pralsetinib (Gavreto™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO220

Description

Pralsetinib (Gavreto) is an orally administered kinase inhibitor of RET.

Length of Authorization

- N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pralsetinib (Gavreto)	RET Fusion-Positive Non-Small Cell Lung Cancer; RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory	100 mg capsules	120 capsules/30 days

Initial Evaluation

I. **Pralsetinib (Gavreto)** is considered not medically necessary when used for RET fusion-positive medullary thyroid cancer and investigational when used for all other indications, including but not limited to Non-Small Cell Lung Cancer (NSCLC) and Thyroid Cancer.

Renewal Evaluation

I. N/A

Supporting Evidence

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers.

II. Pralsetinib (Gavreto) was evaluated in one Phase 1/2, dose expansion and escalation, multi-cohort, open-label, single-arm trial. Interim results showed potential antitumor activity via overall response rate (ORR) and duration of response (DoR). The primary outcome is ORR, and the secondary outcomes include DoR and proportion of patients with DoR six months or greater.

III. For RET fusion-positive NSCLC: Patients with advanced or metastatic disease that were either treatment naïve (n=27) or progressed on platinum-based chemotherapy (n=87) were assessed. For RET-mutant MTC, patients were either treatment naïve (n=29) or progressed on cabozantinib (Cometriq) or vandetanib (Caprelsa) (n=55). All patients had progressed on standard of care for RET-fusion-positive TC (n=9).

Clinical Efficacy in Pretreated Patients			
Outcome	**RET Fusion+ NSCLC (n=87)**	**RET-Mutant MTC (n=55)**	**RET Fusion-Positive TC (n=9)**
ORR (%)	57% (46, 68)	60% (46, 73)	89% (52, 100)
CR (%)	5.7%	1.8%	0
PR (%)	52%	58%	89%
DoR (mo)	NR (15.2-NE)	NR (15.1, NE)	NR (NE, NE)
DoR ≥ 6 mo (%)	80%	79%	100%
Clinical Efficacy in Treatment-Naïve Patients			
Outcome	**RET Fusion+ NSCLC (n=27)**	**RET-Mutant MTC (n=29)**	**RET Fusion-Positive TC***
ORR (%)	70% (50, 86)	66% (46, 82)	N/A
CR (%)	11%	10%	
PR (%)	59%	55%	
DoR (mo)	9 (6.3-NE)	NR (NE, NE)	
DoR ≥ 6 mo (%)	58%	84%	

*All patients were refractory to standard therapy.

IV. The quality of the evidence is considered low given the open-label and single-arm trial design and small sample size; thus, true medication efficacy remains uncertain given the nature of observational data. Additionally, outcomes such as ORR and DoR have not been correlated with clinically meaningful outcomes such as improved survival or quality of life.

V. Phase 3 trial, AcceleRET, is planned to evaluate pralsetinib (Gavreto) in advanced or metastatic, RET fusion-positive NSCLC versus platinum-based chemotherapy. It will be evaluated in an open-label, randomized trial for first-line metastatic systemic therapy. Outcomes of interest include PFS, OS, time to intracranial progression, and quality of life. This international trial has a target enrollment of 250 patients, with an estimated completion date of November 2024.

VI. Pralsetinib (Gavreto) was initially approved under accelerated approval for RET fusion-positive NSCLC, advanced or metastatic. The conversion to regular approval was based on data from an additional 123 patients and 25 months of additional follow-up to assess durability of response. A total of 237 participants with locally advanced or metastatic RET fusion-positive NSCLC demonstrated an ORR of 78% (95% CI: 68, 85) with a median DOR of 13.4 months (95% CI: 9.4, 23.1). Among 130 patients previously treated with platinum-based chemotherapy, ORR was 63% (95% CI: 54, 71) with a median DOR of 38.8 months (95% CI: 14.8, not estimable). NCCN guidelines include pralsetinib (Gavreto) and selpercatinib (Retevmo) as preferred first-line and subsequent-line therapy (category 2a). Cabozantinib (Cometriq) is listed as useful in certain circumstances (category 2a) and vandetanib (Caprelsa) was recently removed as a treatment option.

