NEW DRUG APPROVAL

Brand Name	Exkivity™
Generic Name	mobocertinib
Drug Manufacturer	Takeda Pharmaceuticals America, Inc

New Drug Approval

FDA Approval Date: September 15, 2021
Review Designation: Priority, Orphan
Type of Review: Type 1 - New Molecular Entity; New Drug Application (NDA): 215310
Dispensing Restrictions: Limited Distribution, Speciality only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

There are 2 main subtypes of lung cancer: small cell lung cancer and non–small cell lung cancer (NSCLC). According to estimates from the American Cancer Society, NSCLC accounts for approximately 80%–85% of all lung cancer cases; only around 2%–3% of patients have NSCLC with the epidermal growth factor receptor (*EGFR*) exon 20 insertion genetic mutation.

An estimated 1.8 million people are diagnosed with lung cancer worldwide each year. Non–small cell lung cancer (NSCLC) is the most common type of lung cancer; it accounts for about 85% of all lung cancer diagnoses.

Approximately 2%–3% of patients have EGFR exon 20 insertion mutations, which are the third most common type of EGFR mutation. Patients with the EGFR exon 20 insertion mutation have a worse prognosis than those with other EGFR mutations.

Each year, an estimated 2000–4000 people in the United States are diagnosed with an EGFR exon 20 insertion mutation. Tumors with the EGFR exon 20 mutation are more aggressive than other types of EGFR tumor mutations. Patients with NSCLC with EGFR exon 20 insertion mutations are currently treated with chemotherapy, immunotherapy, and tyrosine kinase inhibitors (TKIs) approved for other types of EGFR mutations.

Efficacy

Exkivity™ efficacy was evaluated in a pooled subset of patients with EGFR exon 20 insertion mutation–positive metastatic or locally advanced NSCLC whose disease had progressed on or after platinum-based chemotherapy.

The accelerated approval of Exkivity™ was based on results of a 3-part, open-label, Phase 1/2 dose-escalation/expansion and extension trial (NCT02716116) with 7 cohorts. The trial demonstrated a confirmed overall response rate (ORR) of 28% per independent review committee (IRC) (35% per investigator) and a median duration of response (DOR) of 17.5 months per IRC, as well as a median overall survival of 24 months. The median progression-free survival was 7.3 months per IRC.

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Study Population	**Efficacy Population:** 114 adult male and female patients with histologically or cytologically confirmed locally advanced (and not a candidate for definitive therapy) or metastatic NSCLC disease (Stage IIIB or IV) or other solid tumors and *EGFR* exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. • Median age: 60 years (range, 27–84 years) • 66% female • 60% Asian, 37% White, 3% Black • Median number of prior therapies: 2 (range, 1–7) • 75% had ECOG performance status of 1 at baseline • 71% never smoked • 99% had metastatic disease • 98% had adenocarcinoma histology • 35% had brain metastases • 43% received prior immunotherapy **Safety Population (pooled):** 256 adult male and female patients, including 114 patients with *EGFR* exon 20 insertion mutation–positive locally advanced or metastatic NSCLC and 96 patients from the EXCLAIM safety cohort, who had other solid tumors. • 34% had brain metastases • 60% were exposed for ≥6 months • 14% were exposed for >1 year **Key exclusion criteria:** Patients with a history of ILD, drug-related pneumonitis, radiation pneumonitis requiring steroid treatment; significant, uncontrolled, active CVD; or prolonged QTc interval were not eligible for the study.
Interventions	All patients received Exkivity™ 160 mg once daily until disease progression or intolerable toxicity.
Endpoints	• **Primary endpoint:** Confirmed ORR according to RECIST v1.1 as evaluated by BICR. • **Key secondary endpoints:** Safety, tolerability, PK, efficacy.

Table 1. AP32788-15-101 (NCT02716116): Study Design Summary

Efficacy Results

Exkivity™ Efficacy **Results**

	Exkivity™ **(N = 114)**
ORR[a] (95% CI)	28% (20, 37) [b]
DOR	
Median, months[c] (95% CI)	17.5 (7.4, 20.3)
Patients with DOR ≥6 months[d]	59%

- In addition to the efficacy results summarized above, patients in the trial lived a median of 24 months with a median follow-up of 14 months.

Safety Results

- The safety profile observed was manageable and consistent with previous findings.
- The most common TRAEs (≥20%) in PPPs were diarrhea (91%), rash (45%), paronychia (38%), decreased appetite (35%), nausea (34%), dry skin (31%), and vomiting (30%).
- The only Grade ≥3 TRAE (≥5%) was diarrhea (21%).
- AEs leading to discontinuation in >2% were diarrhea (4%) and nausea (4%).

Abbreviations: AE, adverse event; BICR, blinded independent central review; CBR, clinical benefit rate. CI, confidence interval; **CVD**, cardiovascular disease; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PPP, platinum-pretreated patients; QTc, heart rate–corrected QT; RECIST, Response Evaluation Criteria in Solid Tumors; TRAE, treatment-related adverse event.

a. Per BICR.
b. All responses were partial responses.
c. Kaplan-Meier estimate using confirmed responses only.
d. Based on observed duration of response.

Safety

ADVERSE EVENTS

The most common (>20%) adverse reactions are diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.

WARNINGS & PRECAUTIONS

- **Interstitial Lung Disease (ILD)/Pneumonitis:** Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold Exkivity™ in patients with suspected ILD/pneumonitis and permanently discontinue Exkivity™ if ILD/pneumonitis is confirmed.
- **Cardiac Toxicity:** Monitor cardiac function, including left ventricular ejection fraction, at baseline and during treatment. Withhold, resume at reduced dose, or permanently discontinue based on severity.
- **Diarrhea:** Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Monitor electrolytes and advise patients to start an antidiarrheal agent at first episode of diarrhea and to increase fluid and electrolyte intake. Withhold, reduce the dose, or permanently discontinue Exkivity™ based on the severity.
- **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

Mobocertinib is a kinase inhibitor of the epidermal growth factor receptor (EGFR) that irreversibly binds to and inhibits EGFR exon 20 insertion mutations at lower concentrations than wild type (WT) EGFR. Two pharmacologically active metabolites (AP32960 and AP32914) with similar inhibitory profiles to mobocertinib have been identified in the plasma after oral administration of mobocertinib. In vitro, mobocertinib also inhibited the activity of other EGFR family members (HER2 and HER4) and one additional kinase (BLK) at clinically relevant concentrations (IC50 value <2nM).
In cultured cell models, mobocertinib inhibited the proliferation of cells driven by different EGFR exon 20 insertion mutation variants at 1.5- to 10-fold lower concentrations than WT-EGFR signaling inhibition.
In animal tumor implantation models, mobocertinib exhibited anti-tumor activity against xenografts with the EGFR exon 20 insertions NPH or ASV.

Dose & Administration

ADULTS

Recommended Dosage: 160 mg orally once daily, with or without food.

PEDIATRICS

The safety and effectiveness of Exkivity™ in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

The recommended dosage of Exkivity™ has not been established for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2).

HEPATIC IMPAIRMENT

The recommended dosage of Exkivity™ has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 40 mg.