RAISING EXPECTATIONS IN ALK+ aNSCLC POST CRIZOTINIB

EXCEEDS 1 YEAR MEDIAN PFS[a] IN ALK+ aNSCLC PATIENTS POST CRIZOTINIB[2]

ALUNBRIG (brigatinib) is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (aNSCLC) previously treated with crizotinib[2]

For more information, please visit www.ALUNBRIG.co.uk

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

[a]IRC and investigator assessed

UK/BRIG/1810/0042a Date of preparation: February 2019

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WHY ANOTHER ALK TKI TREATMENT OPTION?

ALK+ aNSCLC patients typically progress on 1st-line therapy

- Despite improvements in 1st-line ALK-targeted therapy, treatment is **not curative** and all patients eventually progress as a result of treatment resistance.[3,4]
- Post crizotinib, patients on 2nd-line ALK inhibitors typically acquire resistance and **progress within 8–10 months**.[5-7]

CNS-active agents are needed

- **Up to 60% of patients** develop CNS metastases during treatment with crizotinib.[8,9]
- Complications of CNS metastases can include: neurocognitive dysfunction, decreased life expectancy, psychological abnormalities, physical impairment, and/or severe comorbidities.[8]

"My experience of using Alunbrig along with the clinical trial data enables me to give my patients with ALK-translocated aNSCLC the confidence that they are highly likely to achieve a rapid, long-term response at all sites of disease including the brain. The tolerability profile and robust dosing evidence reassures me that Alunbrig is an important treatment in patients previously treated with crizotinib."

Dr. Rohit Lal
Consultant medical oncologist
Guy's and St Thomas' NHS Foundation Trust, London

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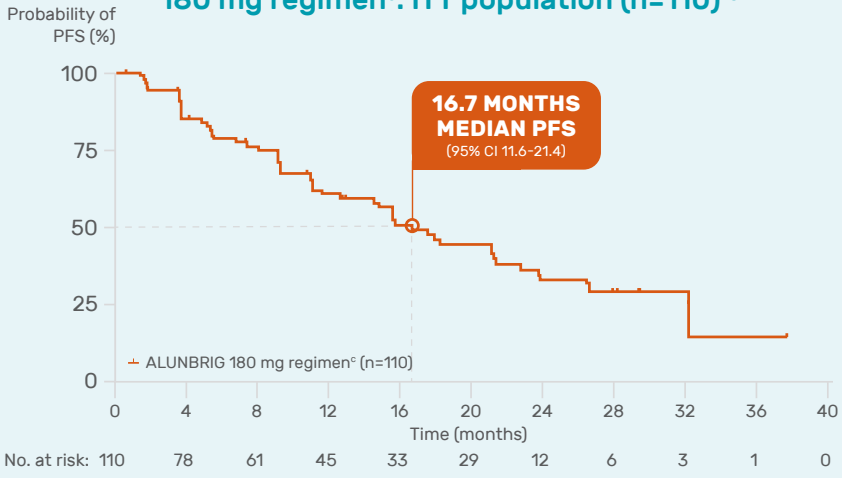
EXCEEDS 1 YEAR mPFS[a] IN ALK+ aNSCLC PATIENTS POST CRIZOTINIB[2]

Systemic ORR[b] of 56% (97.5% CI 45–67) of patients on 180 mg regimen[10]

IRC-assessed systemic PFS with the 180 mg regimen[c]: ITT population (n=110)[10]



Adapted from Huber RM, et al. 2018[10]

- Systemic mPFS[d] of **16.7 months** (95% CI 11.6–21.4 months)[10]
- mOS of **34.1 months** (95% CI 27.7–NR)[10]

Effective in the CNS

- Intracranial mPFS[d,e] of **18.4 months** (95% CI 12.6–23.9) in patients (n=74) with any brain metastases at baseline[10-13]
- Intracranial mDOR[d] of **16.6 months** (95% CI 3.7–NR) in patients (n=12) with measurable brain metastases at baseline[10-13]

ALTA was a phase 2, global, randomised, open-label, multicentre trial enrolling 222 adult patients with locally advanced or metastatic ALK+ NSCLC, previously treated with crizotinib. They were randomised to one of two ALUNBRIG regimens, (90 mg or 180 mg with a 7-day 90 mg lead-in) with a planned follow-up of 2 years. The primary study outcome was systemic objective overall response rate according to RECIST criteria, as assessed by investigator.

