ALUNBRIG® (brigatinib) FOR FIRST-LINE USE IN ALK+ METASTATIC NSCLC

INDICATION

ALUNBRIG® (brigatinib) is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

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 the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), ILD/pneumonitis occurred in 5.1% of patients receiving ALUNBRIG. ILD/pneumonitis occurred within 8 days of initiation of ALUNBRIG in 2.9% of patients, with Grade 3 to 4 reactions occurring in 2.2% of patients. In Trial 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 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.

ALK+, anaplastic lymphoma kinase-positive; FDA, Food and Drug Administration.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

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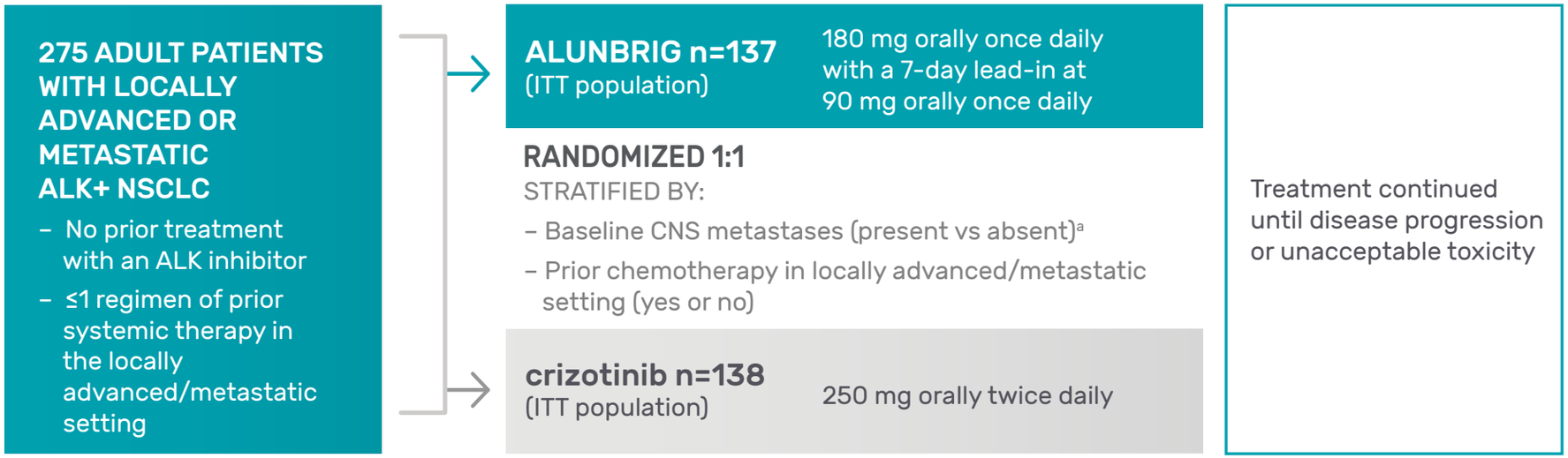
TABLETS

ALTA 1L: A PHASE 3, RANDOMIZED, OPEN-LABEL, MULTICENTER TRIAL



Major efficacy outcome measure:
Progression-free survival (PFS) as evaluated by Blinded Independent Review Committee (BIRC) according to Response Evaluation Criteria In Solid Tumors (RECIST v1.1).

Additional efficacy outcome measures:
BIRC-assessed confirmed overall response rate (ORR), duration of response (DOR), intracranial ORR, and intracranial DOR.

[a]In ALTA 1L, 30% of patients had CNS metastasis at baseline. Seven of these patients had leptomeningeal involvement at the time of enrollment, including 4 patients in the brigatinib arm and 3 patients in the crizotinib arm.[1]

CNS, central nervous system; ITT, intention to treat.

