res* (2021) 27:5452–6. doi: 10.1158/1078-0432.CCR-21-0967

18. Hess LM, Han Y, Zhu YE, Bhandari NR, Sireci A, et al. Characteristics and outcomes of patients with RET-fusion positive non-small lung cancer in real-world practice in the United States. *BMC Cancer* (2021) 21:28. doi: 10.1186/s12885-020-07714-3

19. Verrienti A, Grani G, Sponziello M, Pecce V, Damante G, Durante C, et al. Precision oncology for RET-related tumors. *Front Oncol* (2022) 12:992636. doi: 10.3389/fonc.2022.992636

20. Takahashi M. RET receptor signaling: Function in development, metabolic disease, and cancer. *Proc Jpn Acad Ser B Phys Biol Sci* (2022) 98:112–25. doi: 10.2183/pjab.98.008

21. Conway JA, Ince S, Black S, Kramer ER, et al. GDNF/RET signaling in dopamine neurons in vivo. *Cell Tissue Res* (2020) 382:135–46. doi: 10.1007/s00441-020-03268-9

22. Subbiah V, Shen T, Terzyan SS, Liu X, Hu X, Patel KP, et al. Structural basis of acquired resistance to selpercatinib and pralsetinib mediated by non-gatekeeper RET mutations. *Ann Oncol* (2021) 32:261–8. doi: 10.1016/j.annonc.2020.10.599

23. Schubert L, Le AT, Estrada-Bernal A, Doak AE, Yoo M, Ferrara SE, et al. Novel human-derived RET fusion NSCLC cell lines have heterogeneous responses to RET inhibitors and differential regulation of downstream signaling. *Mol Pharmacol* (2021) 99:435–47. doi: 10.1124/molpharm.120.000207

24. Drusbosky LM, Rodriguez E, Dawar R, Ikpeazu CV, et al. Therapeutic strategies in RET gene rearranged non-small cell lung cancer. *J Hematol Oncol* (2021) 14:50. doi: 10.1186/s13045-021-01063-9

25. Della Corte CM, Morgillo F. Rethinking treatment for RET-altered lung and thyroid cancers: selpercatinib approval by the EMA. *ESMO Open* (2021) 6:100041. doi: 10.1016/j.esmoop.2020.100041

26. Solomon BJ, Tan L, Lin JJ, Wong SQ, Hollizeck S, Ebata K, et al. RET solvent front mutations mediate acquired resistance to selective RET inhibition in RET-driven malignancies. *J Thorac Oncol* (2020) 15:541–9. doi: 10.1016/j.jtho.2020.01.006

27. Santoro M, Moccia M, Federico G, Carlomagno F, et al. RET gene fusions in malignancies of the thyroid and other tissues. *Genes (Basel)* (2020) 11(4):424. doi: 10.3390/genes11040424

28. Zheng X, Ji Q, Sun Y, Ge M, Zhang B, Cheng Y, et al. Efficacy and safety of selpercatinib in Chinese patients with advanced RET-altered thyroid cancers: results from the phase II LIBRETTO-321 study. *Ther Adv Med Oncol* (2022) 14:17588359221119318. doi: 10.1177/17588359221119318

29. Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, et al. Cancer treatment and survivorship statistics, 2022. *CA Cancer J Clin* (2022) 72:409–36. doi: 10.3322/caac.21731

30. Nooreldeen R, Bach H. Current and future development in lung cancer diagnosis. *Int J Mol Sci* (2021) 22(16):8661. doi: 10.3390/ijms22168661

31. Kazdal D, Hofman V, Christopoulos P, Ilié M, Stenzinger A, Hofman P, et al. Fusion-positive non-small cell lung carcinoma: Biological principles, clinical practice, and diagnostic implications. *Genes Chromosomes Cancer* (2022) 61:244–60. doi: 10.1002/gcc.23022

