

**Company**

Blueprint Medicines

**Drug or Device Name**

GAVRETO® (pralsetinib)

**Category**

Pharmaceutical

**Compound/Technical Name**

Pralsetinib

**Trade Name**

Gavreto

**Date of Approval**

09/04/2020

**Therapeutic Categories**

Targeted therapy for RET-altered cancers

**Indications**

On September 4, 2020, Gavreto (pralsetinib) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test. In addition, on December 1, 2020, Gavreto was FDA approved for the treatment of adults and children 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, or with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). Previously, the FDA granted breakthrough therapy designation to Gavreto for the treatment of RET fusion-positive NSCLC that has progressed following platinum-based chemotherapy, and RET mutation-positive MTC that requires systemic treatment and for which there are no acceptable alternative treatments. Blueprint Medicines is currently developing Gavreto for the treatment of other RET-altered cancers, as well as additional early-line treatment settings in NSCLC and thyroid cancer.

**Background**

Gavreto, a selective and potent inhibitor of oncogenic RET alterations, is one of nine approved or investigational precision therapies designed by scientists at Blueprint Medicines using the company's precision therapy platform. Since our founding just a decade ago, Blueprint Medicines has evolved into one of the world's leading precision therapy companies and, as a fully integrated enterprise, we are now delivering two approved medicines – including Gavreto – directly to patients. The RET tyrosine kinase is an oncogenic driver in subsets of patients across multiple tumor types. RET fusions are implicated in approximately 1 to 2 percent of patients with NSCLC and approximately 10 to 20 percent

of patients with papillary thyroid cancer (PTC), while RET mutations are implicated in approximately 90 percent of patients with advanced MTC. In addition, oncogenic RET alterations are observed at low frequencies in colorectal, breast, pancreatic and other cancers. Prior to Gavreto, patients with RET-altered cancers were often treated with multi-kinase inhibitors with RET activity (e.g., cabozantinib, vandetanib). However, the efficacy observed with these therapies was modest, and patients commonly experienced toxicities due to off-target activity leading to dose modification and discontinuation. Beginning in 2013, just one year after the first RET fusions were reported in patients with NSCLC, Blueprint Medicines initiated a research program to design a highly selective and potent RET inhibitor with the goal of delivering profound benefit to patients with RET-altered cancers. Leveraging our proprietary library of agnostically designed kinase inhibitors fully annotated against the human kinome, along with expertise in iterative medicinal chemistry, we designed a RET-targeted compound to achieve sub-nanomolar potency against common oncogenic RET fusions and mutations and approximately 100-fold greater selectivity for RET over nearly all other kinases tested. Based on this work, we nominated Gavreto – then called BLU-667 – as a development candidate in 2016.

## Development

The development of Gavreto has been a remarkable journey culminating in FDA approval just three years after the first patient was dosed, which is among the fastest registration paths for a targeted cancer therapy. In the first quarter of 2017, we initiated the Phase 1/2 ARROW trial. Initial data were reported at the AACR Annual Meeting in early 2018, showing promising evidence of activity and supporting selection of a once-daily recommended dose and initiation of the expansion cohorts across multiple tumor types. A spectrum of subsequent congress presentations and publications contributing to the scientific understanding of RET-altered cancers included a plenary presentation at the 2019 ASCO Annual Meeting. In 2019, ARROW trial data supported the granting of FDA breakthrough therapy designations for RET fusion-positive NSCLC and RET mutation-positive MTC. In 2020, based on ARROW trial data, we submitted New Drug Applications to the FDA for RET fusion-positive NSCLC, RET-mutation-positive MTC and RET fusion-positive PTC, leading to sequential approvals for NSCLC in September and for MTC and PTC in December, each ahead of the FDA's target action date for an approval decision. Also in 2020, Blueprint initiated a global strategic collaboration with Roche to develop and commercialize Gavreto. With \$775 million in upfront payments and nearly \$1 billion in additional potential milestone payments plus royalties, the deal represented one of the largest biopharmaceutical collaborations of 2020. The two companies agreed to co-commercialize Gavreto in the U.S., and Roche gained an exclusive license to commercialize Gavreto outside of the U.S., excluding Greater China where Gavreto is now being commercialized by CStone Pharmaceuticals under a separate partnership initiated in 2018. Over time, the ongoing ARROW trial has expanded to include about 80 sites around the world and enroll approximately 500 patients. Additional global trials of Gavreto across a range of treatment settings are now ongoing or planned.