WARNINGS AND PRECAUTIONS (continued)

Hypertension: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), hypertension was reported in 32% of patients receiving ALUNBRIG; Grade 3 hypertension occurred in 13% of patients. 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, resume ALUNBRIG at the same 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.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

ALTA 1L: BASELINE CHARACTERISTICS

Demographics and baseline factors were balanced across treatment arms.[2]

Baseline Demographics	ALUNBRIG (n=137)	crizotinib (n=138)
Median age (range)	58 years (27-86)	60 years (29-89)
Race	57% Non-Asian 43% Asian	64% Non-Asian 36% Asian
Female	50%	59%
ECOG performance status (PS)		
PS 0 or 1	96%	96%
PS 2	4%	4%

Disease Characteristics	ALUNBRIG (n=137)	crizotinib (n=138)
Stage IV disease	94%	91%
Adenocarcinoma	92%	99%
Prior chemotherapy in the locally advanced or metastatic setting	26%	27%
Prior radiation to the CNS	13%	14%
CNS metastases at baseline	29%	30%

ECOG, Eastern Cooperative Oncology Group.

WARNINGS AND PRECAUTIONS (continued)

Bradycardia: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), heart rates less than 50 beats per minute (bpm) occurred in 8.1% of patients receiving ALUNBRIG. Grade 3 bradycardia occurred in 1 patient (0.7%). 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 the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), Grade 1 or 2 adverse reactions leading to visual disturbance including blurred vision, photophobia, photopsia, and reduced visual acuity were reported in 7.4% of patients receiving ALUNBRIG. 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.

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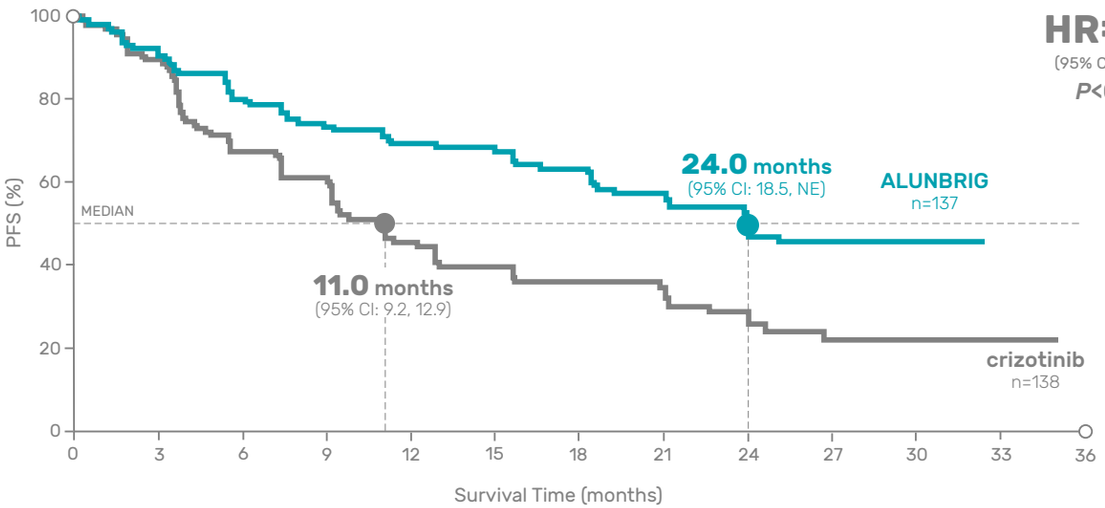
SYSTEMIC EFFICACY

Major Efficacy Outcome Measure: Progression-Free Survival (BIRC-Assessed)

Kaplan-Meier Plot of Progression-Free Survival by BIRC in ALTA 1L



Number at risk												
ALUNBRIG	137	114	97	89	84	81	75	66	39	18	3	
crizotinib	138	116	80	68	49	41	37	36	17	8	2	1

CI, confidence interval; HR, hazard ratio; NE, not estimable.