VII. RET fusion-positive thyroid cancer: NCCN recommends radioactive iodine as first line therapy. In those not amenable to RAI, treatment options include selpercatinib (Retevmo) (category 1) and pralsetinib (category 2B).

VIII. Pralsetinib (Gavreto) was previously approved under an accelerated pathway for treatment of advanced or metastatic RET-mutant medullary thyroid cancer (MTC) in patients aged 12 years and older. In June 2023, the manufacturer was unable to provide confirmatory MTC study results to fulfill the FDA post marketing requirement and voluntarily withdrawn this indication

from the market. This decision is not based on efficacy or safety of pralsetinib and does not affect other approved indications.

IX. Safety data is based on a pooled population of 438 patients. Common adverse events (AE) that occurred ≥15% or more of the population: fatigue, constipation, musculoskeletal pain, hypertension, edema, diarrhea, dry mouth, cough, and pneumonia. Serious AE that occurred ≥2%: pneumonia, sepsis, UTI, pyrexia, increased ALT/AST, and phosphatase, and decreased lymphocytes, neutrophils, hemoglobin, phosphate, calcium, sodium, and platelets. Fatal AE occurred in 5% of patients (pneumonia and sepsis) in the NSCLC cohort. Warnings and precautions: interstitial lung disease, hypertension, hepatotoxicity, hemorrhage, tumor lysis syndrome, impaired wound healing, and embryo-fetal toxicity.

X. Dose reductions due to AE occurred in up to 67% of patient, which varied by cohort. Dose reductions occurred in up to 44%, and permanent discontinuation rate in up to 15%. The true safety profile of pralsetinib (Gavreto) remains unknown given the observational evaluation.

XI. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

XII. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents may remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for the treatment of majority of cancer types (e.g., NSCLC, cholangiocarcinoma, neuroendocrine, sarcoma) note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, and category 2A recommendations from NCCN, continued approval of selpercatinib (Retevmo) as a subsequent-line treatment of tumors harboring RET fusions in thyroid cancer refractory to radioactive iodine, remains contingent upon verification of clinical benefit in confirmatory trials.

Investigational or Not Medically Necessary Uses

I. Pralsetinib (Gavreto) in treatment of RET fusion-positive medullary thyroid cancer (MTC) is being withdrawn based on the confirmatory Phase III randomized AcceleRET study, which did not meet its primary endpoint and thus did not fulfill the confirmatory data requirements of the Accelerated

Approval granted by the U.S. FDA nor the conditional marketing approvals granted in other countries. Genetech is working with the FDA towards the withdrawal of this indication.

II. Pralsetinib (Gavreto) has not yet been sufficiently studied for safety and efficacy for any condition.

References

1. Gavreto (pralsetinib) [prescribing information]. South San Francisco, CA: Genentech Inc; June 2023.
2. Retevmo [Prescribing Information]. Eli Lilly and Company. Indianapolis, IN. May 2020.
3. Adeniran AJ, Ahu Z, Gandhi M, et al. Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. Am J Surg Pathol. 2006. 30(2): 216-222.
4. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol. 2018a Mar;15(3):151-67.
5. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Treatment Guidelines V2.2024. February 9, 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
6. National Comprehensive Cancer Network. Thyroid Carcinoma Guidelines V1.2024. February 1, 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
7. European Society for Medical Oncology. Metastatic non-small-cell lung cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 15, 2020.
8. FDA Approves Pralsetinib for Non-Small Cell Lung Cancer with RET Gene Fusions. FDA.gov, August 9, 2023.Available at https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pralsetinib-non-small-cell-lung-cancer-ret-gene-fusions

Related Policies

Policy Name	Disease state
selpercatinib (Retevmo)	RET Fusion-Positive Non-Small Cell Lung Cancer; RET-Mutant Medullary Thyroid Cancer; RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory
cabozantinib (Cabometyx, Cometriq)	Progressive or metastatic medullary thyroid carcinoma
vandetanib (Caprelsa)	Locally advanced or metastatic medullary thyroid cancer
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated supporting evidence to include extension study results to change FDA approval of pralsetinib (Gavreto) from accelerated to traditional in treatment of NSCLC and updated NCCN guideline recommendations. Moved RET-positive fusion MTC from covered indication to non-medically necessary due to withdrawn indication.	3/2024
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy created	02/2021