NEW DRUG APPROVAL

Brand Name	Krazati™
Generic Name	adagrasib
Drug Manufacturer	Mirati Therapeutics, Inc

New Drug Approval

FDA approval date: December 12, 2022

Review designation: Standard; Orphan

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 216340

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Non-small cell lung cancer (NSCLC) begins when healthy cells in the lung change and grow out of control, forming a mass called a tumor, a lesion, or a nodule. This can begin anywhere in the lung and the tumor can be cancerous or benign. When a cancerous lung tumor grows, it may shed cancer cells. These cells can be carried away in blood or float away in the fluid, called lymph, that surrounds lung tissue. Lymph flows through tubes called lymphatic vessels that drain into collecting stations called lymph nodes.

According to the tumor node metastases (TNM) international staging system, approximately thirty percent of patients affected with non-small cell lung cancer (NSCLC) are diagnosed with “locally advanced” disease. This group includes a wide spectrum of clinical presentations with often a considerable tumor burden (T3-T4 and N2-N3). Beyond stages III A and B, the latest TNM (8th edition) also introduces stage IIIC.

In lung cancer, KRAS G12C mutations occur in approximately 14% of adenocarcinomas and about 2% to 4% of squamous cell carcinoma patients. That amounts to about 25,000 patients per year in the United States across all lines of therapy. Approximately 13,000 patients are diagnosed annually with KRAS G12C– mutated NSCLC in the first-line setting, and about 7000 patients are diagnosed annually in the second-line setting, with later lines of therapy making up the rest.

Efficacy

Krazati™ was evaluated in the KRYSTAL-1 trial (NCT03785249), a multicenter, single-arm, open-label expansion cohort study. The trial consisted of nine experimental arms, which included Phases 1, 1b, and 2.

- Phase 1 addressed safety concerns such as the maximum tolerated dose of Krazati™.
- Phase 1b expanded the cohort of patients and evaluated the effects of Krazati™ in combination with pembrolizumab, cetuximab, and afatinib separately.
- Lastly, Phase 2 examined the clinical activity of Krazati™ on its own and in combination with cetuximab. The approval of Krazati™ was based on Cohort A from the Phase 2 portion of the KRYSTAL-1 trial, which evaluated Krazati™ at a dose of 600 mg orally twice daily in patients with KRAS G12C–mutated NSCLC previously treated with chemotherapy and anti–programmed cell death protein 1 (PD-1) or anti–programmed death ligand 1 (PD-L1) therapy. Table 1 provides a summary of this portion of the study’s design.

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Table 1. KRYSTAL-1 (NCT03785249): Phase 2 Cohort A Study Design Summary

Study Population	• 112 adult patients with locally advanced or metastatic KRAS G12C–mutated advanced NSCLC with disease progression after receiving platinum-based chemotherapy and an immune checkpoint inhibitor (given either concurrently or sequentially), an ECOG PS of 0 or 1, and at least one measurable lesion as defined by RECIST v1.1.
	• Median age: 64 years (range, 25 to 89 years)
	  ○ 55% female
	  ○ 83% White; 8% Black or African American; 4% Asian; 4% race not reported; 0.9% American Indian or Alaska Native
	  ○ 83% ECOG PS 1; 16% ECOG PS 0
	• Treated, stable CNS metastases were allowed
	  ○ Tumor histology: 97% adenocarcinoma; 89% had metastatic disease.
	• Median prior systemic therapies: 2 (range, 1 to 7)
	  ○ 43% received 1 prior line.
	  ○ 35% received 2 prior lines.
	  ○ 10% received 3 prior lines
	  ○ 12% received 4 or more prior lines
	  ○ 98% received both prior platinum and prior anti-PD-1/PD-L1 therapy
	Exclusion criteria: History of intestinal disease or major gastric surgery or inability to swallow oral drugs; other active cancer

Intervention	Study participants received Krazati™ 600 mg orally twice daily until disease progression or unacceptable toxicity
Endpoints	• Primary endpoint: ORR (RECIST v1.1) per BICR • Secondary endpoints: DOR, PFS, OS, safety

Abbreviations: BICR, blinded independent central review; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

Efficacy Results

Table 2 summarizes the efficacy results from KRYSTAL-1.

Table 2. Efficacy Results from KRYSTAL-1 (NCT03785249)

Efficacy Parameter	Krazati™ (n = 112)
ORR (95% CI),[a] %	43 (34, 53)
Complete response rate, %	0.9
Partial response rate, %	42
DOR[a]	
Median[b] in months (95% CI)	8.5 (6.2, 13.8)
Patients with duration ≥6 months,[c] %	58

Abbreviations: CI, confidence interval; DOR, duration of response; ORR, objective response rate.

[a] Assessed by BICR.
[b] Estimate using Kaplan-Meier method.
[c] Observed proportion of patients with duration of response beyond landmark time.

Pooled Efficacy Analysis
In a pooled efficacy analysis (n = 132) including Phase 1/1b NSCLC and registrational Phase 2 NSCLC cohorts from the KRYSTAL-1 study, Krazati™showed an ORR of 44% and a DCR of 81% based on blinded independent central review (BICR), a median DOR of 12.5 months (95% CI: 7.3 to not evaluable), and a median OS of 14.1 months (94% CI: 9.2 to 19.2).