[a]IRC and investigator assessed [b]Investigator-assessed [c]180 mg once daily with 7-day lead-in at 90 mg once daily [d]IRC assessed [e]Intracranial PFS does not include systemic (non-cranial) disease progression events

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A GENERALLY MANAGEABLE TOLERABILITY PROFILE[2]

Adverse reactions reported in patients receiving ALUNBRIG at the recommended dosing regimen[2]

Most common adverse reactions (≥25%)

Increased AST, hyperglycaemia, hyperinsulinaemia, anaemia, increased CPK, nausea, increased lipase, decreased lymphocyte count, increased ALT, diarrhoea, increased amylase, fatigue, cough, headache, increased alkaline phosphatase, hypophosphataemia, increased APTT, rash, vomiting, dyspnoea, hypertension, decreased white blood cell count, myalgia, peripheral neuropathy

Most common serious adverse reactions (≥2%)

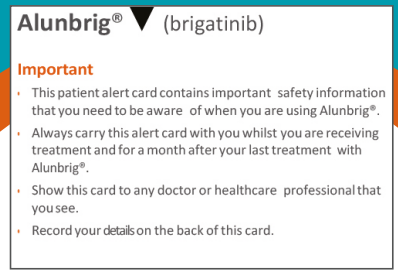
Pneumonitis, pneumonia, dyspnoea

Please refer to the Summary of Product Characteristics for complete side effect and licensing information

[a]Dyspnoea, hypoxia, cough, pneumonia or pneumonitis

Severe pulmonary adverse reactions, including those with features consistent with ILD/ pneumonitis, can occur in patients treated with ALUNBRIG[2,14]

- In ALTA, 14 patients (6%) experienced pulmonary adverse reactions[a] of any grade within 9 days of treatment initiation (median onset 2 days). These adverse events occurred at 90 mg, in both arms, and none occurred after escalation to 180 mg.[14]
- Grade 1-2 pulmonary adverse reactions resolved with interruption of treatment or dose modification.[14]
- Factors independently associated with an increased rate of these pulmonary adverse reactions:[14]
  - Increased age.
  - Shorter interval (<7 days) between the last dose of crizotinib and the first dose of ALUNBRIG.
- Patients should be monitored for new or worsening respiratory symptoms (e.g. dyspnoea, cough), particularly in the first week of treatment. But note that some patients experienced pneumonitis later in treatment with ALUNBRIG.[2]
- See the Summary of Product Characteristics for recommended dose modifications for managing adverse reactions.[2]



Patients should be provided with a **patient alert card (PAC)**.

They should be monitored for adverse reactions, especially pulmonary adverse reactions, and the dose adjusted or discontinued if necessary, particularly in the first 7 days of treatment.

See the Summary of Product Characteristics for further information on dose modification and management.[2]

