Regulatory Approvals of RET Inhibitors for NSCLC and Thyroid Cancer

ESMO Updates the Guidelines for the Diagnosis of *RET*-Altered Cancer to Herald a New Era in Targeted Therapy

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The *RET* gene encodes a tyrosine kinase receptor that regulates cell survival and proliferation by triggering key downstream pathways.¹ *RET* gene mutations and *RET* gene fusions are involved in the pathogenesis of lung, thyroid and other cancers. Recently, in 2021, the European Society for Medical Oncology (ESMO) has developed recommendations for the laboratory diagnosis of targetable *RET* rearrangements and mutations.² Following the results from phase I/II clinical trials^{3,4}, selpercatinib, a *RET* tyrosine kinase inhibitor (TKI), received the FDA⁵ and Swissmedic⁶ authorization for the treatment of adult patients with *RET* fusion-positive non-small cell lung cancer (NSCLC) and advanced *RET* fusion-positive thyroid cancer who require systemic therapy and who have progressed after prior treatment. Selpercatinib is also indicated for the treatment of adults and adolescents ≥ 12 years old with advanced *RET*-mutated medullary thyroid carcinoma (MTC) who require systemic therapy and who have experienced progression after prior treatment with TKIs. In this clinical setting, the Food and Drug Administration (FDA) has recently approved another *RET* TKI, pralsetinib.⁷ In addition, the FDA also granted accelerated approval to pralsetinib for adult patients with metastatic *RET* fusion-positive NSCLC.⁸ This review aims to summarize the new ESMO recommendations for the laboratory diagnosis of *RET*-altered cancers and the clinical trial data that support the regulatory approvals of selpercatinib and pralsetinib for *RET*-altered NSCLC and thyroid cancer.

Keywords: *RET* inhibitors, selpercatinib, pralsetinib, NSCLC, thyroid cancer

RET-altered cancers with *RET* gene mutations and gene fusions

The proto-oncogene rearranged during transfection (*RET*) gene is located on the long arm of chromosome 10 and encodes a transmembrane glycoprotein receptor with tyrosine kinase activity.¹ Activation of the *RET* receptor occurs via autophosphorylation of intracellular tyrosine residues. *RET* receptor activation triggers several downstream pathways that include PI3K-AKT, RAS-MAPK, JAK-STAT, PKC, and PLC γ , which have key roles

in cell survival and proliferation (**Figure 1**). *RET* gene alterations have been identified in many solid tumors and include *RET* gene mutations and *RET* gene fusions, termed *RET*-altered cancers.^{1,2} *RET* point mutations are associated with medullary thyroid cancer (MTC), whereas *RET* fusions are found in 10% of papillary thyroid carcinoma and 1–2% of lung adenocarcinoma (**Figure 2**).⁹

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Table 1. The European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group recent recommendations for currently available techniques for routine clinical laboratory detection of targetable RET rearrangements and mutations, with their strengths and limitations.

^aFalse-positive up to 40%. ^bFalse-negative up to 40%. ^cRequires the use of specific fusion partner probe. ^dUse in settings with several possible fusion partners, there is risk of lower sensitivity. ^eDoes not allow the detection of novel fusion partners. ^fFalse-positive: detected rearrangements by DNA-based assays may not result in fusions, and correlation with RNA-based confirmation of predicted fusion transcript is required. ^gFalse-negative: some introns involved in RET rearrangements may be inadequately evaluated, for technical reasons. ^hIndication on the in-frame nature of the fusion (functionality). DNA-seq NGS, DNA sequencing by next-generation sequencing; FISH, fluorescent *in situ* hybridization; IHC, immunohistochemistry; RNA-seq NGS, RNA sequencing by next-generation sequencing; RT-PCR, reverse transcription-polymerase chain reaction. Adapted from Belli et al. 2021.²

Method	Sensitivity	Specificity	Detection of partner	Detection of expression	Use in screening
IHC	moderate ^a	moderate ^b	no	yes	no
FISH	high	high	no/yes ^c	no	rarely
RT-PCR	moderate/high ^d	high	yes/no ^e	yes	rarely
DNA-seq NGS	moderate ^f	high/moderate ^g	yes	no	yes
RNA-seq NGS	high	high	yes	yes ^h	yes

Figure 1. Outline of RET signaling pathways. Adapted from Prazeres et al. 2011.²¹

The most common somatic mutation in sporadic MTC is M918T, which is present in up to 40% of MTC patients and is associated with disease aggressiveness.¹⁰ Other single amino acid changes might occur at residues C611, C618, C620, C630, C634, E768, A883 and S891.

