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REVIEW

Non-small-cell lung cancer: how to manage *RET*-positive disease

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Abstract

Targeted therapy has dramatically changed the history and outcomes of oncogene-addicted non-small-cell lung cancer (NSCLC). *RET* rearrangements are typically observed in about 1–2% of NSCLC, resulting in constitutive activation of downstream signalling pathways commonly involved in cell growth and survival. *RET*-positive NSCLCs are generally associated with young age, non-smoking history, a high rate of brain metastases at diagnosis and an immunologically 'cold' tumour microenvironment. Multi-kinase inhibitors, such as cabozantinib, lenvatinib and vandetanib, showed limited efficacy but significant toxicity mainly linked to off-target effects. In contrast, two RET-selective tyrosine kinase inhibitors (TKIs), selpercatinib and pralsetinib, demonstrated high response rates and manageable safety profiles, and have received FDA approval for the treatment of advanced *RET*-positive NSCLC regardless of previous lines of treatment. Despite the initial high response rate to RET-TKIs, most patients inevitably develop disease progression due to acquired resistance mechanisms by both on-target or off-target mechanisms. To date, new potent and selective next-generation RET-TKIs are currently being evaluated in ongoing clinical trials in order to overcome resistance and improve efficacy and blood–brain barrier crossing. Genomic recharacterization at progression could help guide treatment choice or enrolment in clinical trials of specific next-generation RET inhibitors. Here, we review the biology, clinicopathological characteristics, targeted therapies and mechanisms of resistance of advanced NSCLC harbouring *RET* fusions to provide treatment guidance for these patients.

Keywords: RET, non-small-cell lung cancer, next-generation sequencing, tyrosine kinase inhibitors, pralsetinib, selpercatinib.

Citation

Andrini E, Mosca M, Galvani L, Sperandi F, Ricciuti B, Metro G, Lamberti G. Non-small-cell lung cancer: how to manage RET-positive disease. *Drugs Context*. 2022;11:2022-1-5. https://doi.org/10.7573/dic.2022-1-5

