ALUNBRIG™
BRIGATINIB
30 mg TABLETS

Now Approved for Patients With ALK+ Metastatic NSCLC Who Have Progressed on or Are Intolerant to Crizotinib

Takeda Oncology is proud to announce the FDA approval of ALUNBRIG™ (brigatinib), a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

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

The FDA approval of ALUNBRIG was primarily based on results from the pivotal Phase 2 ALTA (**A**LK in **L**ung Cancer **T**rial of **A**P26113) trial of brigatinib in adults. This ongoing, two-arm, open-label, multicenter trial enrolled 222 patients with locally advanced or metastatic ALK+ NSCLC who had progressed on crizotinib. Patients received either 90 mg of ALUNBRIG once daily (n=112) or 180 mg once daily following a 7-day lead-in of 90 mg once daily (n=110). The major efficacy outcome measure was confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included Investigator-assessed ORR, duration of response (DOR), intracranial ORR, and intracranial DOR.

The recommended dosing regimen for ALUNBRIG is 90 mg orally once daily for the first 7 days. If 90 mg is tolerated during the first 7 days, increase the dose to 180 mg orally once daily.

With a median follow-up of 8 months (range: 0.1-20.2), efficacy data are as follows:

ALTA Efficacy Results

EFFICACY PARAMETER	IRC ASSESSMENT		INVESTIGATOR ASSESSMENT	
	90 mg once daily (n=112)	90→180 mg once daily (n=110)	90 mg once daily (n=112)	90→180 mg once daily (n=110)
Overall Response Rate (95% CI)	48% (39-58)	53% (43-62)	45% (35-54)	54% (44-63)
Complete Response, n (%)	4 (3.6)	5 (4.5)	1 (0.9)	4 (3.6)
Partial Response, n (%)	50 (45)	53 (48)	49 (44)	55 (50)
Duration of Response, median in months (95% CI)	13.8 (7.4-NE)	13.8 (9.3-NE)	13.8 (5.6-13.8)	11.1 (9.2-13.8)

CI = Confidence Interval; NE = Not Estimable

IRC assessment of intracranial efficacy is shown below:

Intracranial Objective Response in Patients With Measurable Brain Metastases in ALTA

EFFICACY PARAMETER	IRC ASSESSMENT	
	90 mg once daily (n=26)	90→180 mg once daily (n=18)
Intracranial Overall Response Rate, (95 % CI)	42% (23-63)	67% (41-87)
Complete Response, n (%)	2 (7.7)	0
Partial Response, n (%)	9 (35)	12 (67)
Duration of Intracranial Response, median (months) (range)	NE (1.9+ - 9.2+)	5.6 (1.9+ - 9.2+)

CI = Confidence Interval; NE = Not Estimable

Among the 23 patients who exhibited an intracranial response, 78% of patients in the 90 mg arm and 68% of patients in the 90→180 mg arm maintained a response for at least 4 months.

Important Safety Information

The warnings and precautions for ALUNBRIG are: interstitial lung disease (ILD)/pneumonitis, hypertension, bradycardia, visual disturbance, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevation, hyperglycemia and embryo-fetal toxicity. For additional information, see Important Safety Information.

Serious adverse reactions occurred in 38% of patients in the 90 mg arm and 40% of patients in the 90→180 mg arm. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg arm, and 7.3% in the 90→180 mg arm) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg arm and 7.3% in the 90→180 mg arm). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

At the recommended dosing regimen, the most common adverse reactions (≥25%) with ALUNBRIG were nausea, diarrhea, fatigue, cough, and headache.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease (ILD)/Pneumonitis: Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG. In Trial ALTA (ALTA), ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90 → 180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily). Adverse reactions consistent with possible ILD/pneumonitis occurred early (within 9 days of initiation of ALUNBRIG; median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%. Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

Hypertension: In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90 → 180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall. Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension. Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

Bradycardia: Bradycardia can occur with ALUNBRIG. In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90 → 180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided. For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

Visual Disturbance: In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients treated with ALUNBRIG in the 90 mg group and 10% of patients in the 90 → 180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90 → 180 mg group. Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances.

Creatine Phosphokinase (CPK) Elevation: In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90 mg → 180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90 → 180 mg group. Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90 → 180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Pancreatic Enzyme Elevation: In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90 → 180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90 → 180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90 → 180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90 → 180 mg group. Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Hyperglycemia: In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG. Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

ALUNBRIG™
BRIGATINIB
30 mg TABLETS

Important Safety Information

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

ADVERSE REACTIONS

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90 → 180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90 → 180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90 → 180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

The most common adverse reactions (≥25%) in the 90 mg group were nausea (33%), fatigue (29%), headache (28%), and dyspnea (27%) and in the 90 → 180 mg group were nausea (40%), diarrhea (38%), fatigue (36%), cough (34%), and headache (27%).

DRUG INTERACTIONS

CYP3A Inhibitors: Avoid concomitant use of ALUNBRIG with strong CYP3A inhibitors. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose of ALUNBRIG.

CYP3A Inducers: Avoid concomitant use of ALUNBRIG with strong CYP3A inducers.

CYP3A Substrates: Coadministration of ALUNBRIG with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates.

USE IN SPECIFIC POPULATIONS

Pregnancy: ALUNBRIG can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus.

Lactation: Advise lactating women not to breastfeed during treatment with ALUNBRIG and for 1 week following the final dose.

Females and Males of Reproductive Potential:

Contraception: Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility: ALUNBRIG may cause reduced fertility in males.

Pediatric Use: The safety and efficacy of ALUNBRIG in pediatric patients have not been established.

Geriatric Use: Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 222 patients in ALTA, 19.4% were 65-74 years and 4.1% were 75 years or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 and younger patients.

Hepatic or Renal Impairment: No dose adjustment is recommended for patients with mild hepatic impairment or mild or moderate renal impairment. The safety of ALUNBRIG in patients with moderate or severe hepatic impairment or severe renal impairment has not been studied.

Please see accompanying full Prescribing Information for ALUNBRIG on the following pages.

We hope you share our excitement over the approval of this important new therapy.
To learn more about ALUNBRIG, please visit **www.ALUNBRIG.com**.

Takeda
ONCOLOGY