- **The median BIRC-assessed PFS was 24 months for ALUNBRIG** (95% CI: 18.5, NE) **vs 11 months for crizotinib** (95% CI: 9.2, 12.9)
  - **HR=0.49** (95% CI: 0.35, 0.68; *P*<0.0001)

WARNINGS AND PRECAUTIONS (continued)

Creatine Phosphokinase (CPK) Elevation: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), creatine phosphokinase (CPK) elevation occurred in 81% of patients who received ALUNBRIG. The incidence of Grade 3 or 4 CPK elevation was 24%. Dose reduction for CPK elevation occurred in 15% of patients. In ALTA, CPK elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90→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 with Grade 2 or higher muscle pain or weakness. Upon resolution or recovery to Grade 1 CPK elevation or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Pancreatic Enzyme Elevation: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), amylase elevation occurred in 52% of patients and Grade 3 or 4 amylase elevation occurred in 6.8% of patients. Lipase elevations occurred in 59% of patients and Grade 3 or 4 lipase elevation occurred in 17% of patients. 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.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Systemic Efficacy Outcomes

Efficacy Results in ALTA 1L

Efficacy Parameters (BIRC-Assessed)	ALUNBRIG n=137	crizotinib n=138	
Median progression-free survival (PFS)	**24.0 months** (95% CI: 18.5, NE)	**11.0 months** (95% CI: 9.2, 12.9)	**HR=0.49** (95% CI: 0.35, 0.68) *P*<0.0001[a]
Confirmed overall response rate (ORR)	**74%** (95% CI: 66, 81)	**62%** (95% CI: 53, 70)	*P*=0.0342[a]
Complete response	15% (95% CI: 9, 22)	9% (95% CI: 5, 15)	
Partial response	59% (95% CI: 50, 67)	53% (95% CI: 44, 61)	
Median duration of response (DOR)	**NR** (95% CI: 19.4, NE) 101 responders	**13.8 months** (95% CI: 9.3, 20.8) 85 responders	
Response ≥24 months	**51%**	**30%**	

[a]Stratified by presence of iCNS metastases at baseline and prior chemotherapy for locally advanced or metastatic disease for log-rank test and Cochran Mantel-Haenszel test, respectively.

iCNS, intracranial central nervous system; NR, not reached.

WARNINGS AND PRECAUTIONS (continued)

Hyperglycemia: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), 56% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 7.5% of patients. 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.

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.

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INTRACRANIAL EFFICACY

Intracranial Overall Response in Patients With Measurable[a] CNS Metastases in ALTA 1L

Confirmed Intracranial Overall Response Rates

ALUNBRIG
(n=14/18)

28% complete response (5/18)
(95% CI: 10, 53)

50% partial response (9/18)
(95% CI: 26, 74)

crizotinib
(n=6/23)

0 complete response
(95% CI: 0, 15)

26% partial response (6/23)
(95% CI: 10, 48)

64% of responders achieved an intracranial response duration ≥24 months[b] with ALUNBRIG vs NE for crizotinib.

BIRC assessment of confirmed intracranial ORR and intracranial DOR according to RECIST v1.1 in the subgroup of 41 patients with measurable CNS metastases (≥10 mm in longest diameter) at baseline.

[a]≥10 mm in longest diameter (at baseline).

[b]Duration of intracranial response was measured from date of first intracranial response until intracranial disease progression (new lesions, intracranial target lesion diameter growth ≥20% from nadir, or unequivocal progression of intracranial nontarget lesions) or death.

ADVERSE REACTIONS

In ALTA 1L, serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most common serious adverse reactions were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions occurred in 2.9% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%).

In ALTA, 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%) with ALUNBRIG were diarrhea (49%), fatigue (39%), nausea (39%), rash (38%), cough (37%), myalgia (34%), headache (31%), hypertension (31%), vomiting (27%), and dyspnea (26%).

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

ALTA 1L SAFETY PROFILE

Serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most common serious adverse reactions were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions occurred in 2.9% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%).

In ALTA 1L, 13% of patients receiving ALUNBRIG permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (3.7%) and pneumonia (2.2%).

In ALTA 1L, 38% of patients required a dose reduction due to adverse reactions. The most common adverse reactions that led to dose reductions were increased creatine phosphokinase (15%), increased lipase (6.6%), increased amylase (4.4%), increased aspartate aminotransferase (2.2%), ILD/pneumonitis (2.2%) and hypertension (2.2%).

DRUG INTERACTIONS

CYP3A Inhibitors: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If coadministration of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG.

CYP3A Inducers: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inducers. If coadministration of moderate CYP3A inducers cannot be avoided, increase the dose of ALUNBRIG.

CYP3A Substrates: Coadministration of ALUNBRIG with sensitive CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of sensitive 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: There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG.