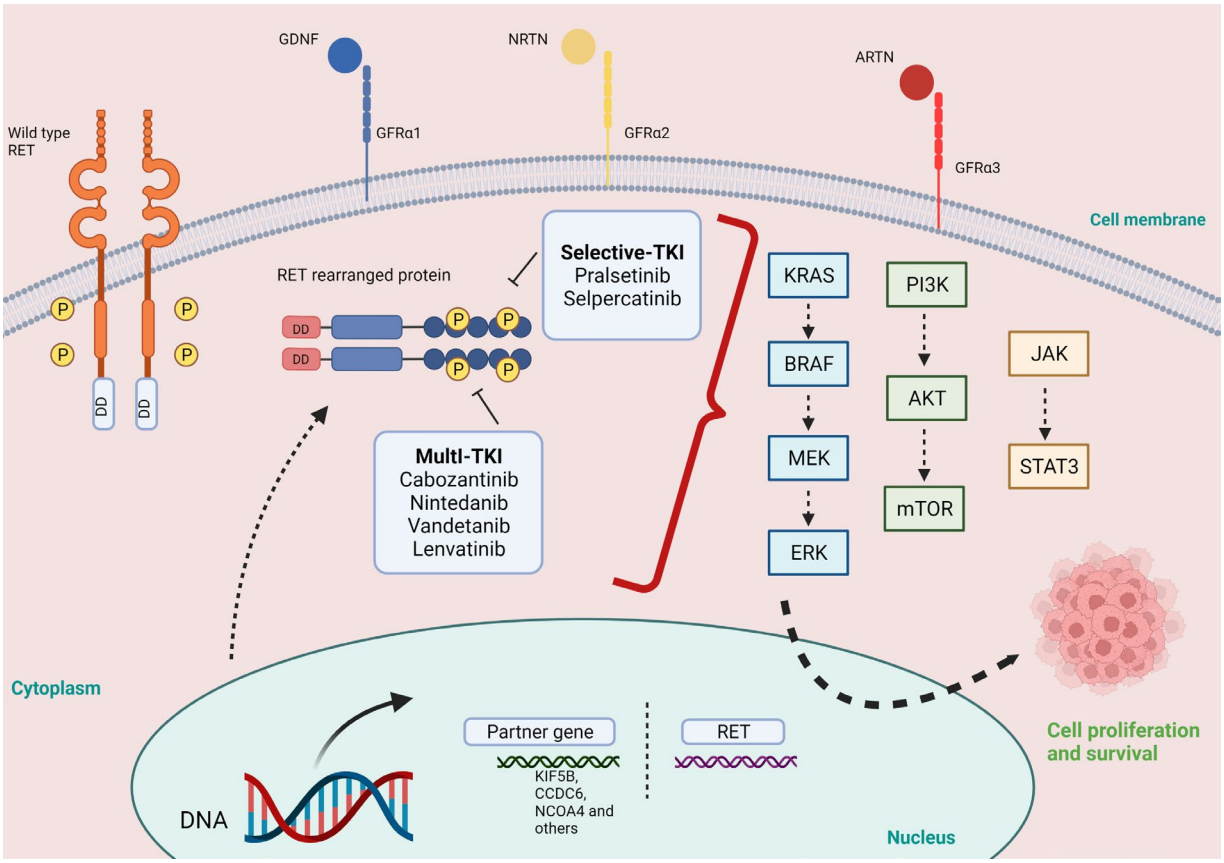
Introduction

The *RET* proto-oncogene encodes a transmembrane tyrosine kinase receptor that plays a central role in enteric and nervous system development and in renal morphogenesis.[1] In physiological conditions, RET protein consists of three domains, the extracellular domain, containing a ligand-binding site, the hydrophobic transmembrane domain and the intracellular domain with tyrosine kinase activity. RET activation requires the interaction among glial cell line-derived neurotrophic factor (GDNF) family ligands and GDNF family receptor-α proteins.[2] This complex binds RET extracellular domain, leading to auto-phosphorylation of the intracellular tyrosine kinase domain and, consequently, to activation of several downstream signalling pathways.[3,4] *RET* gain-of-function alterations can be found in multiple solid tumours, including thyroid carcinoma and non-small-cell lung cancer (NSCLC). Activating *RET* point mutations are typical of medullary thyroid cancer, whereas *RET* chromosomal rearrangements are found in NSCLC and in papillary thyroid carcinoma, resulting in overexpression and ligand-independent activation of RET protein and downstream pathways involved in proliferation and survival, including RAS–MAPK, PI3K–AKT, PKC and JAK–STAT[3–6] (Figure 1).

Methods

We searched PubMed for papers in English language containing the following terms, alone or in combination: "RET", "RET fusion", "RET rearrangement", "NSCLC", "adenocarcinoma", "oncogene-addicted", "pralsetinib", "selpercatinib", "cabozantinib", "vandetanib" AND "lenvatinib". Moreover, a literature search was conducted for clinical trials (either

Figure 1. RET molecular mechanism of activation and corresponding targeted therapies.



The RET proto-oncogene encodes a single-pass transmembrane tyrosine kinase normally activated by the interaction with a soluble neurotrophic factor (GDNF, NRTN or ARTN) and requires a co-receptor of the GDNF family receptor-α (GFRα). The complex formed by GDNF–NRTN–ARTN and GFRα binds *RET* extracellular domain determining heterodimerization and auto-phosphorylation of intracellular tyrosine kinase domains with consequent activation of downstream signalling pathways, including RAS–MAPK, PI3K–AKT, PKC and JAK–STAT. *RET* rearrangements are the result of the fusion between the *C*-terminal region of *RET* and the *N*-terminal region of partner genes as *KIF5B*, *CCDC6*, *NCOA4* and others. The resulting chimeric fusion protein lacks the extracellular portion, is constitutively active, and activates downstream signalling pathways with consequent aberrant cell proliferation. AKT, protein kinase B; ARTN, artemin; BRAF, V-Raf murine sarcoma viral oncogene homolog B; ERK, extracellular signal-regulated kinases; GDNF, glial cell line-derived neurotrophic factor; JAK, Janus kinase; KRAS, Kirsten rat sarcoma viral oncogene homolog; MEK, Mitogen-activated and extracellular signal regulated kinase; mTOR, mammalian target of rapamycin; NRTN, neurturin; PI3K, phosphatidylinositol-3-kinase; PKC, protein kinase C; STAT3, signal transducer and activator of transcription 3; TKI, tyrosine kinase inhibitor. Created with BioRender.com

published or ongoing) investigating the role of tyrosine kinase inhibitors (TKIs; i.e. non-selective and selective RET inhibitors), chemotherapy and immunotherapy in patients with *RET*-positive NSCLC. Information about ongoing studies was obtained from ClinicalTrials.gov (last accessed: 16/01/2022).

Review

Biology and clinicopathological features of *RET*-positive NSCLC

RET rearrangements occur in about 1–2% of patients with NSCLC, usually in young, light/never smokers, with adenocarcinoma histology, and are associated with a high rate of brain metastases at diagnosis.[7–10] Fusions between the *C*-terminal region of *RET*, encoding the intracellular kinase domain, with the *N*-terminal region of gene partners, leads to aberrant expression of chimeric fusion proteins with cytosol localization, resulting in ligand-independent constitutive activation of RET and of downstream signalling pathways, promoting cancer cell proliferation and survival.[11] To date, several fusion gene partners have been identified, the most common being *KIF5B*, accounting for 70–80% of cases, followed by *CCDC6*, whereas less common fusion partners are *NCOA4*, *TRIM33* and *CLIP1*.[12,13]

RET fusions in tumours can be demonstrated by means of fluorescence in situ hybridization (FISH) and next-generation

sequencing (NGS), whereas reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC) show low sensitivity and highly variable specificity and are therefore not a standard diagnostic tool.[12] However, FISH is associated with frequent false-positive results related to the detection of all *RET* rearrangements, including those that do not result in a functional oncogenic fusion.[14] Consequently, FISH is not an optimal method in the context of multiplex screening to detect patients who might benefit from RET-selective TKIs.[15] To date, considering the overall cost effectiveness and the ability to simultaneously detect several molecular alterations, NGS is considered the method of choice.[16,17] Specifically, DNA-based NGS has some limitations compared to RNA-based sequencing, such as the lack of coverage of introns, where genomic breakpoints producing fusion genes can occur, and the absence of information on the transcription level, potentially leading to false-negative results.[17] Furthermore, in patients with insufficient/inadequate tissue for genomic profiling, the use of liquid biopsies is a viable alternative to tissue genotyping.[15] Indeed, circulating cell-free DNA testing with NGS-based methods is able to detect *RET* genetic alterations with a high concordance with tissue testing, even though the sensitivity for fusions of NGS is lower in plasma than in tissue.[18]