The 2021 ESMO guidelines for the diagnosis of RET-altered cancer

Accurate detection of *RET* gene fusions and mutations is the basis for targeted therapy with the new *RET* inhibitors and essentials to ensure personalized medicine. Similar to regulatory approval for drug treatment, diagnostics require regulatory evaluation and authorization. The ESMO Translational Research and Precision Medicine Working Group has recently issued recommendations for the routine clinical detection of targetable *RET* rearrangements and mutations (Table 1).² The main methods were immunohistochemistry (IHC), fluorescent *in situ* hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR), DNA sequencing by next-generation sequencing (DNA-seq NGS), and RNA sequencing by next-generation sequencing (RNA-seq NGS). The ESMO guidelines highlight that IHC alone is not suitable as a routine diagnostic screening tool to identify *RET* alterations due to lack of sensitivity and specificity and lack of standardization of laboratory methods. Recently, in 2021, ESMO has developed recommendations for *RET* testing of malignant tumors to identify patients eligible for anti-*RET* therapy (Table 1).

The rationale for selective RET inhibitors as targeted therapy in NSCLC and thyroid carcinoma

An early approach to targeting therapy in *RET*-altered solid cancer was made with multikinase inhibitors (MKIs) with anti-*RET* activities.² However, the limitations of using MKIs include low target specificity and high frequency of side effects due to off-target toxicities. In 2012, vandetanib, a small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR) and *RET* tyrosine kinases, was approved by Swissmedic for the treatment of patients with unresectable, rapidly progressive and symptomatic MTC.¹¹ This approval was based on the results from a phase III study, which demonstrated that vandetanib versus placebo was associated with significantly prolonged PFS and improved response rates in patients with MTC.¹² Unlike selective *RET* inhibitors however, vandetanib only shows moderate efficacy in the treatment of NSCLC harboring *RET* rearrangement.¹³

New highly selective *RET* inhibitors have recently been approved based on evidence of safety and efficacy from randomized clinical trials (RCTs).^{3–5,8,14} The importance of accurate and widely available diagnostics has been highlighted by the regulatory approvals of selpercatinib (Swissmedic and FDA) and pralsetinib (FDA only), two selective *RET* inhibitors, following the results of phase I/II RCTs.

In Switzerland, despite federal authorization of selpercatinib for the treatment of *RET* fusion-positive NSCLC, reimbursement has to be requested at the insurance company through article 71b of the Health Insurance Ordinance (KVV/OAMal). For pralsetinib, which is currently not approved in Switzerland for treatment of *RET* fusion-positive NSCLC, reimbursement can be requested through article 71c. For patients with thyroid cancer, vandetanib is an alternative therapy reimbursed through insurance.

Selpercatinib for the treatment of RET fusion-positive NSCLC and thyroid cancer, and RET mutation-positive MTC

Selpercatinib (LOXO-292) is an orally bioavailable, selective inhibitor of wildtype, mutant, and fusion products of *RET*.⁵ Regulatory approval of selpercatinib was based on the results from the open-label, phase I/II LIBRETTO-001 trial in patients with advanced solid tumors, *RET* fusion-positive solid tumors, and MTC.^{3,4,6,15}

LIBRETTO-001 included 105 patients with *RET* fusion-positive NSCLC who were pretreated with platinum chemotherapy.³ All study participants had confirmed *RET* fusion status using either RT-PCR, NGS, or FISH. In phase I portion of the study, patients were treated with oral selpercatinib at 20 mg once daily to 240 mg twice daily (n=49). In the phase II study, patients received 160 mg of selpercatinib twice daily (n=56). The results showed an overall response rate (ORR) of 64% (95% CI: 54–73%), regardless of previous MKI or immune checkpoint inhibitor (ICI) therapy (Figure 3). The median duration of response (DoR) was

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17.5 months (95% CI: 12 months–not estimable [NE]). In 39 treatment-naïve patients, the ORR was 85% (95% CI: 70–94%), and the median DoR was not achieved. This trial included 11 pretreated *RET* fusion-positive patients with cerebral metastases diagnosed at study entry.⁸ A disease response occurred in 91% (10/11) of patients, including 3 complete responses (27%). These data provide evidence that selpercatinib could cross the blood-brain barrier to reach the central nervous system (CNS).

