U.S. Food and Drug Administration Approves Augtyro™ (repotrectinib), a Next-Generation Tyrosine Kinase Inhibitor (TKI), for the Treatment of Patients with NTRK-Positive Locally Advanced or Metastatic Solid Tumors

2024年 6月 13日

Augtyro *is the only FDA-approved treatment option for* NTRK*-positive tumors studied in both TKI-na* ï *ve and TKI-pretreated patients across solid tumors* , *demonstrating clinically meaningful response rates in the TRIDENT-1 trial*[1]

***This accelerated approval marks the second indication for* Augtyro *in the U.S.*[1]**

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has granted accelerated approval of *Augtyro*™(repotrectinib) for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase *(NTRK)* gene fusion, are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy.[1] The approval is based on results from the Phase 1/2 TRIDENT-1 study, which evaluated *Augtyro* in adult patients with *NTRK*-positive solid tumors.[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.[1]

"*NTRK* fusion-positive tumors can present challenges in the clinical setting, which is why it is important that we have additional treatment options for these patients," said Alexander Drilon, MD, TRIDENT-1 global trial lead and Chief of the Early Drug Development Service at Memorial Sloan Kettering Cancer Center.[2,3] "The FDA approval of repotrectinib adds an important tool to our toolbox, offering oncologists a next-generation TKI that can be used across a broad range of *NTRK* fusion-positive solid tumors for both TKI-naïve and TKI-pretreated patients."[1]

The TRIDENT-1 trial included both TKI-naïve (n=40) and TKI-pretreated (n=48) patients with *NTRK*-positive locally advanced/metastatic solid tumors collectively representing 15 different types of cancer.[1] In TKI-naïve patients, with a median follow up of 17.8 months, 58% (95% CI: 41 to 73) had a confirmed objective response rate (cORR); of those, 43% experienced partial responses (PR) and 15% had complete responses (CR).[1,4] Of the TKI-naïve responding patients, 83% were still in response at one year with *Augtyro*. The median duration of response (mDOR) was not yet reached. In TKI-pretreated patients, with a median follow up of 20.1 months, the cORR was 50% (95% CI: 35 to 65); of those, 50% experienced PR and no patients achieved CR.[1,4] Additionally, 42% of TKI-pretreated responding patients were still in response at one year with *Augtyro*.[1] The mDOR was 9.9 months (95% CI: 7.4 to 13.0).[1] Among those who had measurable central nervous system (CNS) metastases at baseline, intracranial response was observed in 2 out of 2 TKI-naïve patients and in 3 out of 3 TKI-pretreated patients.[1]

Augtyro is associated with the following Warnings & Precautions: central nervous system (CNS) effects, interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, myalgia with creatine phosphokinase elevation, hyperuricemia, skeletal fractures, and embryo-fetal toxicity.[1] Please see Important Safety Information below.

"Today's FDA approval of *Augtyro* for patients with *NTRK*-positive tumors adds to its indication in *ROS1*-positive NSCLC, showing its clinical value for more people across multiple genetic markers," said Nick Botwood, senior vice president of Medical Oncology at Bristol Myers Squibb. [1] "Previously, there was not an FDA approved treatment option for *NTRK*-positive cancers that was studied in both TKI-naïve and TKI-pretreated patients across solid tumors. This milestone helps address this area of unmet need and builds on Bristol Myers Squibb's longstanding legacy of bringing innovations to individuals who are facing cancer and urgently seeking new treatment options."

"Cancer can be frightening regardless of the type, but having a rare gene fusion driving it can be especially stressful and isolating," said Susan Spinosa, president and patient co-founder of NTRKers, a patient advocacy group. "It's exciting to know that there's a new targeted therapy option for patients with *NTRK*-positive gene fusions, as this may offer hope to patients and their loved ones navigating this difficult journey."

Based on clinical and pharmacokinetic data, the recommended dose for *Augtyro* for pediatric patients aged 12 years and older is the same as for adults, 160 mg orally once daily for 14 days followed by 160 mg twice daily until disease progression or unacceptable toxicity.[1] The safety and effectiveness of *Augtyro* have not been established in pediatric patients younger than 12 years of age with solid tumors who have an *NTRK* gene fusion.[1] This is the second indication for *Augtyro* in the U.S., following its full approval for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC in November 2023.[1]

Disclosure: Dr. Drilon has provided advisory and speaking services to Bristol Myers Squibb.