At pathology, *RET*-positive tumours are more frequently poorly differentiated compared to *ALK*-positive or *EGFR*-mutated tumours and are associated with some subtypes of adenocarcinoma, that is, solid, papillary and lepidic pattern,[12,19] and with lymphangitic spread and psammoma bodies, suggesting that the combination of these two features should trigger suspicion for the potential presence of *RET* rearrangements.[20] Moreover, *RET*-rearranged tumours typically occur as small peripheral lesions (<3 cm) but with early lymph node involvement (N2 disease) and high incidence of pleural dissemination and brain metastases (up to 25% at diagnosis).[7,9]

Generally, *RET* rearrangements are mutually exclusive with other known oncogenic driver mutations, although some cases of co-occurrence with *EGFR* mutations and *MET* amplifications were described.[21–23] Furthermore, some case reports documented the presence of acquired *RET* fusion in patients with *EGFR*-mutant NSCLC who progressed on EGFR inhibitors, suggesting that *RET* fusions could be a potential mechanism of acquired resistance to this class of drugs.[24,25] In addition, *RET*-positive tumours are associated with a low expression of the thymidylate synthetase enzyme, which could explain the high sensitivity to pemetrexed-based chemotherapy of *RET*-positive NSCLC.[21,26] Finally, *RET* rearrangement was associated with a low tumour mutational burden, defined as the number of non-synonymous mutations per megabase of sequenced genome, as well as with low PD-L1 expression.[27]

Early-stage and locoregional disease

Because RET-positive NSCLC is a rare disease, there is no data about the treatment of early-stage and locoregional disease (stage IB–IIIA); thus, treatment guidelines follow the general recommendations for NSCLC.[28] After radical surgical resection, adjuvant chemotherapy with four cycles of platinum-based chemotherapy provides a 5-year survival benefit of 4–5% compared to observation or placebo in stage II–IIIA resectable tumours or when the primary tumour is larger than 4 cm, whilst observation is the preferred choice in earlier stage tumours.[29,30]

The role of TKIs in this setting has not yet been defined as data are limited and standard molecular testing is not routinely performed in clinical practice. However, several studies have been designed to evaluate the role of both EGFR-TKIs and ALK-TKIs in early-stage NSCLC. The phase III trial ADAURA showed that adjuvant osimertinib, a third-generation EGFR-TKI, was associated with significantly longer disease-free survival compared to placebo in patients with resected stage IB–IIIA *EGFR*-positive NSCLC, irrespective of chemotherapy administration, whilst overall survival (OS) data were still immature.[31,32]

Similarly, several ongoing clinical trials are currently evaluating the efficacy of RET-TKIs in early-stage *RET*-positive NSCLC (Table 1). The NAUTIKA1 is a multicentre, multi-arm, phase II study of neoadjuvant pralsetinib, a selective RET inhibitor, in patients with resectable stage II–III *RET*-positive NSCLC (NCT04302025). Patients with pathological response will be treated with adjuvant therapy, consisting of four cycles of chemotherapy followed by up to 2 years of pralsetinib. The LIBRETTO-432 is a double-blinded, randomized phase III study investigating the efficacy of selpercatinib (another selective RET inhibitor) compared to placebo in terms of event-free survival (i.e. time to recurrence, progression or death) in patients with stage IB–IIIA *RET*-positive NSCLC after definitive locoregional treatment (surgery or radiation therapy) (NCT04819100).

Advanced disease

In metastatic advanced *RET*-positive NSCLC, several multitarget TKIs (MKIs) with activity against RET, such as cabozantinib, vandetanib and lenvatinib, have been investigated. However, MKIs also have activity against other targets (e.g. VEGFR2, MET, KIT, EGFR), which contribute to their overall modest clinical benefit and their toxicity profile, mainly linked to off-target effects.[3] In contrast, selective RET inhibitors, such as pralsetinib and selpercatinib, selectively inhibit RET and are associated with high response rates and a manageable safety profile.

Non-selective RET inhibitors

Cabozantinib

Cabozantinib is an oral MKI inhibiting vascular endothelial growth factor 2 (VEGFR2), MET, ROS1, AXL, c-KIT, TIE2, FLT3 and RET.[33] Cabozantinib was the first MKI whose efficacy and safety were investigated in a prospective, single-arm, phase II trial enrolling 26 patients with *RET*-positive advanced NSCLC.[34] The primary endpoint of overall response rate (ORR) was met, with 7 partial responses among 25 response-assessable patients (ORR 28%, 95% CI 12–49), whereas median progression-free survival (mPFS) was 5.5 months (95% CI 3.8–8.4) and median

Table 1. Ongoing clinical trials in RET-positive NSCLC.