PRESCRIBING INFORMATION

ALUNBRIG®▼ (brigatinib) PRESCRIBING INFORMATION

Refer to the Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** Brigatinib 180 mg, 90 mg and 30 mg film-coated tablets. **Indication:** As monotherapy for the treatment of adult patients with anaplastic lymphoma kinase-positive advanced non-small cell lung cancer previously treated with crizotinib. **Dosage & Administration:** Recommended starting dose is 90 mg once daily for the first 7 days, then 180 mg once daily. If Alunbrig is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose. If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be administered and the next dose should be taken at the scheduled time. Treatment should continue as long as clinical benefit is observed. Dosing interruption and/or dose reduction may be required. See SmPC for full dosage information and dose modifications. Paediatric populations: No data are available. Elderly patients: Dose adjustment is not required in elderly patients. No available data on patients aged > 85 years. Hepatic impairment: A reduced starting dose of 60 mg once daily for the first 7 days, then 120 mg once daily is recommended for patients with severe hepatic impairment (Child-Pugh class C). Renal impairment: A reduced starting dose of 60 mg once daily for the first 7 days, then 90 mg once daily is recommended for patients with severe renal impairment (eGFR < 30 mL/min). Patients with severe renal impairment should be closely monitored for new or worsening respiratory symptoms (e.g., dyspnoea, cough, etc.). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** See SmPC for recommended dose modifications. Pulmonary adverse reactions: Patients should be monitored for new or worsening respiratory symptoms (e.g., dyspnoea, cough, etc.), particularly in the first week of treatment. If pneumonitis is suspected, the dose of Alunbrig should be withheld, and the patient evaluated for other causes of symptoms (e.g., pulmonary embolism, tumour progression, and infectious pneumonia). Dose modification may be required; Hypertension: Heart rate and blood pressure should be monitored regularly. Withhold Alunbrig in patients with severe hypertension (≥ Grade 3) until hypertension has recovered to Grade 1 or to baseline. Modify dose accordingly; Bradycardia: Caution should be exercised when administering Alunbrig in combination with other agents known to cause bradycardia. If symptomatic bradycardia occurs, treatment with Alunbrig should be withheld and concomitant medicinal products known to cause bradycardia should be evaluated. Upon recovery, the dose should be modified according to SmPC. In case of life-threatening bradycardia, if no contributing concomitant medication is identified or in case of recurrence, treatment with Alunbrig should be discontinued; Visual disturbance: Advise patients to report any visual symptoms. Consider ophthalmologic evaluation / dose reduction for new or worsening severe symptoms. Creatine phosphokinase (CPK) elevation: Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be monitored regularly during Alunbrig treatment. Based on the severity of the CPK elevation, treatment with Alunbrig should be withheld, and the dose modified. Elevations of pancreatic enzymes: Lipase and amylase should be monitored regularly during treatment with Alunbrig. Based on the severity of the laboratory abnormalities, treatment with Alunbrig should be withheld, and the dose modified. Hepatotoxicity: Liver function, including AST, ALT and total bilirubin should be assessed prior to the initiation of Alunbrig and then every 2 weeks during the first 3 months of treatment. Thereafter, monitoring should be performed periodically. Based on the severity of the laboratory abnormalities, treatment should be withheld, and the dose modified. Hyperglycaemia: Fasting serum glucose should be assessed prior to initiation of Alunbrig and monitored periodically thereafter. Antihyperglycaemic medications should be initiated or optimised as needed. If adequate hyperglycaemic control cannot be achieved with optimal medical management, Alunbrig should be withheld until adequate hyperglycaemic control is achieved; upon recovery, dose reduce Alunbrig as per the SmPC or permanent discontinuation may be considered; Lactose: Alunbrig contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take Alunbrig. **Interactions:** Avoid use with strong CYP3A inhibitors. See SmPC for dosage modifications for Alunbrig if concomitant use with a strong CYP3A inhibitor cannot be avoided. Strong and moderate CYP3A inducers should be avoided. Grapefruit or grapefruit juice should be avoided. Coadministration of Alunbrig with CYP3A substrates with a narrow therapeutic index should be avoided as Alunbrig may reduce their effectiveness. Co-administration of Alunbrig with substrates of P-gp, BCRP, organic cation transporter 1, multidrug and toxin extrusion protein (MATE) 1 and 2K may increase their plasma concentrations. Patients should be closely monitored when Alunbrig is co-administered with substrates of these transporters with a narrow therapeutic index. **Fertility, Pregnancy and Lactation:** Women of reproductive potential should be advised not to become pregnant and to use effective non-hormonal contraception during treatment with Alunbrig and for at least 4 months following the final dose. Men should be advised not to father a child during Alunbrig treatment. Men with female partners of reproductive potential should be advised to use effective contraception during and for at least 3 months after the last Alunbrig treatment. No clinical data on the use of Alunbrig in pregnant women. Alunbrig should not be used during pregnancy unless the clinical condition of the mother requires treatment. Breast-feeding should be stopped during treatment with Alunbrig. No human data are available on the effect of Alunbrig on fertility. **Undesirable Effects:** Very common (≥1/10): Pneumonia, upper respiratory tract infection, anaemia, lymphocyte count decreased, APTT increased, white blood cell count decreased, neutrophil count decreased, decreased platelet count, hyperglycaemia, hyperinsulinaemia, hypophosphataemia, decreased appetite, hypokalaemia, hypomagnesaemia, hyponatraemia, hypercalcaemia, insomnia, headache, peripheral neuropathy, dizziness, visual disturbance, hypertension, cough, dyspnoea, lipase increased, nausea, diarrhoea, amylase increased, vomiting, constipation, abdominal pain, dry mouth, stomatitis, AST increased, ALT increased, alkaline phosphatase increased, rash, pruritus, blood CPK increased, myalgia, arthralgia, musculoskeletal chest pain, blood creatinine increased, fatigue, oedema, pyrexia. Common (≥1/100 to <1/10): Memory impairment, dysgeusia, tachycardia, electrocardiogram QT prolonged, bradycardia, palpitations, pneumonitis, dyspepsia, flatulence, blood lactate dehydrogenase increased, hyperbilirubinaemia, dry skin, phtosensitivity reaction, pain in extremity, musculoskeletal stiffness, pain, non-cardiac chest pain, chest discomfort, weight decreased. Other serious uncommon (≥1/1,000 to <1/100) undesirable effects: pancreatitis. **Refer to the SmPC for details on full side effect profile and interactions. Legal Classification:** POM. **UK Basic NHS Price:** 30mg x56: £2,450, 90mg tablets x 28: £3,675, 90mg tablets x 7: £918.75, 180mg tablets x 28: £4,900 **Marketing Authorisation Numbers:** EU/1/18/1264/003, EU/1/18/1264/008, EU/1/18/1264/005, EU/1/18/1264/010 **Additional information is available on request from:** Takeda UK Ltd. Building 3, Glory Park, Glory Park Avenue, Wooburn Green, Buckinghamshire, HP10 0DF. Tel: 01628 537900 Fax: 01628 526617. **PI Approval Code:** UK/BRIG/1810/0036(1) **PI Date of Preparation:** December 2018