Females and Males of Reproductive Potential:

Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating ALUNBRIG.

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.

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ALTA 1L SAFETY PROFILE (continued)

Adverse Reactions in ≥10% (All Grades[a]) or ≥2% (Grades 3-4) of Patients by Arm (N=273)

Adverse Reactions	ALUNBRIG (n=136)		crizotinib (n=137)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Diarrhea	53	2.2	57	2.9
Nausea	30	2.2	58	2.9
Abdominal pain[b]	24	0.7	33	3.6
Vomiting	21	0.7	44	2.2
Constipation	18	0	42	0
Stomatitis[c]	13	0.7	8.8	0
Dyspepsia	8	0	16	0.7
Gastroesophageal reflux disease	0.7	0	11	0
Skin and Subcutaneous Tissue Disorders				
Rash[d]	40	2.9	17	0
Pruritus[e]	20	0.7	5.8	0.7
Respiratory, Thoracic and Mediastinal Disorders				
Cough	35	0	20	0
Dyspnea[f]	25	2.9	22[r]	3.6
ILD/Pneumonitis	5.1	2.9	2.2	0.7
Pulmonary embolism	2.2	2.2	5.8[r]	2.9
Vascular Disorders				
Hypertension[g]	32	13	8	2.9
General Disorders and Administration Site Conditions				
Fatigue[h]	32	1.5	40	2.2
Edema[i]	18	0.7	48	0.7
Pyrexia	15	0.7	15	0

[a] Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[b] Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort.
[c] Includes aphthous ulcer, mouth ulceration, oral mucosal blistering and stomatitis.
[d] Includes dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis contact, drug eruption, erythema, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption, urticaria.
[e] Includes pruritus, allergic pruritus, and generalized pruritus.
[f] Includes dyspnea and exertional dyspnea.
[g] Includes hypertension and systolic hypertension.
[h] Includes asthenia and fatigue.
[i] Includes angioedema, eye swelling, eyelid edema, face edema, generalized edema, lip swelling, peripheral edema, periorbital edema, peripheral swelling, skin swelling, swelling and swelling face.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

ALTA 1L SAFETY PROFILE (continued)

Adverse Reactions in ≥10% (All Grades[a]) or ≥2% (Grades 3-4) of Patients by Arm (continued)

Adverse Reactions	ALUNBRIG (n=136)		crizotinib (n=137)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Musculoskeletal and Connective Tissue Disorders				
Myalgia[j]	28	0	23	0
Back pain	21	0.7	17	1.5
Arthralgia	14	0	12	0
Pain in extremity	5.1	0	15	0.7
Nervous System Disorders				
Headache[k]	22	2.2	17	0
Dizziness	15	0.7	20	0.7
Peripheral neuropathy[l]	11	0.7	18	0
Dysgeusia	2.9	0	14	0
Investigations				
Increased blood cholesterol[m]	13	0	0.7	0
Cardiac Disorders				
Bradycardia[n]	12	0.7	23	0
Infections and Infestations				
Pneumonia[o]	15[r]	5.1	6.6[r]	2.9
Upper respiratory tract infection[p]	12	0	10	0
Nasopharyngitis	8	0	11	0
Urinary tract infection	5.9	0.7	8.8	2.2
Metabolism and Nutrition Disorders				
Decreased appetite	8.8	0.7	19	2.9
Eye Disorders				
Visual disturbance[q]	7.4	0	53	0.7

[j] Includes muscle spasms, muscle twitching, musculoskeletal discomfort, musculoskeletal pain, and myalgia.
[k] Includes headache and migraine.
[l] Includes burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, peripheral neuropathy, paraesthesia, peripheral sensory neuropathy and polyneuropathy.
[m] Includes blood cholesterol increased, hypercholesterolemia.
[n] Includes bradycardia, heart rate decreased, sinus bradycardia.
[o] Includes lower respiratory tract infection, lung infection, pneumonia, aspiration pneumonia, and cryptococcal pneumonia.
[p] Includes upper respiratory tract infection and viral upper respiratory tract infection.
[q] Includes cataract, glaucoma, hypermetropia, night blindness, papilloedema, photophobia, photopsia, blurred vision, reduced visual acuity, visual field defect, visual impairment, and vitreous floaters.
[r] Includes Grade 5 events.