NCT	Phase	Drug	Setting	Population	Primary outcomes
NCT03780517	I	BOS172738	After standard	Advanced solid tumours	AEs MTD RP2D
NCT03157128 (LIBRETTO-001)	I–II	Selpercatinib	After standard or ineligible for standard	Advanced solid tumours	Phase I: MTD and RP2D Phase II: ORR
NCT03037385 (ARROW)	I–II	Pralsetinib	Any line	Advanced solid tumours	Phase I: MTD and RP2D Phase II: ORR
NCT04161391	I–II	TPX-0046	After standard or ineligible for standard	Advanced solid tumours	Phase I: DLT, MTD and RP2D Phase II: ORR
NCT04683250 (MARGARET)	I–II	TAS0953/HM0	After standard or ineligible for standard	Advanced *RET* fusion-positive NSCLC, with or without prior exposure to RET-selective TKI therapy	Phase I: MTD and RP2D Phase II: ORR
NCT04131543 (CRETA)	II	Cabozantinib	≥2nd line	Advanced, previously treated, *RET* fusion-positive NSCLC	ORR
NCT04302025 (NAUTIKA1)	II	Pralsetinib	Neoadjuvant and adjuvant	Resectable stage II–III *RET*-positive NSCLC	MPR
NCT01639508	II	Cabozantinib	Any line	Advanced *RET* fusion-positive NSCLC, with or without prior systemic therapy	ORR
NCT04268550 (LUNG-MAP Sub-Study)	II	Selpercatinib	≥2nd line or disease progression within 1 year from the last platinum-based chemotherapy (for recurrent disease)	Metastatic or recurrent, previously treated, *RET* fusion-positive NSCLC	ORR
NCT0419494 (LIBRETTO-431)	III	Selpercatinib *versus* platinum-pemetrexed with or without pembrolizumab	First-line	*RET* fusion-positive metastatic NSCLC without previous systemic therapy	PFS
NCT04819100 (LIBRETTO-432)	III	Selpercatinib *versus* placebo	Adjuvant	Stage IB–IIIA RET fusion-positive NSCLC after definitive locoregional treatment (surgery or radiation)	EFS
NCT04222972 (AcceleRET)	III	Pralsetinib *versus* platinum doublet alone or with pembrolizumab	First-line	*RET* fusion-positive metastatic NSCLC without previous systemic therapy	PFS

AEs, adverse events; DLT, dose-limiting toxicity; EFS, event-free survival; MTD, maximum tolerated dose; MPR, major pathologic response; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase II dose.

OS (mOS) was 9.9 months (8.1–not estimable [NE]). The dose of cabozantinib was 60 mg orally once a day, with cycles of 28 days. Among 26 patients, 19 (73%) required dose reductions and 2 (8%) discontinued the drug due to treatment-related adverse events (TRAEs), the most common being palmar-plantar erythrodysaesthesia, fatigue and diarrhoea. The most common grade 3 TRAEs were asymptomatic lipase elevation (15%), increased AST or ALT (8% each), thrombocytopenia (8%), and hypophosphataemia (8%). In addition, a retrospective study evaluated outcomes with MKIs among 165 patients with *RET*-positive NSCLC from the Global Multicenter RET Registry (GLORY), showing a limited clinical activity of cabozantinib (ORR 37%), vandetanib (ORR 18%), sunitinib (ORR 22%), lenvatinib (ORR 50%) and nintedanib (ORR 50%), regardless of *RET* fusion partners,[35] with an mPFS of 2.2–3.6 months and mOS of 4.9–10.2 months. Moreover, a separate analysis showed that outcomes among patients with *RET*-positive NSCLC and brain metastases were suboptimal with MKIs, despite the small sample size, as a confirmed intracranial response was observed in only 2 of 11 cases (18%).[9]

Vandetanib

Vandetanib is an oral MKI that selectively targets RET, VEGFR and EGFR.[36] A retrospective analysis of four randomized phase III trials evaluating the efficacy of vandetanib in advanced unselected NSCLC as monotherapy or in combination with chemotherapy (i.e. docetaxel or pemetrexed) showed that, among seven patients with *RET*-positive NSCLC, three received vandetanib and no objective response was observed.[37] Moreover, among 11 patients with *RET*-rearranged NSCLC in the GLORY registry, the ORR to vandetanib was 18%.[35] The multicentre, phase II trial LURET evaluated efficacy and safety of vandetanib in patients with advanced, previously treated, *RET*-positive NSCLC.[38] Among 17 eligible patients, ORR was 53% (95% CI 28–77%), mPFS was 4.7 months (95% CI 2.8–8.5) and mOS was 11.1 months (95% CI 9.4–not reached). The most common TRAEs of grade ≥3 were hypertension (58%), rash (16%), diarrhoea (11%), QT prolongation (11%) and dry skin (5%). Another phase II trial investigated the efficacy of vandetanib in patients with *RET*-positive NSCLC previously treated with platinum-based chemotherapy.[39] Among 17 evaluable patients, ORR was 18% and the disease control rate was 65%, whereas mPFS was 4.5 months and mOS was 11.6 months. Grade 3 TRAEs included hypertension (17%), QT prolongation (11%) and increased transaminases (6%).

Lenvatinib

Lenvatinib is an oral MKI with activity against VEGFR1–3, fibroblast growth factor receptor 1–4 (FGFR1–4), platelet-derived growth factor receptor-α (PDGFRα), c-KIT and RET.[40] A phase II, multicentre trial investigated the activity and safety of lenvatinib among 25 patients with *RET* fusion-positive NSCLC, of whom 23 (92%) received previous treatment.[41] The ORR was 16% (95% CI 4.5–36.1%), the mPFS was 7.3 months (95% CI 3.6–10.2) and the mOS was not reached. Interestingly, mPFS was longer among patients with *KIF5B–RET* fusions compared to those with *CCDC6–RET* fusions (9.1 months *versus* 3.6 months, respectively). The most common reported TRAEs of grade ≥3 were hypertension (56%), hyponatraemia (20%), proteinuria (16%) and pneumonia (16%).

