Mirati Therapeutics Announces U.S. FDA Accelerated Approval of KRAZATI™ (adagrasib) as a Targeted Treatment Option for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) with a KRASG12C Mutation

December 12, 2022

SAN DIEGO, Dec. 12, 2022 /PRNewswire/ -- Mirati Therapeutics, Inc. (NASDAQ: MRTX), a targeted oncology company, today announced that the U.S. Food and Drug Administration (FDA) has granted accelerated approval for KRAZATI ™ (*adagrasib*), a targeted treatment option for adult patients with KRAS^{G12C}-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

Experience the full interactive Multichannel News Release here: https://www.multivu.com/players/English/8999051-mirati-therapeutics-fda-accelerated-approval-of-krazati-adagrasib/

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial(s).

To view the multimedia assets associated with this release, please visit: Mirati.com/approval

"The FDA approval of KRAZATI is a positive development for thousands of patients with KRAS^{G12C} mutations, including the approximately 14% of patients with NSCLC adenocarcinomas histology that harbor a KRAS^{G12C} mutation.[1] Mirati is thrilled to make KRAZATI available in a tablet formulation to patients in the U.S. with advanced NSCLC who have progressed beyond a first-line treatment for the historically difficult-to-treat KRAS mutation," David Meek, chief executive officer, Mirati Therapeutics, Inc., continued, "We look forward to continuing to advance our KRAZATI development program including several monotherapy and combination studies in KRAS^{G12C}-mutated solid tumors."

KRAZATI has demonstrated a positive benefit-risk profile with accelerated approval based on the Phase 2 registration-enabling cohort of the KRYSTAL-1 study, evaluating KRAZATI 600 mg capsules administered orally twice daily in 116 patients with KRAS^{G12C}-mutated advanced NSCLC who previously received treatment with a platinum-based regimen and an immune checkpoint inhibitor. The primary efficacy endpoints were confirmed ORR and DOR as evaluated by blinded independent central review (BICR) according to response evaluation criteria in solid tumors (RECIST v1.1).

The trial demonstrated an ORR of 43% (95% CI: 34-53) with 80% (95% CI: 71-87) of patients achieving disease control. The median DOR was 8.5 months (95% CI: 6.2-13.8).

In a pooled efficacy analysis (n=132) including Phase 1/1b NSCLC and registrational Phase 2 NSCLC cohorts from the KRYSTAL-1 study evaluating *adagrasib* as a single agent at 600 mg capsules orally twice daily, *adagrasib* showed an ORR of 44% and a disease control rate of 81% based on BICR, a median DOR of 12.5 months (95% CI, 7.3-NE) and median overall survival of 14.1 months (94% CI, 9.2-19.2).

The safety profile of KRAZATI was evaluated in a pooled patient population with NSCLC and other solid tumors as a single agent at 600 mg orally twice daily in 366 patients enrolled in KRYSTAL-1 and KRYSTAL-12. The most common (≥ 25%) adverse reactions were nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, renal impairment, edema, dyspnea and decreased appetite. Permanent discontinuation of KRAZATI due to an adverse reaction occurred in 13% of patients.

Although KRAS^{G12C} is the most common KRAS mutation in NSCLC, patients have had limited options for the treatment of this debilitating and difficult-to-treat condition.[2,3]

"The approval of KRAZATI offers an effective therapy for patients with advanced NSCLC harboring the KRAS^{G12C} mutation. The positive ORR and DOR results, as observed in previously treated patients with NSCLC harboring the KRAS^{G12C} mutation, demonstrate the effectiveness of KRAZATI as an option for these difficult-to-treat patients," said Shirish M. Gadgeel, MD, chief of the Division of Hematology and Oncology, Department of Internal Medicine, Henry Ford Cancer Institute/Henry Ford Health System.

"KRAS^{G12C} in NSCLC is an area of high unmet need and new treatment options offer patients and our community new hope for survivorship," said Bonnie J. Addario, co-founder and board chair of the GO2 Foundation for Lung Cancer. "I'm pleased that patients have options, there's more awareness of this disease and we are all focused on improving the journeys of people living with KRAS^{G12C}-mutated NSCLC."

The Company partnered with Agilent and QIAGEN to develop blood- and tissue-based companion diagnostics (CDx), respectively, for KRAZATI that are now available. With tissue and blood modalities for companion diagnostics, patients have more flexibility, and clinicians have greater options for biomarker testing. These solutions help to personalize a patient's treatment path.