About TRIDENT-1

TRIDENT-1 is a global, multicenter, single-arm, open-label, multi-cohort Phase 1/2 clinical trial evaluating the safety, tolerability, pharmacokinetics and anti-tumor activity of *Augtyro* in patients with locally advanced or metastatic neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion-positive (*NTRK1/2/3)* solid tumors.[1,5] The trial excludes patients with symptomatic brain metastases, among other exclusion criteria.[1] Phase 1 of the trial

included the dose escalation that determined the recommended Phase 2 dose.[5]

Phase 2 of the trial in *NTRK*-positive locally advanced/metastatic solid tumor cohorts has a primary endpoint of objective response rate (ORR) as assessed by Blinded Independent Central Review (BICR).[5] Among others, key secondary endpoints include duration of response (DOR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as assessed by BICR, and intracranial response in patients with measurable brain metastases.[5]

Select Safety Profile from TRIDENT-1

The safety profile for *Augtyro* was evaluated in 426 patients who received *Augtyro* in the TRIDENT-1 pivotal trial.[1] Permanent discontinuation of *Augtyro* due to an adverse reaction occurred in 7% of patients.[1] There were no specific adverse reactions that accounted for ≥1% of permanent discontinuations. *Augtyro* dosage was interrupted due to an adverse reaction in 50% of patients, and dose reductions due to an adverse reaction occurred in 38% of patients.[1] Serious adverse reactions occurred in 35% of patients who received *Augtyro.* [1] Serious adverse reactions in ≥2% of patients included pneumonia (6.3%), dyspnea (3.1%), pleural effusion (2.8%) and hypoxia (2.6%).[1] Fatal adverse reactions occurred in 3.5% of patients who received *Augtyro,* including pneumonia, pneumonia aspiration, cardiac arrest, sudden cardiac death, cardiac failure, hypoxia, dyspnea, respiratory failure, tremor, and disseminated intravascular coagulation.[1] The most common (≥20%) adverse reactions were dizziness (65%), dysgeusia (54%), peripheral neuropathy (49%), constipation (38%), dyspnea (30%), fatigue (30%), ataxia (28%), cognitive impairment (25%), muscular weakness (20%) and nausea (20%).[1] Grade 3 dizziness occurred in 2.8% of patients.[1]

About *NTRK*-Positive Solid Tumors

Neurotrophic tropomyosin receptor kinase (*NTRK*) are a family of receptors involved in neural development.[6] An *NTRK* gene fusion is an alteration that occurs when a piece of the chromosome containing the *NTRK* gene breaks off and joins with a gene on another chromosome.[7] These fusions lead to abnormal proteins, which may cause cancer cells to grow.[7] While *NTRK* gene fusions are rare in patients with solid tumors, testing for *NTRK* gene fusions allows for the identification of patients who may benefit from TRK inhibitor therapy.[8,9,10,11]

INDICATIONS

AUGTYRO™ is indicated for the treatment of:

- adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC)
- adult and pediatric patients 12 years of age and older with solid tumors that:
  - have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion,
  - are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
  - have progressed following treatment or have no satisfactory alternative therapy.

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

IMPORTANT SAFETY INFORMATION

Warnings & Precautions

Central Nervous System Adverse Reactions

- Among the 426 patients who received AUGTYRO in the Study TRIDENT-1, a broad spectrum of central nervous system (CNS) adverse reactions including dizziness, ataxia, and cognitive disorders occurred in 77% of patients with Grade 3 or 4 events occurring in 4.5%.
- Dizziness, including vertigo, occurred in 65%; Grade 3 dizziness occurred in 2.8% of patients. The median time to onset was 7 days (1 day to 1.4 years). Dose interruption was required in 9% of patients, and 11% required dose reduction of AUGTYRO due to dizziness.
- Ataxia, including gait disturbance and balance disorder, occurred in 28% of patients; Grade 3 ataxia occurred in 0.5%. The median time to onset was 15 days (1 day to 1.4 years). Dose interruption was required in 5% of patients, 8% required dose reduction and one patient (0.2%) permanently discontinued AUGTYRO due to ataxia.
- Cognitive impairment, including memory impairment and disturbance in attention, occurred in 25% of patients. Cognitive impairment included memory impairment (15%), disturbance in attention (12%), and confusional state (2%); Grade 3 cognitive impairment occurred in 0.9% of patients. The median time to onset of cognitive disorders was 37 days (1 day to 1.4 years). Dose interruption was required in 2% of patients, 2.1% required dose reduction and 0.5% permanently discontinued AUGTYRO due to cognitive adverse reactions.
- Mood disorders occurred in 6% of patients. Mood disorders occurring in >1% of patients included anxiety (2.6%); Grade 4 mood disorders (mania) occurred in 0.2% of patients. Dose interruption was required in 0.2% of patients and 0.2% required a dose reduction due to mood disorders.
- Sleep disorders including insomnia and hypersomnia occurred in 18% of patients. Sleep disorders observed in >1% of patients were somnolence (9%), insomnia (6%) and hypersomnia (1.6%). Dose interruption was required in 0.7% of patients, and 0.2% required a dose reduction due to sleep disorders.
- The incidences of CNS adverse reactions reported were similar in patients with and without CNS metastases.
- Advise patients not to drive or use machines if they are experiencing CNS adverse reactions. Withhold and then resume at