Altogether, these data suggest that mPFS and mOS, as well as ORR, are unsatisfactory on RET MKIs, especially if compared to outcomes on the respective MKIs in *ALK*-positive and *ROS1*-positive NSCLC, suggesting the need for novel selective RET TKIs.

Selective RET inhibitors

In order to overcome MKI toxicities and improve outcomes in patients with RET-positive NSCLC, potent and selective RET inhibitors have been developed.[42] To date, selpercatinib and pralsetinib received FDA approval for the treatment of advanced RET-positive NSCLC.

Selpercatinib

Selpercatinib (LOXO-292) is an oral, ATP-competitive, TKI with potent activity against several RET alterations, including fusions and point mutations, of interest in NSCLC.[42] Furthermore, selpercatinib is active against secondary gatekeeper resistance mutations (e.g. RET^{V804M} gatekeeper mutation, associated with acquired resistance to Vandetanib) and crosses the blood–brain barrier.[43] The safety and efficacy of selpercatinib are currently being investigated in the phase I–II LIBRETTO-001 in *RET*-positive NSCLC, both in patients progressing to platinum-based chemotherapy, and in treatment-naive patients (NCT03157128). Among the first 105 previously treated patients, the ORR was 64% (95% CI 54–73%), with a median duration of response (DOR) of 17.5 months (95% CI 12–NE), irrespective of RET fusion partner.[44] The mPFS was 16.5 months (95% CI 13.7–NE), with 66% of patients alive and progression-free at 1 year. Among 11 patients with brain metastases, the objective intracranial response was 91% (95% CI 59–100%), with a DOR of 10.1 months (95% CI 6.7–NE), showing remarkable intracranial activity. In the cohort of 39 untreated patients, the ORR was 85% (95% CI 70–94%), whereas median DOR and mPFS were not reached at a median follow-up of 7.4 and 9.2 months, respectively. The safety profile of selpercatinib was manageable, with the most common TRAEs of grade ≥3 being hypertension (14%), increased levels of transaminases (12% for ALT, 10% for AST), hyponatraemia and lymphopenia (6%, both), leading to treatment discontinuation in only 2% of patients (12/531).

Based on these results, the FDA granted an accelerated approval to selpercatinib (at a dose of 120 mg for patients <50 kg and 160 mg for those ≥50 kg or greater, twice daily with 28-day cycles) for the treatment of patients with advanced *RET*-positive NSCLC, regardless of previous treatment. Recently, the European Medicines Agency (EMA) approved selpercatinib for the treatment of advanced *RET*-positive NSCLC, only after previous treatment with platinum-based chemotherapy and/or immunotherapy.

Pralsetinib

Pralsetinib (BLU-667) is another TKI that selectively and potently inhibits RET and is active against both common *RET* oncogenic alterations (e.g. *KIF5B–RET* and *CCDC6–RET* fusions) and known gatekeeper mutations associated with resistance to MKI treatment.[45] The safety and activity of pralsetinib are currently being investigated in patients with *RET*-positive NSCLC, either as first-line or in subsequent lines of treatment, in the multicentre phase I–II ARROW trial (NCT03037385). Preliminary results from this study showed that ORR was 61% (95% CI 50–71%) among 87 patients previously treated with platinum-based chemotherapy, including 6% (5/87) with complete responses (CR), whereas the ORR was 70% (95% CI 50–86%) among 27 treatment-naive patients not candidates for standard therapies, including 11% (3/27) with a CR.[46] Median DOR was not reached (95% CI 15.2–NE) in pretreated patients and was 9.0 months (95% CI 6.3–NE) in untreated patients, whereas mPFS was 17.1 months and 9.1 months, respectively. At a median follow-up of 17.1 months and 13.6 months in previously treated and treatment-naive patients, respectively, mOS was not reached. In addition, pralsetinib demonstrated to have intracranial activity, with an intracranial ORR of 56% (95% CI 21–86), including 3 CRs. Overall, the safety profile of pralsetinib was manageable at a dose of 400 mg once daily, with the most common TRAEs of grade ≥3 being neutropenia (18%), hypertension (11%) and anaemia (10%), with only 6% of patients discontinuing the drug due to TRAEs.

Based on these data, the FDA has granted treatment line-agnostic approval of pralsetinib (at a dose of 400 mg once daily) for the treatment of patients with advanced *RET*-positive NSCLC. Recently, EMA approved pralsetinib for both patients previously treated and treatment-naive with *RET*-positive NSCLC.

The available evidence suggests that a selective RET-TKI, either selpercatinib or pralsetinib, is the preferred treatment choice in patients with advanced *RET*-positive NSCLC, regardless of the line of therapy.