## Innovation

Historically, a primary limitation of targeted therapy in cancer has been the emergence of resistance. In designing Gavreto, we aimed to overcome this limitation by designing a candidate with exquisite selectivity for oncogenic RET fusions and mutants, with the goal of enabling highly potent target inhibition and improved safety relative to multi-kinase inhibitors. In addition, a common vulnerability of kinase inhibitors is the development of certain on-target resistance mutations. To address this, we designed Gavreto to not only inhibit activating RET fusions and mutations, but also inhibit additional RET mutations predicted to emerge over time and drive resistance, with the goal of delivering profound and prolonged benefit to patients. Beyond Gavreto, this scientific approach is the organizing

principle for our rapidly expanding precision therapy portfolio. These scientific innovations built into the design of Gavreto have translated into transformative clinical outcomes in patients with previously limited treatment options. In the dataset supporting its approval, Gavreto demonstrated a 70% overall response rate (ORR), with 11% of patients achieving a complete response (CR), in patients with treatment-naïve NSCLC. Per the trial protocol, this treatment-naïve population only included patients ineligible for standard chemotherapy. A subsequent presentation of updated ARROW trial data at the 2021 ASCO Meeting reported an 88% ORR for Gavreto, with the median duration of response (DOR) not reached, in treatment-naïve NSCLC patients eligible for standard therapy. In patients with treatment-naïve MTC, Gavreto showed a 66% ORR, with 10% of patients achieving a CR, and the median DOR was not reached. In patients with PTC, Gavreto showed an 89% ORR and the median DOR was not reached. Gavreto was generally well-tolerated, and the most common adverse reactions were constipation, hypertension, fatigue, musculoskeletal pain and diarrhea. Additional detailed clinical data, including the FDA approved prescribing information, are attached to this nomination as references.

### Pubmed

Subbiah V, et al. Precision Targeted Therapy with BLU-667 for RET-Driven Cancers. *Cancer Discov.* 2018 Jul;8(7):836-849. doi: 10.1158/2159-8290.CD-18-0338. Epub 2018 Apr 15. Link: <https://cancerdiscovery.aacrjournals.org/content/8/7/836.long> Subbiah V, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. *Lancet Diabetes Endocrinol.* 2021 Jun 9;S2213-8587(21)00120-0. doi: 10.1016/S2213-8587(21)00120-0. Online ahead of print. Link: [https://www.thelancet.com/journals/landia/article/PIIS2213-8587\(21\)00120-0/fulltext](https://www.thelancet.com/journals/landia/article/PIIS2213-8587(21)00120-0/fulltext) Gainor J, et al. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. *Lancet Oncol.* 2021 Jun 9;S1470-045(21)00247-3. doi: 10.1016/S1470-2045(21)00247-3. Online ahead of print. Link: [https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(21\)00247-3/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00247-3/fulltext)

### Attachments

- 1625020849Blueprint-Medicines-Announces-FDA-Approval-GAVRETO-Thyroid-Cancers.pdf
- 1625020862BPMC-Roche\_press\_release-FINAL.pdf
- 1625020886Subbiah\_et\_al.\_BLU\_667\_RET\_Cancer\_Discovery\_2018.pdf
- 1625020901Subbiah,\_Hu\_et\_al\_Lancet\_Endo\_Pralsetinib.pdf
- 1625020927Gainor\_et\_al\_Pralsetinib\_Lancet\_Oncology.pdf
- 1625021501Blueprint-Medicines-ASCO-2020-Pralsetinib-Registrational-Dataset-NSCLC-Poster.pdf
- 1625021515Blueprint-Medicines-ESMO-2020-Pralsetinib-Medullary-Thyroid-Cancer-Presentation.pdf
- 1625021530Blueprint-Medicines-ASCO-2020-Pralsetinib-Clinical-Activity-RET-Fusion-Solid-Tumors-Presentation-1.pdf
- 1625020690Gavreto\_prescribing\_information.pdf
- 1625020722HBS-Case-Study-BPMC.PDF
- 1625020839Blueprint-Medicines-Announces-FDA-Approval-of-GAVRETO-NSCLC.pdf

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