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. Adverse events should also be reported to Takeda UK Ltd 01628-537900

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1. NICE Final Appraisal Determination: Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib. https://www.nice.org.uk/guidance/gid-ta10268/documents/final-appraisal-determination-document. Accessed February 2019. **2.** Alunbrig Summary of Product Characteristics. **3.** Gainor JF, et al. Cancer Discov 2016:6:1118–33. **4.** Gainor JF, et al. Clin Cancer Res 2013;19:4273–81. **5.** Shaw AT, et al. Lancet Oncology 2017;18:874-86. **6.** Novello S, et al. Ann Oncol 2017;28 (Suppl 5): Abstract 12990_PR. **7.** Crinò L, et al. J Clin Oncol 2016;20;34:2866–73. **8.** Guérin A, et al. J Med Econ 2015;18:312–22. **9.** Zhang I, et al. Lancet Oncol 2015;16:e510–21. **10.** Huber RM, et al. Poster presentation at ASCO Annual Meeting 2018, Poster 384. **11.** Camidge DR, et al. J Clin Oncol 2018;36:2693–701. **12.** Ahn M-J, et al. Oral presentation at IASLC 18th World Conference on Lung Cancer, 2017. **13.** Ou S-HI, et al. Oral presentation at ESMO 2017, poster 1345P. **14.** Kim DW, et al. J Clin Oncol 2017;35:2490–8.

ABBREVIATIONS

ALK, anaplastic lymphoma kinase; **ALT,** alanine aminotransferase; **aNSCLC,** advanced non-small cell lung cancer; **APTT,** activated partial thromboplastin time; **AST,** aspartate aminotransferase; **CI,** confidence interval; **CNS,** central nervous system; **CPK,** creatine phosphokinase; **ILD,** interstitial lung disease; **IRC,** independent review committee; **ITT,** intention to treat; **mDOR,** median duration of response; **mOS,** median overall survival; **mPFS,** median progression-free survival; **NR,** not reached; **ORR,** objective response rate; **RECIST,** Response Evaluation Criteria In Solid Tumors; **TKI,** tyrosine kinase inhibitor.

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