Resistance to selective RET inhibitors

Despite the high initial response rates to selective RET inhibitors, most patients inevitably develop disease progression related to acquired resistance mechanisms, similarly to what is observed in other TKIs administered in oncogene-addicted NSCLC[25,47,48] (Figure 2). The first reported mechanism of resistance to selpercatinib was *RET* G810 solvent front mutation, which decreases the activity of both selective and multi-kinase RET inhibitors by preventing drug binding (on-target mechanism).[49] A retrospective multi-institutional study analysed a total of 23 tissue and/or liquid biopsies from a cohort of 18 patients with advanced *RET*-positive NSCLC treated with pralsetinib or selpercatinib.[50] The analysis identified two cases (10%) of acquired *RET* mutations, both affecting the kinase RET G810 residue exposed to solvent, whereas three cases (15%) harboured *MET* amplification and one *KRAS* amplification as *RET*-independent mechanisms of resistance (or off-target). Another study identified *MET* amplification in post-treatment biopsies from four patients with *RET*-rearranged NSCLC treated with selpercatinib.[51] In this study, the combination of selpercatinib and crizotinib (an *MET/ALK/ROS1* inhibitor) was associated with some clinical activity, with one response lasting 10 months and a manageable safety profile, suggesting that *MET* amplification may result in resistance to RET-TKIs, which could be overcome by the combined inhibition of *RET* and *MET*.

A phase I trial investigated the safety and activity of BOS172738, a next-generation, potent and selective RET-TKI, in patients with *RET*-fusion positive advanced solid tumours.[52] Among 67 enrolled patients, BOS172738 showed a favourable safety profile, with the most common treatment-emergent AEs being creatine phosphokinase elevation (54%), dyspnoea (34%), facial oedema (25%), increased AST (25%), anaemia (25%), neutropenia (22%), diarrhoea (22%), fatigue (21%) and constipation (20%). The ORR in patients with NSCLC was 33% (10/30).

The ongoing phase I–II, first-in-human, SWORD-1 trial is currently investigating the safety and activity of TPX-0046, a new potent RET inhibitor with preclinical activity against *RET* solvent-front mutations, in patients with *RET*-positive solid tumours after progression to previous treatments (NCT04161391).[53] Preliminary results among 21 enrolled patients (10 with NSCLC and 11 with medullary thyroid carcinoma) were encouraging, with tumour regressions observed in 4 of 5 RET-TKI-naive patients and 3 of 9 TKI-pretreated patients.[54]

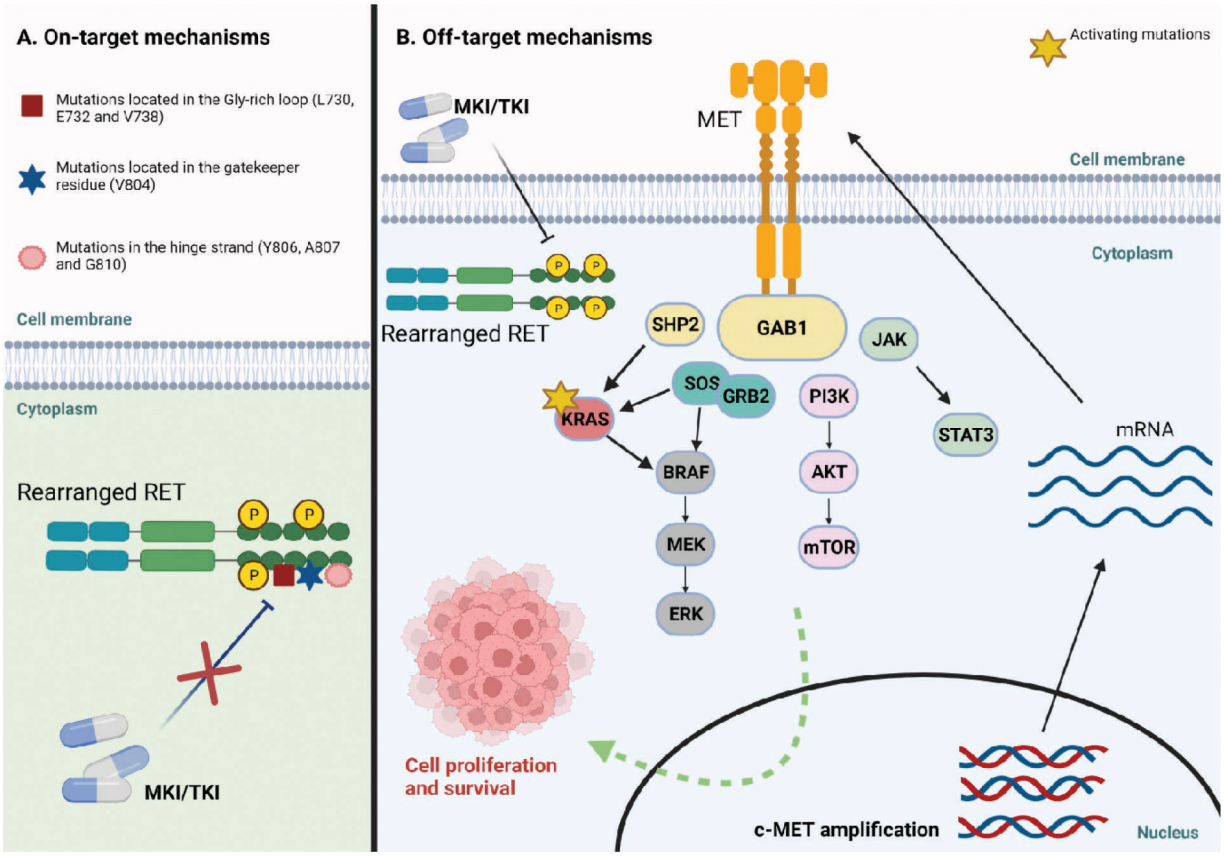
In patients whose disease progresses on a RET inhibitor (either MKI or selective TKI), repeat biopsy for genetic profiling could help identify resistance mechanisms to RET inhibitors and guide subsequent treatment strategy or address patients to clinical trials.