32. Cong XF, Yang L, Chen C, Liu Z, et al. KIF5B-RET fusion gene and its correlation with clinicopathological and prognostic features in lung cancer: a meta-analysis. *Onco Targets Ther* (2019) 12:4533–42. doi: 10.2147/OTT.S186361

33. Li AY, McCusker MG, Russo A, Scilla KA, Gittens A, Arensmeyer K, et al. RET fusions in solid tumors. *Cancer Treat Rev* (2019) 81:101911. doi: 10.1016/j.ctrv.2019.101911

34. Takeuchi K. Discovery stories of RET fusions in lung cancer: A mini-review. *Front Physiol* (2019) 10:216. doi: 10.3389/fphys.2019.00216

35. Salvatore D, Santoro M, Schlumberger M. The importance of the RET gene in thyroid cancer and therapeutic implications. *Nat Rev Endocrinol* (2021) 17:296–306. doi: 10.1038/s41574-021-00470-9

36. Shi M, Wang W, Zhang J, Li B, Lv D, Wang D, et al. Identification of RET fusions in a Chinese multicancer retrospective analysis by next-generation sequencing. *Cancer Sci* (2022) 113:308–18. doi: 10.1111/cas.15181

37. Negrao MV, Skoulidis F, Montesion M, Schulze K, Bara I, Shen V, et al. Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. *J Immunother Cancer* (2021) 9(8):e002891. doi: 10.1136/jitc-2021-002891

38. Bhandari NR, Hess LM, Han Y, Zhu YE, Sireci AN, et al. Efficacy of immune checkpoint inhibitor therapy in patients with RET fusion-positive non-small-cell lung cancer. *Immunotherapy* (2021) 13:893–904. doi: 10.2217/imt-2021-0035

39. Pizzato M, Li M, Vignat J, Laversanne M, Singh D, Vecchia CL, et al. The epidemiological landscape of thyroid cancer worldwide: GLOBOCAN estimates for incidence and mortality rates in 2020. *Lancet Diabetes Endocrinol* (2022) 10:264–72. doi: 10.1016/S2213-8587(22)00035-3

40. Kobaly K, Kim CS, Mandel SJ. Contemporary management of thyroid nodules. *Annu Rev Med* (2022) 73:517–28. doi: 10.1146/annurev-med-042220-015032

41. Shi X, Sun Y, Shen C, Zhang Y, Shi R, Zhang F, et al. Integrated proteogenomic characterization of medullary thyroid carcinoma. *Cell Discov* (2022) 8:120. doi: 10.1038/s41421-022-00479-y

42. Fallahi P, Ferrari SM, Galdiero MR, Varricchi G, Elia G, Ragusa F, et al. Molecular targets of tyrosine kinase inhibitors in thyroid cancer. *Semin Cancer Biol* (2022) 79:180–96. doi: 10.1016/j.semcancer.2020.11.013

43. Thomas GA, Bunnell H, Cook HA, Williams ED, Nerovnya A, Cherstvoy ED, et al. High prevalence of RET/PTC rearrangements in Ukrainian and belarussian post-Chernobyl thyroid papillary carcinomas: a strong correlation between RET/PTC3 and the solid-follicular variant. *J Clin Endocrinol Metab* (1999) 84:4232–8. doi: 10.1210/jcem.84.11.6129

44. Zheng H, Chen ZS, Li J. Selpercatinib for lung and thyroid cancers with RET gene mutations or fusions. *Drugs Today (Barc)* (2021) 57:621–9. doi: 10.1358/dot.2021.57.10.3313852

45. Kant R, Davis A, Verma V. Thyroid nodules: Advances in evaluation and management. *Am Fam Physician* (2020) 102:298–304.

46. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* (2019) 30:1856–83. doi: 10.1093/annonc/mdz400

47. Mulligan LM, Eng C, Healey CS, Clayton D, Kwok JB, Gardner E, et al. Specific mutations of the RET proto-oncogene are related to disease phenotype in MEN 2A and FMTC. *Nat Genet* (1994) 6:70–4. doi: 10.1038/ng0194-70

48. Grimm D. Recent advances in thyroid cancer research. *Int J Mol Sci* (2022) 23(9):4631. doi: 10.3390/ijms23094631

49. Spanheimer PM, Bashir A, Lorenzen AW, Beck AC, Liao J, Lizarraga IM, et al. A pilot study of preoperative vandetanib on markers of proliferation and apoptosis in breast cancer. *Am J Clin Oncol* (2021) 44:456–62. doi: 10.1097/COC.0000000000000845

50. Lo Nigro C, Rusmini M, Ceccherini I. RET in breast cancer: pathogenic implications and mechanisms of drug resistance. *Cancer Drug Resist* (2019) 2:1136–52. doi: 10.20517/cdr.2019.66

51. Andreucci E, Francica P, Fearns A, Martin LA, Chiarugi P, Isacke CM, et al. Targeting the receptor tyrosine kinase RET in combination with aromatase inhibitors in ER positive breast cancer xenografts. *Oncotarget* (2016) 7:80543–53. doi: 10.18632/oncotarget.11826

52. Zheng ZZ, Xia L, Hu GS, Liu JY, Hu YH, Chen YJ, et al. Super-enhancer-controlled positive feedback loop BRD4/ERα-RET-ERα promotes ERα-positive breast cancer. *Nucleic Acids Res* (2022) 50:10230–48. doi: 10.1093/nar/gkac778

53. Paratala BS, Chung JH, Williams CB, Yilmazel B, Petrosky W, Williams K, et al. RET rearrangements are actionable alterations in breast cancer. *Nat Commun* (2018) 9:4821. doi: 10.1038/s41467-018-07341-4

54. Gattelli A, Hynes NE, Schor IE, Vallone SA, et al. Ret receptor has distinct alterations and functions in breast cancer. *J Mammary Gland Biol Neoplasia* (2020) 25:13–26. doi: 10.1007/s10911-020-09445-4

55. Nguyen Ho-Bouldoires TH, Sollier K, Zamfirov L, Zamfirov L, Broders-Bondon F, Mitrossilis D, et al. Ret kinase-mediated mechanical induction of colon stem cells by tumor growth pressure stimulates cancer progression in vivo. *Commun Biol* (2022) 5:137. doi: 10.1038/s42003-022-03079-4

56. Lian EY, Hyndman BD, Moodley S, Maritan SM, Mulligan LM, et al. RET isoforms contribute differentially to invasive processes in pancreatic ductal adenocarcinoma. *Oncogene* (2020) 39:6493–510. doi: 10.1038/s41388-020-01448-z

57. Moran JMT, Le LP, Nardi V, Golas J, Farahani AA, Signorelli S, et al. Identification of fusions with potential clinical significance in melanoma. *Mod Pathol* (2022) 35:1837–47. doi: 10.1038/s41379-022-01138-z

58. Koehler VF, Adam P, Frank-Raue K, Raue F, Berg E, Hoster E, et al. Real-world efficacy and safety of cabozantinib and vandetanib in advanced medullary thyroid cancer. *Thyroid* (2021) 31:459–69. doi: 10.1089/thy.2020.0206

59. Wirth LJ, Brose MS, Sherman EJ, Licitra L, Schlumberger M, Sherman SI, et al. Open-label, single-arm, multicenter, phase II trial of lenvatinib for the treatment of patients with anaplastic thyroid cancer. *J Clin Oncol* (2021) 39:2359–66. doi: 10.1200/JCO.20.03093

60. Lei ZN, Teng QX, Gupta P, Zhang W, Narayanan S, Yang DH, et al. Cabozantinib reverses topotecan resistance in human non-small cell lung cancer NCI-H460/TPT10 cell line and tumor xenograft model. *Front Cell Dev Biol* (2021) 9:640957. doi: 10.3389/fcell.2021.640957