same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity.

Interstitial Lung Disease (ILD)/Pneumonitis

- Among the 426 patients treated with AUGTYRO, ILD/pneumonitis (pneumonitis [2.8%] and ILD [0.2%]) occurred in 3.1%; Grade 3 ILD/pneumonitis occurred in 1.2%. The median time to onset was 45 days (19 days to 0.9 years). Dose interruption was required in 1.4% of patients, 0.5% required dose reduction, and 1.1% permanently discontinued AUGTYRO due to ILD/pneumonitis.
- Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold AUGTYRO in patients with suspected ILD/pneumonitis and permanently discontinue AUGTYRO if ILD/pneumonitis is confirmed.

Hepatotoxicity

- Among the 426 patients treated with AUGTYRO, increased alanine transaminase (ALT) occurred in 38%, increased aspartate aminotransferase (AST) occurred in 41%, including Grade 3 or 4 increased ALT in 3.3% and increased AST in 2.9%. The median time to onset of increased ALT or AST was 15 days (range: 1 day to 1.9 years). Increased ALT or AST leading to dose interruptions or reductions occurred in 2.8% and 1.2% of patients, respectively. Hyperbilirubinemia leading to dose interruptions occurred in 0.5%.
- Monitor liver function tests, including ALT, AST and bilirubin, every 2 weeks during the first month of treatment, then monthly thereafter and then as clinically indicated. Withhold and then resume at same or reduced dose upon improvement or permanently discontinue AUGTYRO based on the severity.

Myalgia with Creatine Phosphokinase (CPK) Elevation

- AUGTYRO can cause myalgia with or without creatine phosphokinase (CPK) elevation. Among the 426 patients treated with AUGTYRO, myalgia occurred in 13% of patients, with Grade 3 in 0.7%. Median time to onset of myalgia was 19 days (range: 1 day to 2 years). Concurrent increased CPK within a 7-day window was observed in 3.7% of patients. AUGTYRO was interrupted in one patient with myalgia and concurrent CPK elevation.
- Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor serum CPK levels during AUGTYRO treatment and monitor CPK levels every 2 weeks during the first month of treatment and as needed in patients reporting unexplained muscle pain, tenderness, or weakness. Initiate supportive care as clinically indicated. Based on severity, withhold and then resume AUGTYRO at same or reduced dose upon improvement.

Hyperuricemia

- Among the 426 patients treated with AUGTYRO, 21 patients (5%) experienced hyperuricemia reported as an adverse reaction, 0.7% experienced Grade 3 or 4 hyperuricemia. One patient without pre-existing gout required urate-lowering medication.
- Monitor serum uric acid levels prior to initiating AUGTYRO and periodically during treatment. Initiate treatment with urate-lowering medications as clinically indicated. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity.

Skeletal Fractures

- Among 426 adult patients who received AUGTYRO, fractures occurred in 2.3%. Fractures involved the ribs (0.5%), feet (0.5%), spine (0.2%), acetabulum (0.2%), sternum (0.2%), and ankles (0.2%). Some fractures occurred at sites of disease and prior radiation therapy. The median time to fracture was 71 days (range: 31 days to 1.4 years). AUGTYRO was interrupted in 0.3% of patients.
- Of 26 evaluable patients in an ongoing open-label study in pediatric patients, fractures occurred in one 12-year-old patient (ankle/foot) and one 10-year-old patient (stress fracture). AUGTYRO was interrupted in both patients. AUGTYRO is not approved for use in pediatric patients less than 12 years of age.
- Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures. There are no data on the effects of AUGTYRO on healing of known fractures and risk of future fractures.