Safety Results
Pooled Safety Population (n = 366)
The pooled safety population described in the Warnings and Precautions section of the Krazati™ label reflects exposure to Krazati™ as a single agent at 600 mg orally twice daily in 366 patients with NSCLC and other solid tumors enrolled in KRYSTAL-1 and KRYSTAL-12. Among 366 patients who received Krazati™, 39% of patients were exposed for 6 months or longer and 12% were exposed for greater than 1 year.
In this pooled safety population, the most common (≥25%) adverse reactions (ARs) were nausea (70%), diarrhea (69%), vomiting (57%), fatigue (55%), musculoskeletal pain (38%), hepatotoxicity (37%), renal impairment (33%), edema (30%), dyspnea (26%), and decreased appetite (29%).
In this pooled safety population, the most common Grade 3 or 4 (≥ 2%) laboratory abnormalities were decreased lymphocytes (20%), decreased hemoglobin (7%), increased alanine aminotransferase (4.5%), increased aspartate aminotransferase (4.2%), hypokalemia (3.6%), hyponatremia (3.4%), increased lipase (2.5%), decreased leukocytes (2.5%), decreased neutrophils (2.3%), and increased alkaline phosphatase (2.0%).

NSCLC Population (n = 116)
The safety of Krazati™ was evaluated in patients with *KRAS G12C*–mutated, locally advanced or metastatic NSCLC in KRYSTAL-1. Patients received Krazati™ 600 mg orally twice daily. Among patients who received Krazati™, 45% were exposed for 6 months or longer and 4% were exposed for greater than 1 year.
Serious ARs occurred in 57% of patients who received Krazati™. Serious ARs occurring in ≥2% of patients were pneumonia (17%), dyspnea (9%), renal impairment (8%), sepsis (5%), hypoxia (4.3%), pleural effusion (4.3%), respiratory failure (4.3%), anemia (3.4%), cardiac failure (3.4%), hyponatremia (3.4%), hypotension (3.4%), muscular weakness (3.4%), pyrexia (3.4%), dehydration (2.6%), diarrhea (2.6%), mental status changes (2.6%), pulmonary embolism (2.6%), and pulmonary hemorrhage (2.6%). Fatal ARs occurred in 11% of patients who received Krazati™ due to pneumonia (3.4%), respiratory failure (1.7%), sudden death (1.7%), cardiac failure (0.9%), cerebrovascular accident (0.9%), mental status change (0.9%), pulmonary embolism (0.9%), and pulmonary hemorrhage (0.9%).
Permanent discontinuation of Krazati™ due to an AR occurred in 13% of patients. ARs that resulted in permanent discontinuation of Krazati™ occurring in two patients each (1.7%) were pneumonia and pneumonitis and occurring in one patient each (0.9%) were cerebrovascular accident, dyspnea, decreased ejection fraction, encephalitis, gastrointestinal obstruction, hemorrhage, hepatotoxicity, hypotension, muscular weakness, pulmonary embolism, pyrexia, respiratory failure, and sepsis.
Dose interruptions of Krazati™ due to an AR occurred in 77% of patients. Adverse reactions requiring dosage interruption in ≥2% of patients who received Krazati™ included nausea, hepatotoxicity, fatigue, vomiting, pneumonia, renal impairment, diarrhea, QTc interval prolongation, anemia, dyspnea, increased lipase, decreased appetite, dizziness, hyponatremia, muscular weakness, increased amylase, pneumonitis, sepsis, and decreased weight.

Dose reductions of Krazati™ due to an AR occurred in 28% of patients. ARs that required dose reductions in ≥2% of patients who received Krazati™ included hepatotoxicity, fatigue, nausea, diarrhea, vomiting, and renal impairment.
The most common ARs (≥20%) were diarrhea, nausea, fatigue, vomiting, musculoskeletal pain, hepatotoxicity, renal impairment, dyspnea, edema, decreased appetite, cough, pneumonia, dizziness, constipation, abdominal pain, and QTc interval prolongation. The most common laboratory abnormalities (≥25%) were decreased lymphocytes, increased aspartate aminotransferase, decreased sodium, decreased hemoglobin, increased creatinine, decreased albumin, increased alanine aminotransferase, increased lipase, decreased platelets, decreased magnesium, and decreased potassium.

Safety

ADVERSE EVENTS

- The most common (≥ 25%) adverse reactions were nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, renal impairment, edema, dyspnea, and decreased appetite.
- The most common Grade 3 or 4 (≥ 2%) laboratory abnormalities were decreased lymphocytes, decreased hemoglobin, increased alanine aminotransferase, increased aspartate aminotransferase, hypokalemia, hyponatremia, increased lipase, decreased leukocytes, decreased neutrophils and increased alkaline phosphatase.

WARNINGS & PRECAUTIONS

Gastrointestinal Adverse Reactions: Monitor patients for diarrhea, nausea and vomiting and provide supportive care as needed. Withhold, reduce the dose or permanently discontinue based on severity.

QTc Interval Prolongation: Avoid concomitant use of Krazati™ with other products with a known potential to prolong the QTc interval.
Monitor ECG and electrolytes in patients at risk, and in patients taking medications known to prolong the QT interval. Withhold, reduce the dose, or permanently discontinue based on severity.

Hepatotoxicity: Monitor liver laboratory tests prior to the start of Krazati™ and monthly for 3 months after and as clinically indicated.
Reduce the dose, withhold, or permanently discontinue based on severity.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Adagrasib is an irreversible inhibitor of KRAS G12C that covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive state that prevents downstream signaling without affecting wild-type KRAS protein. Adagrasib inhibits tumor cell growth and viability in cells harboring KRAS G12C mutations and results in tumor regression in KRAS G12C-mutated tumor xenograft models with minimal off-target activity.

Dose & Administration

ADULTS

600 mg orally twice daily.

PEDIATRICS

The safety and effectiveness of Krazati™ has not been established in pediatric patients.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Mild, Moderate, or Severe Renal Impairment (CrCl 15 to 89 mL/min): Dosage adjustments are not necessary.

HEPATIC IMPAIRMENT

Mild, Moderate, or Severe Hepatic Impairment (Child-Pugh A, B, or C): Dosage adjustments are not necessary.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 200 mg.