61. Illini O, Hochmair MJ, Fabikan H, Weinlinger C, Tufman A, Swalduz A, et al. Selpercatinib in RET fusion-positive non-small-cell lung cancer (SIREN): a retrospective analysis of patients treated through an access program. *Ther Adv Med Oncol* (2021) 13:17588359211019675. doi: 10.1177/17588359211019675

62. Griesinger F, Curigliano G, Thomas M, Subbiah V, Baik CS, Tan DSW, et al. Safety and efficacy of pralsetinib in RET fusion-positive non-small-cell lung cancer including as first-line therapy: update from the ARROW trial. *Ann Oncol* (2022) 33:1168–78. doi: 10.1016/j.annonc.2022.08.002

63. Mazieres J, Drilon A, Lusque A, Mhanna L, Cortot AB, Mezquita L, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol* (2019) 30:1321–8. doi: 10.1093/annonc/mdz167

64. Guisier F, Dubos-Arvis C, Viñas F, Doubre H, Ricordel C, Ropert S, et al. Efficacy and safety of anti-PD-1 immunotherapy in patients with advanced NSCLC with BRAF, HER2, or MET mutations or RET translocation: GFPC 01-2018. *J Thorac Oncol* (2020) 15:628–36. doi: 10.1016/j.jtho.2019.12.129

65. Dudnik E, Bshara E, Grubstein A, Fridel L, Shochat T, Roisman LC, et al. Rare targetable drivers (RTDs) in non-small cell lung cancer (NSCLC): Outcomes with immune check-point inhibitors (ICPi). *Lung Cancer* (2018) 124:117–24. doi: 10.1016/j.lungcan.2018.07.044

66. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Updated analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced non-Small-Cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol* (2019) 37:537–46. doi: 10.1200/JCO.18.00149

67. Hanna NH, Robinson AG, Temin S, Jr SB, Brahmer JR, Ellis PM, et al. Therapy for stage IV non-Small-Cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. *J Clin Oncol* (2021) 39:1040–91. doi: 10.1200/JCO.20.03570

68. Drilon A, Bergagnini I, Delasos L, Sabari J, Woo KM, Plodkowski A, et al. Clinical outcomes with pemetrexed-based systemic therapies in RET-rearranged lung cancers. *Ann Oncol* (2016) 27:1286–91. doi: 10.1093/annonc/mdw163

69. Lu C, Zhou Q . Diagnostics, therapeutics and RET inhibitor resistance for RET fusion-positive non-small cell lung cancers and future perspectives. *Cancer Treat Rev* (2021) 96:102153. doi: 10.1016/j.ctrv.2021.102153

70. Tan L, Solomon BJ. Defining resistance mechanisms to selective RET tyrosine kinase inhibitors in RET fusion-positive non-small-cell lung cancer. *Ann Oncol* (2020) 31:1599–600. doi: 10.1016/j.annonc.2020.10.002

71. Piotrowska Z, Isozaki H, Lennerz JK, Gainor JF, Lennes IT, Zhu VW, et al. Landscape of acquired resistance to osimertinib in EGFR-mutant NSCLC and clinical validation of combined EGFR and RET inhibition with osimertinib and BLU-667 for acquired RET fusion. *Cancer Discov* (2018) 8:1529–39. doi: 10.1158/2159-8290.CD-18-1022

72. Rosen EY, Johnson ML, Clifford SE, Somwar R, Kherani JF, Son J, et al. Overcoming MET-dependent resistance to selective RET inhibition in patients with RET fusion-positive lung cancer by combining selpercatinib with crizotinib. *Clin Cancer Res* (2021) 27:34–42. doi: 10.1158/1078-0432.CCR-20-2278

73. Fancelli S, Caliman E, Mazzoni F, Brugia M, Castiglione F, Voltolini L, et al. Chasing the target: New phenomena of resistance to novel selective RET inhibitors in lung cancer. updated evidence and future perspectives. *Cancers (Basel)* (2021) 13(5):1091. doi: 10.3390/cancers13051091