Embryo-Fetal Toxicity

- Based on literature reports in humans with congenital mutations leading to changes in tropomyosin receptor tyrosine kinase (TRK) signaling, findings from animal studies, and its mechanism of action, AUGTYRO can cause fetal harm when administered to a pregnant woman.
- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with AUGTYRO and for 2 months following the last dose, since AUGTYRO can render some hormonal contraceptives ineffective.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AUGTYRO and for 4 months after the last dose.

Adverse Reactions

- The safety of AUGTYRO was evaluated in 426 patients in TRIDENT-1. The most common adverse reactions (≥20%) were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness, and nausea.

Drug Interactions

Effects of Other Drugs on AUGTYRO

Strong and Moderate CYP3A Inhibitors

- Avoid concomitant use with strong or moderate CYP3A inhibitors. Concomitant use of AUGTYRO with a strong or a moderate CYP3A inhibitor may increase repotrectinib exposure, which may increase the incidence and severity of adverse reactions of AUGTYRO. Discontinue CYP3A inhibitors for 3 to 5 elimination half-lives of the CYP3A inhibitor prior to initiating AUGTYRO.

P-gp Inhibitors

- Avoid concomitant use with P-gp inhibitors. Concomitant use of AUGTYRO with a P-gp inhibitor may increase repotrectinib exposure, which may increase the incidence and severity of adverse reactions of AUGTYRO.

Strong and Moderate CYP3A Inducers

- Avoid concomitant use with strong or moderate CYP3A inducers. Concomitant use of AUGTYRO with a strong or moderate CYP3A inducer may decrease repotrectinib plasma concentrations, which may decrease efficacy of AUGTYRO.

Effects of AUGTYRO on other Drugs

Certain CYP3A4 Substrates

- Avoid concomitant use unless otherwise recommended in the Prescribing Information for CYP3A substrates, where minimal concentration changes can cause reduced efficacy. If concomitant use is unavoidable, increase the CYP3A4 substrate dosage in accordance with approved product labeling.
- Repotrectinib is a CYP3A4 inducer. Concomitant use of repotrectinib decreases the concentration of CYP3A4 substrates, which can reduce the efficacy of these substrates.

Contraceptives

- Repotrectinib is a CYP3A4 inducer, which can decrease progestin or estrogen exposure to an extent that could reduce the effectiveness of hormonal contraceptives.
- Avoid concomitant use of AUGTYRO with hormonal contraceptives. Advise females of childbearing potential to use an effective nonhormonal contraceptive.

Please see U.S. Full Prescribing Information for AUGTYRO .

Bristol Myers Squibb: Creating a Better Future for People with Cancer

Bristol Myers Squibb is inspired by a single vision — transforming patients' lives through science. The goal of the company's cancer research is to deliver medicines that offer each patient a better, healthier life and to make cure a possibility. Building on a legacy across a broad range of cancers that have changed survival expectations for many, Bristol Myers Squibb researchers are exploring new frontiers in personalized medicine and, through innovative digital platforms, are turning data into insights that sharpen their focus. Deep understanding of causal human biology, cutting-edge capabilities and differentiated research platforms uniquely position the company to approach cancer from every angle.

Cancer can have a relentless grasp on many parts of a patient's life, and Bristol Myers Squibb is committed to taking actions to address all aspects of care, from diagnosis to survivorship. As a leader in cancer care, Bristol Myers Squibb is working to empower all people with cancer to have a better future.

About Bristol Myers Squibb's Patient Access Support

Bristol Myers Squibb remains committed to providing assistance so that cancer patients who need our medicines can access them and expedite time to therapy.

BMS Access Support®, the Bristol Myers Squibb patient access and reimbursement program, is designed to help appropriate patients initiate and maintain access to BMS medicines during their treatment journey. BMS Access Support offers benefit investigation, prior authorization assistance, as well as co-pay assistance for eligible, commercially insured patients. More information about our access and reimbursement support can be obtained by calling BMS Access Support at 1-800-861-0048 or by visiting www.bmsaccesssupport.com.

About Bristol Myers Squibb

Bristol Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients

prevail over serious diseases. For more information about Bristol Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube, Facebook and Instagram.

Cautionary Statement Regarding Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, whether Augtyro™ (repotrectinib) for the indication described in this release will be commercially successful, that any marketing approvals, if granted, may have significant limitations on their use, and that continued approval of Augtyro for such indication described in this release may be contingent upon verification and description of clinical benefit in confirmatory trials. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol Myers Squibb's business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2023, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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Source: Bristol Myers Squibb