Somatic *RET* mutations occur in more than 65% of sporadic MTCs and up to 90% of advanced MTC.¹⁶ The LIBRETTO-001 trial included 55 patients with *RET* mutation-positive MTC who were previously treated with vandetanib, cabozantinib, or both.⁴ The objective response rate (ORR) was 69% (95% CI: 55–81%), and the 1-year progression-free survival (PFS) was 82% (95% CI: 69–90%). The study also included 88 treatment-naïve patients with *RET*-mutant MTC. Among them, the ORR was 73% (95% CI: 62–82%), and the 1-year PFS was 92% (95% CI: 82–97%). There were also 19 patients with previously treated *RET* fusion-positive thyroid cancer, with a response rate of 79% (95% CI: 54–94%) and

a 1-year PFS rate of 64% (95% CI: 37–82%). The most common adverse events (AEs) of grade 3 or more were hypertension (21%), increased serum levels of alanine aminotransferase (ALT) (11%), increased serum aspartate aminotransferase (AST) (9%), hyponatremia (8%), and diarrhea (6%).

In a post hoc analysis of LIBRETTO-001, selpercatinib demonstrated a favorable safety profile, with low-grade treatment-emergent adverse effects (TEAEs) and early-onset toxicities that were clinically manageable, resulting in low rates of discontinuation of treatment.¹⁷ In this study, the safety population consisted of 702 patients who received at least one dose of selpercatinib, with a follow-up until the cutoff date. The majority of TEAEs were low grade and included dry mouth (38.9%), diarrhea (36.6%) and hypertension (35.9%). Grade 3–4 TEAEs occurred in 59.1% of patients and included hypertension (17.1%), increased serum levels of AST (7.4%) and ALT (9.1%), and QTc prolongation (4.0%), which were manageable with dose adjustments. TEAEs that resulted in dose reduction or drug interruption were dry mouth, diarrhea and hypertension.

Figure 2. *RET* alterations by mutation type in non-small cell lung cancer (NSCLC), papillary thyroid cancer (PTC) and medullary thyroid cancer (MTC). ECD, extracellular domain; KD, kinase domain. Adapted from Iams et al. 2018.⁹

Figure 3. Efficacy data for NSCLC: waterfall plots of the maximum change in tumor size in all target lesions, according to investigator assessment. Adapted from Drilon et al. 2020.³

Figure 4. Clinical response to pralsetinib in patients with prior cabozantinib and/or vandetanib treatment. ^aBlinded independent central review of tumor response at data cutoff. Six patients without measurable disease at baseline on central review and 2 patients without a post-baseline tumor response assessment were not response evaluable. ^b1 PR pending confirmation. C/V, cabozantinib and/or vandetanib; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Hu et al. 2020.¹⁹

The median time to the first onset of TEAEs was within 10 weeks of starting treatment, with the earliest median time to onset for hypersensitivity being 1.7 weeks compared with the latest onset for a rash at 9.3 weeks.¹⁷ When stratified by the treatment duration (<12 months [n=466] vs ≥12 months [n=236]), more patients who received treatment for at least 12 months required dose adjustments due to TEAEs. More specifically, among patients who received selpercatinib <12 months versus ≥12 months, 29.6% and 34.3%, respectively, required dose reduction, 39.5% and 46.6%, respectively, required dose interruptions, and 6.9% and 2.1%, respectively, required treatment discontinuation. To ensure manageability of the adverse effects, patients should be carefully monitored, and the dose should be adjusted promptly.