74. Fujino T, Kobayashi Y, Suda K, Koga T, Nishino M, Ohara S, et al. Sensitivity and resistance of MET exon 14 mutations in lung cancer to eight MET tyrosine kinase inhibitors in vitro. *J Thorac Oncol* (2019) 14:1753–65. doi: 10.1016/j.jtho.2019.06.023

75. Kogami Y, Tsuji T, Tsuji C, Yokoyama S, Furuhara K, Lopatina O, et al. A monoclonal antibody raised against a synthetic oxytocin peptide stains mouse hypothalamic neurones. *J Neuroendocrinol* (2020) 32:e12815. doi: 10.1111/jne.12815

76. Horiike A, Takeuchi K, Uenami T, Kawano Y, Tanimoto A, Kaburaki K, et al. Sorafenib treatment for patients with RET fusion-positive non-small cell lung cancer. *Lung Cancer* (2016) 93:43–6. doi: 10.1016/j.lungcan.2015.12.011

77. Klempner SJ, Borghei A, Hakimian B, Ali SM, Ou SHI, et al. Intracranial activity of cabozantinib in MET exon 14-positive NSCLC with brain metastases. *J Thorac Oncol* (2017) 12:152–6. doi: 10.1016/j.jtho.2016.09.127

78. Drilon A, Lin JJ, Filleron T, Ni A, Milia J, Bergagnini I, et al. Frequency of brain metastases and multikinase inhibitor outcomes in patients with RET-rearranged lung cancers. *J Thorac Oncol* (2018) 13:1595–601. doi: 10.1016/j.jtho.2018.07.004

79. Okamoto K, Kodama K, Takase K, Sugi NH, Yamamoto Y, Iwata M, et al. Antitumor activities of the targeted multi-tyrosine kinase inhibitor lenvatinib (E7080) against RET gene fusion-driven tumor models. *Cancer Lett* (2013) 340:97–103. doi: 10.1016/j.canlet.2013.07.007

80. Sood A, Lang DK, Kaur R, Saini B, Arora S, et al. Relevance of aromatase inhibitors in breast cancer treatment. *Curr Top Med Chem* (2021) 21:1319–36. doi: 10.2174/1568026621666210701143445

81. Offin M, Guo R, Wu SL, Sabari J, Land JD, Ni A, et al. Immunophenotype and response to immunotherapy of RET-rearranged lung cancers. *JCO Precis Oncol* (2019) 3:PO.18.00386. doi: 10.1200/PO.18.00386

82. Hegde A, Andreev-Drakhlin AY, Roszik J, Huang L, Liu S, Hess K, et al. Responsiveness to immune checkpoint inhibitors versus other systemic therapies in RET-aberrant malignancies. *ESMO Open* (2020) 5:e000799. doi: 10.1136/esmoopen-2020-000799

83. Bradford D, Larkins E, Mushti SL, Rodriguez L, Skinner AM, Helms WS, et al. FDA Approval summary: Selpercatinib for the treatment of lung and thyroid cancers with RET gene mutations or fusions. *Clin Cancer Res* (2021) 27:2130–5. doi: 10.1158/1078-0432.CCR-20-3558

84. Tsui DCC, Kavanagh BD, Honce JM, Rossi C, Patil T, Camidge DR, et al. Central nervous system response to selpercartinib in patient with RET-rearranged non-small cell lung cancer after developing leptomeningeal disease on pralsetinib. *Clin Lung Cancer* (2022) 23:e5–8. doi: 10.1016/j.cllc.2021.06.005

85. Subbiah V, Shen T, Tetzlaff M, Weissferdt A, Byers LA, Cascone T, et al. Patient-driven discovery and post-clinical validation of NTRK3 fusion as an acquired resistance mechanism to selpercatinib in RET fusion-positive lung cancer. *Ann Oncol* (2021) 32:817–9. doi: 10.1016/j.annonc.2021.02.010