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ALTA 1L SAFETY PROFILE (continued)

Laboratory Abnormalities in ≥20% (All Grades[a]) of Patients by Arm (N=273)

Laboratory Abnormality	ALUNBRIG (n=136)[b]		crizotinib (n=137)[b]	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased creatine phosphokinase	81	24	68	4.8
Increased aspartate aminotransferase	72	4.5	70	5.2
Increased lipase	59	17	36	9.8
Hyperglycemia[c]	56	7.5	37	3.7
Increased alanine aminotransferase	52	5.2	77	13
Increased amylase	52	6.8	25	3
Decreased phosphorous	41	3.7	39	6
Increased alkaline phosphatase	36	3	49	1.5
Increased creatinine	25	0	33	0
Potassium increased	24	1.5	31	3.7
Increased calcium	22	0	1.5	0
Decreased magnesium	21	0	6.9	0
Decreased albumin	15	0.8	52	3.7
Decreased calcium	15	0	67	1.5
Hematology				
Hemoglobin decreased	41	2.3	36	1.5
Lymphocyte count decreased	42	9.3	30	5.4
Neutrophil count decreased	12	0	34	6.8

[a] Per CTCAE version 4.03.
[b] Denominator for each laboratory parameter may vary and is defined as the number of patients who had both, baseline and post baseline test.
[c] Elevated blood insulin was also observed in both arms.

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DOSING

Once-Daily Dosing Regimen

The recommended dosage for ALUNBRIG is 90 mg orally once daily for the first 7 days; then increase the dose to 180 mg orally once daily.

1 TABLET ONCE DAILY
WITH OR WITHOUT FOOD

- Administer ALUNBRIG until disease progression or unacceptable toxicity
- If ALUNBRIG is interrupted for 14 days or longer for reasons other than adverse reactions, resume treatment at 90 mg once daily for 7 days before increasing to the previously tolerated dose
- ALUNBRIG may be taken with or without food. Instruct patients to swallow tablets whole. Do not crush or chew tablets
- Inform patients to avoid grapefruit or grapefruit juice while taking ALUNBRIG
- If a dose of ALUNBRIG is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of ALUNBRIG at the scheduled time

USE IN SPECIFIC POPULATIONS (continued)

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

Geriatric Use: Of the 359 patients enrolled in the ALTA 1L ALUNBRIG arm and in ALTA, 26.7% were 65 and older and 7.5% were 75 and older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and younger patients.

Hepatic or Renal Impairment: No dose adjustment is recommended for patients with mild or moderate hepatic impairment or mild or moderate renal impairment. Reduce the dose of ALUNBRIG for patients with severe hepatic impairment or severe renal impairment.

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THE ALUNBRIG SMART™ FREE TRIAL PROGRAM

The ALUNBRIG SMART program can help you and your patients with ALK+ metastatic NSCLC assess whether ALUNBRIG® (brigatinib) is right for them by offering a 1-month free trial.

To get your eligible[a] patient started:

1. Download the ALUNBRIG SMART Request Form from **ALUNBRIGSMART.com**
2. Fill out the form and fax it to **1-844-269-3038**
3. Your patient will receive a 1-month trial of ALUNBRIG sent directly to their home

There is no obligation to continue the use of ALUNBRIG after the free trial has been completed. If you decide ALUNBRIG is right for your patient, a prescription will need to be written.

[a]Review patient eligibility criteria—certain restrictions apply.

For more information visit ALUNBRIGSMART.com

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HERE TO SUPPORT YOUR PRACTICE

Takeda Oncology Here2Assist™

Here2Assist is a comprehensive support program committed to helping your patients throughout their therapy.

ACCESS SUPPORT: Takeda Oncology Here2Assist case managers may provide access support for patients prescribed Takeda Oncology medications.

FINANCIAL ASSISTANCE: Takeda Oncology Here2Assist can help identify financial assistance programs that may be able to help your patients with the cost of their treatment.

To learn more about the Takeda Oncology Co-Pay Assistance Program, please visit **www.TakedaOncologyCoPay.com** or call **1-844-817-6468**.

