RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Gavreto®
Generic Name	pralsetinib
Drug Manufacturer	Blueprint Medicines Corporation

New Drug Approval

FDA Approval Date: September 4, 2020

Review Designation: Priority; Orphan (NDA 213721)

Type of Review: Type 1 - New Molecular Entity

Dispensing Restrictions: Limited Distribution; Specialty Only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

About 80% to 85% of lung cancers are non-small cell lung cancer (NSCLC). The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. These subtypes, which start from different types of lung cells are grouped together as NSCLC because their treatment and prognoses (outlook) are often similar.

Lung cancer (both small cell and non-small cell) is the second most common cancer in both men and women.

The American Cancer Society's estimates for lung cancer in the United States for 2020 are:

- About 228,820 new cases of lung cancer (116,300 in men and 112,520 in women).
- About 135,720 deaths from lung cancer (72,500 in men and 63,220 in women).

Lung cancer mainly occurs in older people. Most people diagnosed with lung cancer are 65 or older; a very small number of people diagnosed are younger than 45. The average age of people when diagnosed is about 70.

Lung cancer is by far the leading cause of cancer death among both men and women, making up almost 25% of all cancer deaths. Each year, more people die of lung cancer than of colon, breast, and prostate cancers combined.

Overall, the chance that a man will develop lung cancer in his lifetime is about 1 in 15; for a woman, the risk is about 1 in 17. These numbers include both smokers and non-smokers. For smokers, the risk is much higher, while for non-smokers the risk is lower.

Efficacy

Gavreto® is a once-daily, oral therapy designed to selectively target rearrangement during transinfection (RET) alterations, including fusions and mutations, regardless of the tissue of origin. Preclinical data have shown that the drug inhibits primary RET fusions and mutations that cause cancer in subsets of patients, as well as secondary RET mutations predicted to drive resistance to treatment.

Gavreto® was approved for the treatment of adult patients with metastatic rearranged during transfection (RET) fusion-positive NSCLC. It was approved under FDA's accelerated approval program, which enables patients to have earlier access to a promising new drug while the company continues to conduct clinical trials to confirm that the drug works well.

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The FDA approval is based on the ongoing Phase 1/2 ARROW study, in which the RET inhibitor significantly shrank tumors in 57% of NSCLC patients who had previously received chemotherapy and provoked a response in 70% of untreated patients. The study enrolled, in separate cohorts, patients with metastatic RET fusion-positive NSCLC who had progressed on platinum-based chemotherapy and treatment-naïve patients with metastatic NSCLC. Identification of a RET gene fusion was determined by local laboratories using next generation sequencing (NGS), fluorescence in situ hybridization (FISH), and other tests.

Study Population:

- 438 adult patients with RET altered solid tumors received Gavreto®. Among these patients, 47% were exposed for >6 months and 23% were exposed for >1 year.
- The median age at baseline was 60 years, 48% of patients were male, 50% were White, 41% were Asian, and 4% were Hispanic/Latino.
- The trial consists of two phases: A dose-escalation phase (completed) and an expansion phase (ongoing).
    - The Phase 2 portion of the study included cohorts for patients with RET fusion-positive NSCLC, RET mutation-positive MTC, and those with other RET fusion-positive solid tumors.
    - Eligible patients were those with advanced solid tumors harboring RET alterations and no other driver mutations.
    - Treatment in the Phase 2 portion was administered at 400 mg orally once daily.
- Eligibility criteria: ≥18 years of age, with an unresectable locally advanced or metastatic solid tumor, documented RET fusion or mutation (local testing), measurable disease per RECIST v1.1, ECOG performance status (PS) of 0–1.

Interventions:

- Patients received 400 mg of pralsetinib (BLU-667) capsules once daily until toxicity or disease progression.

Endpoints:

- Primary Outcome Phase 1: Determination of maximum tolerated dose (MTD) and recommended Phase 2 dose
- Primary Outcome Phase 2: Overall response rate (ORR), number of patients with adverse events (AEs), and serious adverse events (SAEs)
- Secondary Outcomes Phase 1: ORR, RET gene status, correlation between RET gene status and ORR, pharmacokinetics, clinical benefit rate (CBR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) and other antineoplastic measures
- Secondary Outcomes Phase 2: CBR, DOR, DCR, PFS, pharmacokinetics, pharmacodynamics, and overall survival

Efficacy Results in ARROW (Metastatic RET Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy)

Efficacy Parameter	Gavreto (N = 87)
Overall Response Rate (ORR)[a] (95% CI)	57 (46, 68)
Complete Response, %	5.7
Partial Response, %	52
Duration of Response (DOR)	**(N = 50)**
Median, months (95% CI)	NE (15.2-NE)
Patients with DOR ≥6 months[b], %	80

