RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Retevmo™
Generic Name	selpercatinib
Drug Manufacturer	Eli Lilly and Company

New Drug Approval

FDA Approval Date: May 08, 2020
Review Designation: Orphan
Type of Review: New Drug Application 213246

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

NSCLC is a disease in which malignant cancer cells form in the tissues of the lung. It is the most common type of lung cancer with up to 90% of all lung carcinomas falling into the non-small cell category. NSCLC occurs when healthy cells become abnormal and grow rapidly. One danger of this form of cancer is that there's a high likelihood that the cancer cells will spread from the lungs to other organs and body parts. Cancer metastasis consists of a sequential series of events, and MET exon 14 skipping is recognized as a critical event for metastasis.

Worldwide, lung cancer occurred in approximately 1.8 million patients in 2012 and caused an estimated 1.6 million deaths. In the United States, lung cancer occurs in approximately 230,000 patients and causes over 135,000 deaths annually.

Both the absolute and relative frequency of lung cancer have risen dramatically. Around 1953, lung cancer became the most common cause of cancer deaths in men, and in 1985, it became the leading cause of cancer deaths in women. Lung cancer deaths have begun to decline in both men and women, reflecting a decrease in smoking.

The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or pulmonary parenchyma. Approximately 95 percent of all lung cancers are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). This distinction is essential for staging, treatment, and prognosis. Other cell types comprise approximately 5 percent of malignancies arising in the lung.

Efficacy

The FDA approved Retevmo on the results of a clinical trial involving patients with each of the three types of tumors. During the clinical trial, patients received 160 mg Retevmo orally twice daily until disease progression or unacceptable toxicity. The major efficacy outcome measures were overall response rate (ORR), which reflects the percentage of patients that had a certain amount of tumor shrinkage, and duration of response (DOR).

Efficacy for NSCLC was evaluated in 105 adult patients with RET fusion-positive NSCLC who were previously treated with platinum chemotherapy. The ORR for the 105 patients was 64%. For 81% of patients who had a response to the treatment, their response lasted at least six months. Efficacy was also evaluated in 39 patients with RET fusion-positive NSCLC who had never undergone treatment. The ORR for these patients was 84%. For 58% of patients who had a response to the treatment, their response lasted at least six months.Efficacy for MTC in adults and pediatric patients was evaluated in those 12 years of age and older with RET-mutant MTC. The study enrolled 143 patients with advanced or metastatic RET-mutant MTC who had been previously treated with cabozantinib, vandetanib or both (types of chemotherapy), and patients with advanced or metastatic RET-mutant MTC who had not received

prior treatment with cabozantinib or vandetanib. The ORR for the 55 previously treated patients was 69%. For 76% of patients who had a response to the treatment, their response lasted at least six months. Efficacy was also evaluated in 88 patients who had not been previously treated with an approved therapy for MTC. The ORR for these patients was 73%. For 61% of patients who had a response to the treatment, their response lasted at least six months. Efficacy for RET fusion-positive thyroid cancer was evaluated in adults and pediatric patients 12 years of age and older. The study enrolled 19 patients with RET fusion-positive thyroid cancer who were radioactive iodine-refractory (RAI, if an appropriate treatment option) and had received another prior systemic treatment, and eight patients with RET fusion-positive thyroid cancer who were RAI-refractory and had not received any additional therapy. The ORR for the 19 previously treated patients was 79%. For 87% of patients who had a response to the treatment, their response lasted at least six months. Efficacy was also evaluated in eight patients who had not received therapy other than RAI. The ORR for these patients was 100%. For 75% of patients who had a response to the treatment, their response lasted at least six months.

Safety

ADVERSE EVENTS

The most common adverse reactions, including laboratory abnormalities, (≥ 25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

WARNINGS & PRECAUTIONS

- Hepatotoxicity: Monitor ALT and AST prior to initiating RETEVMO,every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue RETEVMO based on severity.
- Hypertension: Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure (BP) prior to initiating RETEVMO. Monitor BP after 1 week, at least monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue RETEVMO based on severity.
- QT Interval Prolongation: Monitor patients who are at significant risk of developing QTc prolongation. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment. Monitor QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on severity.
- Hemorrhagic Events: Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage.
- Hypersensitivity: Withhold RETEVMO and initiate corticosteroids. Upon resolution, resume at a reduced dose and increase dose by 1 dose level each week until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper.
- Risk of Impaired Wound Healing: Withhold RETEVMO for at least 7 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 RETEVMO after resolution of wound healing complications has not been established.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the possible risk to the fetus and to use effective contraception.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

Selpercatinib is a kinase inhibitor. Selpercatinib inhibited wild-type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC50 values ranging from 0.92 nM to 67.8 nM. In other enzyme assays, selpercatinib also inhibited FGFR 1, 2, and 3 at higher concentrations that were still clinically achievable. In cellular assays, selpercatinib inhibited RET at approximately 60-fold lower concentrations than FGFR1 and 2 and approximately 8-fold lower concentration than VEGFR3. Certain point mutations in RET or chromosomal rearrangements involving in-frame fusions of RET with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation of tumor cell lines. In in vitro and in vivo tumor models, selpercatinib demonstrated anti-tumor activity in cells harboring constitutive activation of RET protein resulting from gene fusions and mutations, including CCDC6-RET, KIF5B-RET, RET V804M, and RET M918T. In addition, selpercatinib showed Reference ID: 4605720 anti-tumor activity in mice intracranially implanted with a patient-derived RET fusion positive tumor.

Dose & Administration

ADULTS

Recommended dosage in adults and pediatric patients 12 years of age or older is based on weight.

- Less than 50 kg: 120 mg orally twice daily
- 50 kg or greater: 160 mg orally twice daily

PEDIATRICS

Recommended dosage in adults and pediatric patients 12 years of age or older is based on weight.

- Less than 50 kg: 120 mg orally twice daily
- 50 kg or greater: 160 mg orally twice daily

GERIATRICS

Of 702 patients who received RETEVMO, 34% (239 patients) were ≥ 65 years of age and 10% (67 patients) were ≥ 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥ 65 years of age and younger patients.

RENAL IMPAIRMENT

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] > 30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease.

HEPATIC IMPAIRMENT

Reduce the dose when administering RETEVMO to patients with severe [total bilirubin greater than 3 to 10 times upper limit of normal (ULN) and any AST] hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment

NEW DRUG APPROVAL

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 40 mg, 80 mg