HELPFUL RESOURCES: Takeda Oncology Here2Assist case managers can provide your patients with information about additional resources that may assist with the day-to-day support they need.

For more information call **1-844-817-6468** or visit **www.Here2Assist.com.**

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ALTA 1L: A PHASE 3, RANDOMIZED, OPEN-LABEL, MULTICENTER TRIAL

Systemic Efficacy

Efficacy Parameters (BIRC-Assessed)	ALUNBRIG n=137	crizotinib n=138	
Median progression-free survival (PFS)	**24.0 months** (95% CI: 18.5, NE)	**11.0 months** (95% CI: 9.2, 12.9)	**HR=0.49** (95% CI: 0.35, 0.68) *P*<0.0001[a]
Confirmed overall response rate (ORR)	**74%** (95% CI: 66, 81)	**62%** (95% CI: 53, 70)	*P*=0.0342[a]
Complete response	15% (95% CI: 9, 22)	9% (95% CI: 5, 15)	
Partial response	59% (95% CI: 50, 67)	53% (95% CI: 44, 61)	
Median duration of response (DOR)	**NR** (95% CI: 19.4, NE) 101 responders	**13.8 months** (95% CI: 9.3, 20.8) 85 responders	
Response ≥24 months	**51%**	**30%**	

Intracranial Efficacy in Patients with Measurable[b] CNS Metastases at Baseline

Efficacy Parameters (BIRC-Assessed)	ALUNBRIG (n=18)	crizotinib (n=23)
Confirmed intracranial overall response rate	**78%** (14/18) (95% CI: 52, 94)	**26%** (6/23) (95% CI: 10, 48)
Complete response	28% (5/18) (95% CI: 10, 53)	0 (95% CI: 0, 15)
Partial response	50% (9/18) (95% CI: 26, 74)	26% (6/23) (95% CI: 10, 48)
Duration of intracranial response[c]		
Number of confirmed responders	n=14	n=6
Intracranial response duration ≥24 months	64%	NE

Adverse Reactions in ALTA 1L

The WARNINGS AND PRECAUTIONS for ALUNBRIG include: interstitial lung disease (ILD)/pneumonitis, hypertension, bradycardia, visual disturbance, creatine phosphokinase (CPK) elevation, pancreatic enzymes elevation, hyperglycemia, and embryo-fetal toxicity.

Serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most common serious adverse reactions were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions occurred in 2.9% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%).

The most common adverse reactions (≥25%) in clinical trials with ALUNBRIG were diarrhea (49%), fatigue (39%), nausea (39%), rash (38%), cough (37%), myalgia (34%), headache (31%), hypertension (31%), vomiting (27%), and dyspnea (26%).

ALTA 1L Study Design

- **Design:** Phase 3, randomized (1:1), open-label, multicenter trial in adults with advanced ALK+ NSCLC who had not previously received an ALK-targeted therapy
- **Interventions:** Patients received ALUNBRIG 180 mg orally once daily with a 7-day lead-in at 90 mg orally once daily (n=137) or crizotinib 250 mg orally twice daily (n=138)
- **Major efficacy outcome measure:** PFS according to RECIST v1.1 as evaluated by a BIRC
- **Additional efficacy outcome measures:** Percentage of participants with adverse events, BIRC-assessed ORR, DOR, intracranial ORR, and intracranial DOR

To learn more, visit ALUNBRIG.com/hcp.

[a]Stratified by presence of iCNS metastases at baseline and prior chemotherapy for locally advanced or metastatic disease for log-rank test and Cochran Mantel-Haenszel test, respectively.
[b]≥10 mm in longest diameter (at baseline).
[c]Duration of intracranial response was measured from date of first intracranial response until intracranial disease progression (new lesions, intracranial target lesion diameter growth ≥20% from nadir, or unequivocal progression of intracranial nontarget lesions) or death.

References: 1. ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Data on file. **2.** Camidge DR, Kim HR, Ahn MJ, et al. *N Engl J Med*. 2018;379(21):2027-2039.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

ALUNBRIG® BRIGATINIB 180mg | 90mg | 30mg TABLETS

Takeda | ONCOLOGY