NE = not estimable
a Confirmed overall response rate assessed by BICR
b Calculated using the proportion of responders with an observed duration of response at least 6 months or greater

Efficacy Results in ARROW (Treatment-Naïve Metastatic RET Fusion-Positive NSCLC)

Efficacy Parameter	Gavreto (N = 27)
Overall Response Rate (ORR)[a] (95% CI)	70 (50, 86)
Complete Response, %	11
Partial Response, %	59
Duration of Response (DOR)	**(N = 19)**
Median, months (95% CI)	9.0 (6.3, NE)
Patients with DOR ≥6 months[b], %	58

NE = not estimable
a Confirmed overall response rate assessed by BICR
b Calculated using the proportion of responders with an observed duration of response at least 6 months or greater

Safety

ADVERSE EVENTS

The most common adverse reactions (≥25%) were fatigue, constipation, musculoskeletal pain, and hypertension. The most common Grade 3-4 laboratory abnormalities (≥2 %) were decreased lymphocytes, decreased neutrophils, decreased phosphate, decreased hemoglobin, decreased sodium, decreased calcium (corrected), and increased alanine aminotransferase (ALT).

Table 1: Recommended Dose Reductions for GAVRETO for Adverse Reactions

Dose Reduction	Recommended Dosage
First	300 mg once daily
Second	200 mg once daily
Third	100 mg once daily

Permanently discontinue GAVRETO in patients who are unable to tolerate 100 mg taken orally once daily.

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Table 2: Recommended Dosage Modifications for GAVRETO for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
ILD/Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 1 or 2	Withhold GAVRETO until resolution. Resume by reducing the dose as shown in Table 1. Permanently discontinue GAVRETO for recurrent ILD/pneumonitis.
	Grade 3 or 4	Permanently discontinue for confirmed ILD/pneumonitis.
Hypertension *[see Warnings and Precautions (5.2)]*	Grade 3	Withhold GAVRETO for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.
	Grade 4	Discontinue GAVRETO.
Hepatotoxicity *[see Warnings and Precautions (5.3)]*	Grade 3 or Grade 4	Withhold GAVRETO and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. Resume at reduced dose (Table 1). If hepatotoxicity recurs at Grade 3 or higher, discontinue GAVRETO.
Hemorrhagic Events *[see Warnings and Precautions (5.4)]*	Grade 3 or Grade 4	Withhold GAVRETO until recovery to baseline or Grade 0 or 1. Discontinue GAVRETO for severe or life-threatening hemorrhagic events.
Other Adverse Reactions *[see Adverse Reactions 6.1]*	Grade 3 or 4	Withhold GAVRETO until improvement to ≤ Grade 2. Resume at reduced dose (Table 1). Permanently discontinue for recurrent Grade 4 adverse reactions.

* Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03

WARNINGS & PRECAUTIONS

- Interstitial Lung Disease (ILD)/Pneumonitis: Withhold Gavreto® for Grade 1 or 2 reactions until resolution and then resume at a reduced dose. Permanently discontinue for recurrent ILD/pneumonitis. Permanently discontinue for Grade 3 or 4 reactions.

- Hypertension: Do not initiate Gavreto® in patients with uncontrolled hypertension. Optimize blood pressure (BP) prior to initiating Gavreto®. Monitor BP after 1 week, at least monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue Gavreto® based on severity.
- Hepatotoxicity: Monitor ALT and AST prior to initiating Gavreto®, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue Gavreto® based on severity.
- Hemorrhagic Events: Permanently discontinue Gavreto® in patients with severe or life-threatening hemorrhage.
- Risk of Impaired Wound Healing: Withhold Gavreto® for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Gavreto® after resolution of wound healing complications has not been established.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective non-hormonal contraception.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Pralsetinib is a kinase inhibitor of wild-type RET and oncogenic RET fusions (CCDC6-RET) and mutations (RET V804L, RET V804M and RET M918T). In enzyme assays, pralsetinib also inhibited DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRb, and FGFR1. Certain activating point mutations in RET or chromosomal rearrangements involving in-frame fusions of RET can result in constitutively activated chimeric RET fusion proteins, which may act as oncogenic drivers, promoting tumor cell line proliferation. Pralsetinib has demonstrated antitumor activity in cells harboring oncogenic RET fusions or mutations including CCDC6-RET, KIF5B-RET, RET M918T, RET C634W, RET V804L, and RET V804M.

Dose & Administration

ADULTS

400 mg orally once daily.

PEDIATRICS

The safety and effectiveness of Gavreto® have not been established in pediatric patients.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Refer to adult dosing.

HEPATIC IMPAIRMENT

Refer to adult dosing.

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Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 100 mg