Chemotherapy

For decades, first-line treatment with platinum-based doublet chemotherapy represented the standard of care in advanced NSCLC, with the platinum-pemetrexed combination recently identified as the preferred choice for adenocarcinoma histology, which usually includes *RET*-positive tumours.[55]

The analysis of a cohort of 65 evaluable patients with *RET*-rearranged NSCLC treated with platinum-based chemotherapy as first-line therapy from the GLORY study showed an ORR of 51% (95% CI 38–63), with an mPFS of 7.8 months (95% CI 5.3–10.2) and an mOS of 24.8 months (95% CI 13.6–32.3).[35] Specifically, 79% of patients received a platinum-pemetrexed combination, with an ORR of 49% (95% CI 35–63), an mPFS of 6.4 months (95% CI 4.3–8.8) and an mOS of 23.6 months (95% CI 13.4–33.2). Another retrospective study of *RET*-rearranged NSCLC treated with pemetrexed-based chemotherapy showed an ORR of 45% and an mPFS of 19 months (95% CI 12–NR) among 11 evaluable patients, similar to outcomes reported in *ALK*-rearranged and *ROS1*-rearranged lung cancers and significantly better compared to *KRAS*-mutant lung cancer.

Figure 2. Resistance mechanisms to RET-TKIs.



A. On-target mechanisms. Missense mutations can occur in the RET kinase domain conferring resistance to multi-kinase inhibitors (MKI) or tyrosine kinase inhibitors (TKIs). Most of these mutations are located in the Gly-rich loop (L730, E732 and V738), the gatekeeper residue (V804) or the hinge strand (Y806, A807 and G810). In some cases, mutations determine pan-resistance to MKI/TKIs preventing drug binding whereas, in other cases, *RET* kinase domain mutations (L730V, E732K, A807V, G810A, V871I, M918T, F998V) cause selective resistance to one or more drugs.
B. Off-target mechanisms. *MET* and *KRAS* amplifications determine resistance to RET by activating downstream signal translation pathways, which stimulate cell proliferation and survival, regardless of MKI/TKIs binding to RET kinase domain.
GAB1: Growth factor receptor binding protein 2-associated binding protein 1; SHP2: Src homology-2 domain containing protein tyrosine phosphatase-2; KRAS: Kirsten rat sarcoma viral oncogene homolog; SOS: son of sevenless guanine nucleotide exchange factor; GRB2: growth factor receptor-bound protein 2; BRAF: V-Raf murine sarcoma viral oncogene homolog B; MEK: mitogen-activated and extracellular signal-regulated kinase; ERK: extracellular signal-regulated kinases; PI3K: phosphatidylinositol-3-kinase; AKT: protein kinase B; mTOR: mammalian target of rapamycin; JAK: Janus kinase; STAT3: signal transducer and activator of transcription 3. Created with BioRender.com

This study demonstrated that *RET*-positive NSCLCs are sensitive to pemetrexed-based chemotherapy, which could be explained with the decreased levels of thymidylate synthase mRNA associated with *RET* rearrangement, thus making platinum-pemetrexed the preferred chemotherapy regimen in these patients.[21] Another retrospective analysis of 104 patients with advanced adenocarcinoma with *RET*, *ROS1* or *ALK* rearrangement, or *KRAS* mutations, treated with pemetrexed-based chemotherapy, confirmed the significant clinical activity of this drug among *RET*-rearranged NSCLC, with outcomes comparable to those of *ALK*-rearranged and *ROS1*-rearranged tumours.[26]

Immune-checkpoint inhibitor-containing strategies

RET-rearranged NSCLC generally showed limited response to immune-checkpoint inhibitors (ICIs), similar to what is reported in *EGFR*-mutant and *ALK*-rearranged NSCLC.[56–59] A retrospective study investigating the role of ICIs among 74 patients with *RET*-rearranged NSCLC showed poor outcomes with no response observed among 13 evaluable patients and an mPFS of 3.4 months (95% CI 2.1–5.6).[27] Consistent with these results, the immunophenotype of *RET*-positive tumours was characterized by low PD-L1 expression and a low tumour mutational burden, suggesting that these tumours are immunologically 'cold'. The IMMUNOTARGET was a retrospective study evaluating

outcomes with ICIs in patients with advanced oncogene-addicted NSCLC.[60] Among 16 *RET*-rearranged patients treated with single-agent ICIs, the ORR was 6% and the mPFS 2.1 months (95% CI 1.3–4.7). Another small retrospective study compared the time to treatment discontinuation of ICI compared to non-ICI therapy in *RET*-positive NSCLC patients.[61] Among 29 evaluable patients, non-ICI therapy was associated with a non-statistically significant longer time to treatment discontinuation compared to ICI therapy (9.3 *versus* 3.4 months, respectively). However, in the phase III trial Keynote-189, showing that chemoimmunotherapy was associated with survival improvement compared to standard chemotherapy in untreated metastatic NSCLC, patients with *RET*-positive tumours were not excluded unlike patients with *EGFR* mutations or *ALK* rearrangements.[62] Similarly, the phase III IMpower 150 and CheckMate 9LA trials of combination of ICIs with chemotherapy among untreated patients with non-squamous NSCLC did not exclude patients with *RET*-positive NSCLC and showed a significant PFS and OS improvement as compared to chemotherapy alone.[63,64]

Consequently, patients with *RET*-positive NSCLC are eligible for first-line treatment with platinum-pemetrexed plus ICIs despite no definitive proof of efficacy being available to date in this rare population (Figure 3).

