# RET TUMOR THERAPY: A MILESTONE ACHIEVED

*IQVIA Pipeline Intelligence*

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The characterization of rearranged during transfection (RET) receptor tyrosine kinase alterations as oncogenic drivers in multiple cancers and the development of highly selective RET inhibitors has demonstrated the utility of specific targeting of aberrantly activated RET in patients with cancers and has enhanced the therapeutic landscape of genome-driven precision oncology. This article will outline the latest development activities of RET inhibitors with data sourced from IQVIA™ Pipeline Intelligence.

## Selpercatinib: First-in-Class Selective RET Inhibitor

Lilly's selpercatinib (RETEVMO) was the first therapy to reach the market specifically for cancer patients with RET gene alterations.[1] The drug was granted accelerated approval in May 2020 for the treatment of adult patients with metastatic RET fusion-positive nonsmall cell lung cancer (NSCLC), and for the treatment of adult and pediatric patients aged 12 years and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC), who require systemic therapy, or advanced/metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory.[1]

The accelerated approval of selpercatinib was based on data from the LIBRETTO-001 phase I/II trial, in which selpercatinib treatment resulted in overall response rates (ORR) of 85% in treatment-naive and 64% in treatment-experienced patients with RET fusion-positive NSCLC, 73% in treatment-naive and 69% in treatment-experienced patients with RET-mutant medullary thyroid cancer, and 100% in treatment-naive and 79% in treatment-experienced patients with RET fusion-positive thyroid cancer.[2]

## Current Landscape of the RET-Inhibitor Pipeline

Although Lilly won the race to get the first RET inhibitor to market, it is followed closely by CStone Pharmaceuticals/Blueprint Medicines' pralsetinib (BLU 667), for which a rolling NDA was submitted to the US FDA and completed in April 2020 for RET-fusion positive NSCLC. The rolling NDA was based on topline data from the ARROW phase I/II trial, in which treatment with pralsetinib resulted in an ORR of 61% in patients with RET fusion-positive NSCLC who were previously treated with platinum-based chemotherapy. In treatment-experienced patients with RET-mutant MTC, the ORR was 60% with an 18-month duration of response of 90% following



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treatment with pralsetinib. In addition, the ORR was 74% in treatment-naive patients with RET-mutant MTC who received pralsetinib. Blueprint Medicines plans to file an NDA with the US FDA seeking approval of pralsetinib for RET-mutant MTC during the second quarter of 2020.[3,4] Other companies, including Turning Point and Boston Pharmaceuticals, are close on the heels of selpercatinib with candidates in clinical development for the treatment of RET-induced solid tumors, various cancers and irritable bowel syndrome.

As of 8 June 2020, IQVIA Pipeline Intelligence listed 8 RET inhibitors in active development. Table 1 summarizes the RET inhibitors under development, as sourced from IQVIA Pipeline Intelligence:

| Product | Developer | Phase | Indication |
|---|---|---|---|
| Pralsetinib | Blueprint Medicines/CStone Pharmaceuticals | Pre-registration<br>Phase I/II | RET-mutant NSCLC<br>RET-mutant MTC |
| BOS 589 | Boston Pharmaceuticals | Phase II | Irritable bowel syndrome |
| TPX 0046 | Turning Point | Phase I/II | RET-mutant solid tumors |
| BOS 172738 | Boston Pharmaceuticals | Phase I | RET-mutant solid tumors |
| TY 1036B | TYK Medicines | Preclinical | Preclinical: RET-mutant cancer |
| DDU RET 04 | Cancer Research UK | Preclinical | Preclinical: RET-mutant lung cancer |
| SL 1001 | Stemline | Preclinical | Preclinical: RET-mutant cancer |
| KF 1602 | ImmunoForge | Discovery | RET-mutant cancer |

Table 1: Product profiles of RET inhibitors. Source: IQVIA™ Pipeline Intelligence.

**BOS 589**

Boston Pharmaceuticals' BOS-589, a first-in-class gastrointestinal-restricted RET kinase inhibitor, is currently in a phase II trial to evaluate its safety and efficacy for the treatment of patients with diarrhea-predominant irritable bowel syndrome (IBS-D). IBS-D patients exhibit visceral hypersensitivity and alterations in the gut motility that may be attributed to RET activity in the target cells of the gastrointestinal tissue and enteric nervous tissues.



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**TPX 0046**
Turning Point's TPX 0046 is a multi-targeting RET and SRC tyrosine kinase inhibitor with a three-dimensional macrocyclic structure that is designed to target abnormal RET signaling in cancers. A phase I/II trial to assess the efficacy of TPX 0046 for the treatment of advanced solid tumors with abnormal RET genes is ongoing and estimated to complete in March 2025.

**BOS 172178**
Boston Pharmaceuticals' BOS 172178, a highly-selective, ATP-competitive RET kinase inhibitor, is currently in a phase I trial to evaluate its safety in advanced solid tumor patients with RET gene alterations, which is anticipated to complete in June 2021. BOS 172178 has previously demonstrated antitumor activity in preclinical studies of RET-driven tumors from patient-derived xenografts.

**TY 1036B**
TYK Medicines' is developing TY 1036B, a RET inhibitor, for the treatment of RET-altered cancers; preclinical evaluation is under way.

**DDU RET 04**
Cancer Research UK's DDU RET 04, a RET inhibitor being developed for the treatment of RET-driven adenocarcinomas, is under preclinical evaluation. In a KIF5B-RET lung cancer patient-derived xenograft model, DDU RET 04 exhibited antitumor activity at low doses. The percentage of tumor regression was 50% and 92% for the 20 and 10 mg/kg dosages of DDU RET 04, respectively.

**SL 1001**
Stemline is conducting preclinical evaluation of SL 1001, an oral selective RET inhibitor, for RET-driven cancers.

**KF 1602**
ImmunoForge is conducting a program designated KF 1602, a RET inhibitor, for the treatment of lung and thyroid cancers. Lead optimization is ongoing.

## Conclusion

The approval of selpercatinib and positive data from clinical trials of other RET inhibitors provide further treatment options for patients and opportunities in RET-dependent cancer research, which may include addressing the ability of RET inhibitors to maintain long-term inhibition of tumor cell growth and to tackle potential mechanisms of acquired resistance.



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