Mirati Therapeutics is launching Mirati & Me, a comprehensive program dedicated to supporting patients, caregivers and the oncology community including coverage and access, financial, educational and emotional support services. Learn more by visiting the Mirati & Me website or 1-844-647-2842.

For more information, visit KRAZATI.com.

About KRAZATI (*adagrasib*)

Mirati has risen to meet one of the most challenging mutations in cancer research by developing KRAZATI, a highly selective and potent oral small-molecule inhibitor of $KRAS^{G12C}$.

Intentionally designed to meet the challenge of $KRAS^{G12C}$, *adagrasib* is optimized to sustain target inhibition, an attribute that could be important to treat $KRAS^{G12C}$-mutated cancers, as the $KRAS^{G12C}$ protein regenerates every 24−48 hours.[4] *Adagrasib* has shown clinically to be a CNS penetrant, which may be important given that CNS metastases frequently occur in NSCLC and lead to poor prognosis.[5,6,7]

In the U.S., KRAZATI was reviewed by the FDA for Accelerated Approval (Subpart H), which allows for the approval of drugs that treat serious conditions, and that fill an unmet medical need based on surrogate endpoints. KRAZATI was reviewed under the FDA Real-Time Oncology Review (RTOR) pilot program, which aims to explore a more efficient review process that ensures safe and effective treatments are made available to patients as early as possible. Mirati submitted a Marketing Authorization Application (MAA) in the EU in May 2022. In 2021, *adagrasib* achieved Breakthrough Therapy Designation in the U.S. as a potential treatment for patients with NSCLC harboring the $KRAS^{G12C}$ mutation who have received at least one prior systemic therapy.

Adagrasib continues to be evaluated as monotherapy and in combination with other anti-cancer therapies in patients with advanced $KRAS^{G12C}$-mutated solid tumors, including NSCLC, colorectal cancer, and pancreatic cancer. For more information, visit Mirati.com/science.

Mirati has an Expanded Access Program (EAP) for *adagrasib* for the treatment of eligible patients with $KRAS^{G12C}$-mutated cancers, regardless of tumor type, including patients with treated or untreated CNS metastases, in the U.S. Learn more about the EAP at Mirati.com/expanded-access-policy.

KRAZATI (*adagrasib*) U.S. Indication

KRAZATI is indicated for the treatment of adult patients with $KRAS^{G12C}$-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial(s).

KRAZATI (*adagrasib*) Important Safety Information

WARNINGS AND PRECAUTIONS

Gastrointestinal Adverse Reactions

- In the pooled safety population, serious gastrointestinal adverse reactions observed were gastrointestinal obstruction in 1.6%, including 1.4% grade 3 or 4, gastrointestinal bleeding in 0.5% of patients, including 0.5% grade 3, and colitis in 0.3%, including 0.3% grade 3. In addition, nausea, diarrhea, or vomiting occurred in 89% of 366 patients, including 9% grade 3. Nausea, diarrhea, or vomiting led to dosage interruption or dose reduction in 29% of patients and permanent discontinuation of KRAZATI in 0.3%
- Monitor and manage patients using supportive care, including antidiarrheals, antiemetics, or fluid replacement, as indicated. Withhold, reduce the dose, or permanently discontinue KRAZATI based on severity

QTc Interval Prolongation

- KRAZATI can cause QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (eg, torsades de pointes) or sudden death
- In the pooled safety population, 6% of 366 patients with at least one post-baseline electrocardiogram (ECG) assessment had an average QTc ≥501 ms, and 11% of patients had an increase from baseline of QTc >60 msec. KRAZATI causes concentration-dependent increases in the QTc interval
- Avoid concomitant use of KRAZATI with other products with a known potential to prolong the QTc interval. Avoid use of KRAZATI in patients with congenital long QT syndrome and in patients with concurrent QTc prolongation
- Monitor ECGs and electrolytes prior to starting KRAZATI, during concomitant use, and as clinically indicated in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and in patients who are taking medications that are known to prolong the QT interval. Withhold, reduce the dose, or permanently discontinue KRAZATI, depending on severity

Hepatotoxicity

- KRAZATI can cause hepatotoxicity
- In the pooled safety population, hepatotoxicity occurred in 37%, and 7% were grade 3 or 4. A total of 32% of patients who received KRAZATI had increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST); 5% were grade 3 and 0.5% were grade 4. Increased ALT/AST leading to dose interruption or reduction occurred in 11% of patients. KRAZATI was discontinued due to increased ALT/AST in 0.5% of patients
- Monitor liver laboratory tests (AST, ALT, alkaline phosphatase, and total bilirubin) prior to the start of KRAZATI, and monthly for 3 months or as clinically indicated, with more frequent testing in patients who develop transaminase elevations.