Pralsetinib for *RET*-altered solid tumors including medullary thyroid cancer

The current standard of care for treating *RET*-altered MTC, such as cabozantinib and vandetanib, requires complex dosing regimens and is associated with AEs leading to treatment discontinuation. Pralsetinib (BLU-667) is an orally bioavailable selective inhibitor of wild-type *RET* and oncogenic *RET* alterations.⁸ Following the FDA approval of pralsetinib in December 2020, regulatory approval is being sought from the European Commission, with an application to the European Medicines Agency (EMA) and applications for global authorization in the second half of 2021. Preliminary findings from the ongoing phase I/II ARROW study

of pralsetinib in patients with thyroid cancer, NSCLC, and other advanced solid tumors have been reported.^{18,19}

ARROW is an international, multicenter trial conducted across 84 sites in 11 countries.^{18,19} In this study, eligible patients were those with advanced solid tumors, *RET*-altered disease per local testing, no other driver mutations, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1, and those who previously received standard therapy or who were not candidates for standard therapy.¹⁹ All patients received pralsetinib (400 mg daily) until disease progression or unacceptable toxicity. Four cohorts were included of 67 patients with *RET*-mutant MTC with prior cabozantinib and/or vandetanib, 42 patients with treatment-naïve *RET*-mutant MTC, 10 patients with *RET*-mutant MTC who had received previous systemic therapy other than cabozantinib and vandetanib, and 319 patients with other *RET*-altered tumors. The key study endpoints were ORR, DoR, and safety.

At baseline, in the *RET*-mutant MTC population (n=92), the median age was 59 years (range, 19–83 years) and 68% of the study population was male.¹⁹ About 99% of patients had an ECOG PS of 0 or 1 and 10% of patients had a history of CNS/brain metastases. Regarding *RET* genotype, 61% of patients had *RET* M918T-mutant tumors, 29% had a cysteine-rich domain, 3% had mutations in *RET* V804M/L, and the remaining 7% of patients had other *RET* alterations. Baseline demographics were comparable between the previously treated and treatment-naïve populations.

At data cutoff, a high response rate to pralsetinib was observed among 53 previously treated patients.¹⁹ The ORR was 60% (95% CI: 46–74%), with a CR rate of 2% and a PR rate of 58% (**Figure 4**). There were 36% of patients with stable disease and 4% with progressive disease, resulting in a disease control rate (DCR) of 96% (95% CI: 87–100%). Both, the median DoR and the median PFS were not reached. Overall, 75% of patients remained on treatment at the time of data cutoff, and 94% of patients with a response continued to receive pralsetinib. In the treatment-naïve cohort (n=42), the ORR was 74%, and the DCR was 100%. Again, both, the median DoR and the median PFS were not reached.

Safety data from ARROW showed that pralsetinib was well-tolerated, with a median dose intensity of 92% (range, 18–100%).¹⁹ The majority of treatment-related AEs were mild and reversible and most commonly included an increase in serum levels of AST (34%) and ALT (23%), anemia (24%), constipation (23%), and hypertension (22%). The most frequent grade 3–4 treatment-related AEs were hypertension (11%), neutropenia (10%), anemia (8%) and a decreased neutrophil count (6%). Only 4% of patients discontinued pralsetinib due to treatment-related AEs.

Conflict of interest

A. A. reported receiving personal fees for attending advisory from Bristol-Myers Squibb, AstraZeneca, Roche, Pfizer, Merck Sharp and Dohme, Astellas, Eli Lilly and Boehringer-Ingelheim. He has received fees for speaking bureau for Eli Lilly, AstraZeneca, MSD for work performed outside of the current study. F. S. reported the receipt of personal fees for attending advisory boards from Bristol-Myers Squibb, Roche, Novartis, Pfizer, MSD, Astellas, Ipsen and Incyte.

Authors' contribution

A. A. has drafted the manuscript; F. S. has critically revised the manuscript. Both authors have approved the final version of the publication.

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CONCLUSIONS

- In 2021, ESMO has developed recommendations for the diagnosis of targetable RET rearrangements and mutations.²
- Following the results of the phase I/II LIBRETTO-001 trial, selpercatinib has received FDA, followed by Swissmedic approval for RET fusion-positive NSCLC and papillary thyroid cancer and RET mutation-positive medullary thyroid cancer (MTC).^{5,6}
- Pralsetinib was approved by the FDA for the treatment of patients with lung cancer with RET gene fusion and RET-altered MTC.^{7,8}

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