Based on these data, the use of ICIs as monotherapy for the treatment of *RET*-fusion positive NSCLC should be considered only in subsequent lines of treatment after the administration of selective TKIs and platinum-doublet chemotherapy.

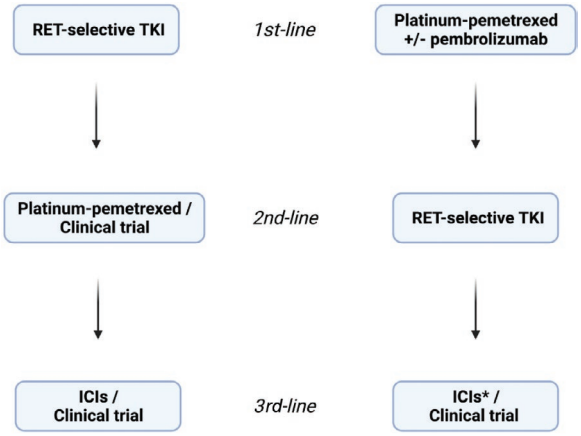
Future perspectives

Considering the remarkable results achieved with effective RET inhibition and the consequent resistance to RET-selective inhibitors, the development of next-generation RET-TKIs is of paramount importance and is currently the aim of several ongoing clinical trials in patients with advanced NSCLC harbouring *RET* fusions (NCT04161391, NCT03780517). Among these new agents, TPX-0046 is active against a range of *RET* fusions and mutations, including solvent front mutations, and demonstrated promising antitumour efficacy in patient-derived xenograft tumour models.[48]

Next-generation RET-TKIs should not only target resistance mutations but also improve clinical activity and blood–brain barrier crossing. Furthermore, the combination of RET inhibitors with other targeted agents (e.g. MET inhibitors) could represent a useful therapeutic strategy to overcome off-target resistance.

In addition, the randomized phase III trial LIBRETTO-431 is currently evaluating selpercatinib compared to platinum-pemetrexed with or without pembrolizumab in treatment-naive patients with locally advanced or metastatic *RET*-positive non-squamous NSCLC (NCT04194944).[59] Finally, the phase III trial AcceleRET Lung of pralsetinib compared to standard-of-care therapy as first-line treatment in *RET*-positive NSCLC is currently ongoing (NCT04222972). The primary endpoint for both trials is PFS. The results of these studies will help further shape the therapeutic algorithm of these patients.

Figure 3. Proposed therapeutic algorithms for *RET*-positive advanced NSCLC.



*If not previously administered.
RET-selective TKI: pralsetinib *or* selpercatinib.
ICIs: nivolumab or atezolizumab (regardless of PD-L1), or pembrolizumab (if PD-L1 ≥1%).
ICIs, immune-checkpoint inhibitors; TKI, tyrosine kinase inhibitor.

Conclusions

RET fusion is an established therapeutic target in advanced NSCLC and testing for *RET* alterations should be included in the standard molecular profiling at diagnosis in patients with metastatic non-squamous NSCLC. To date, the administration of selective RET-TKIs, such as pralsetinib and selpercatinib, is the preferred treatment option in patients with NSCLC harbouring *RET* rearrangements. Two phase III trials are currently comparing selpercatinib (LIBRETTO-431) and pralsetinib (AcceleRET) to platinum-based therapy with or without immunotherapy as first-line treatment in *RET*-positive NSCLC to define the best first-line treatment in these patients.[65] Treatment management after first line should include platinum-pemetrexed chemotherapy in patients treated with RET-TKIs and a selective RET-TKI in patients previously treated with chemotherapy or chemoimmunotherapy, as shown in the proposed treatment algorithm in Figure 3. Considering the limited activity of immunotherapy, the use of ICIs should be reserved to later lines.

New insights about the acquisition of resistance through both on-target and off-target mechanisms highlight the importance of bringing new potent and selective next-generation RET-TKIs to the clinic. In this scenario, genomic recharacterization at progression could help guide treatment choice or enrolment in clinical trials of specific next-generation RET inhibitors. In early-stage NSCLC harbouring *RET* fusions, the role of RET-TKIs is under investigation by several studies but these are not currently recommended outside of clinical trials.

Contributions: Conceptualization: GL, EA and GM; Writing – original draft preparation: EA and MM; figures and tables: EA, LG and MM; Writing – review and editing: GL, EA, FS, BR and GM. All authors have read and agreed to the published version of the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2022/06/dic.2022-1-5-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/non-small-cell-lung-cancer-how-to-manage-ret-positive-disease

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Provenance: Invited; externally peer reviewed.

Submitted: 31 January 2022; **Accepted:** 3 June 2022; **Publication date:** 11 July 2022.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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