Reduce the dose, withhold, or permanently discontinue KRAZATI based on severity

Interstitial Lung Disease /Pneumonitis

- KRAZATI can cause interstitial lung disease (ILD)/pneumonitis, which can be fatal. In the pooled safety population, ILD/pneumonitis occurred in 4.1% of patients, 1.4% were grade 3 or 4, and 1 case was fatal. The median time to first onset for ILD/pneumonitis was 12 weeks (range: 5 to 31 weeks). KRAZATI was discontinued due to ILD/pneumonitis in 0.8% of patients
- Monitor patients for new or worsening respiratory symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever). Withhold KRAZATI in patients with suspected ILD/pneumonitis and permanently discontinue KRAZATI if no other potential causes of ILD/pneumonitis are identified

Adverse Reactions

- The most common adverse reactions (≥25%) are nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, renal impairment, edema, dyspnea, decreased appetite

Females and Males of Reproductive Potential

- Infertility: Based on findings from animal studies, KRAZATI may impair fertility in females and males of reproductive potential

Please see Full Prescribing Information.

About the KRYSTAL-1 Study

KRYSTAL-1 is an open-label Phase 1/2 multiple-expansion cohort trial evaluating *adagrasib* as monotherapy and in combination with other anti-cancer therapies in patients with advanced solid tumors harboring the $KRAS^{G12C}$ mutation.

About $KRAS^{G12C}$ in NSCLC

Lung cancer is one of the most common cancers worldwide, accounting for 2.21 million new cases and 1.8 million deaths worldwide in 2020.[8] Lung cancer consists of NSCLC in approximately 85% of cases and small cell lung cancer (SCLC) in approximately 15% of cases.[9] $KRAS^{G12C}$ is the most common KRAS mutation in NSCLC, present in approximately 14% of patients with lung adenocarcinoma, and is a biomarker mutation of poor prognosis.[1,3]

Virtual Investor Event

Mirati Therapeutics will host a virtual Investor Event on December 13, 2022 at 8:00 a.m. EST / 5:00 a.m. PST, where Company executives will provide an overview of the recent FDA approval of KRAZATI.

Investors and the general public are invited to register and listen to a live webcast of the event through the "Investors and Media" section on Mirati.com. A replay of the event will be available shortly after the conclusion.

About Mirati Therapeutics, Inc.

Mirati Therapeutics, Inc. is a commercial-stage biotechnology company whose mission is to discover, design and deliver breakthrough therapies to transform the lives of patients with cancer and their loved ones. The company is relentlessly focused on bringing forward therapies that address areas of high unmet need, including lung cancer, and advancing a pipeline of novel therapeutics targeting the genetic and immunological drivers of cancer. Unified for patients, Mirati's vision is to unlock the science behind the promise of a life beyond cancer.

For more information about Mirati, visit us at Mirati.com or follow us on Twitter, LinkedIn and Facebook.

Forward Looking Statements

This press release contains forward-looking statements regarding the business of Mirati Therapeutics, Inc. ("Mirati"). Any statement describing Mirati's goals, expectations, financial or other projections, intentions or beliefs, development plans and the commercial potential of Mirati's drug development pipeline, including without limitation *adagrasib* (selective $KRAS^{G12C}$ inhibitor), *sitravatinib* (TAM receptor inhibitor), MRTX1719 (MTA-cooperative PRMT5 inhibitor), MRTX0902 (SOS1 inhibitor), and MRTX1133 (selective KRASG12D inhibitor), is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to risks and uncertainties, particularly those challenges inherent in the process of discovering, developing and commercialization of new drug products that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs.

Mirati's forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Mirati's forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Mirati. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Mirati's programs are described in additional detail in Mirati's quarterly reports on Form 10-Q and annual reports on Form 10-K, which are on file with the U.S. Securities and Exchange Commission (the "SEC") available at the SEC's Internet site (www.sec.gov). These forward-looking statements are made as of the date of this press release, and Mirati assumes no obligation to update the forward-looking statements, or to update the reasons why actual results could differ from those projected in the forward-looking statements, except as required by law.

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