Brigatinib (Alunbrig®) in *ALK*-positive non–small-cell lung cancer (NSCLC)

General information [1]

Drug description	Indication
next-generation ALK-inhibitor	patients with *ALK*-positive locally advanced or metastatic NSCLC with at least 1 measurable lesion according to the RECIST(version 1.1), and had not previously received ALK-targeted therapy

Current treatment [2]

- ❖ Both NICE and European guidelines state that 1st-line treatment with crizotinib is the preferred treatment of patients with ALK-positive NSCLC
- ❖ Crizotinib is an inhibitor of tyrosine kinase, and binds to the tyrosine kinase receptor on the surface of lung cancer cells and inhibits the abnormal ALK protein
- ❖ Studies have found that treatment with crizotinib results in a median PFS of 7 to 10 months, but all patients will eventually experience disease progression through primary or acquired resistance
- ❖ Both NICE and European guidelines recommend ceritinib for patients with ALK-positive NSCLC who progress on treatment with or are intolerant to crizotinib

Regulatory status

EMA [3]	FDA [4]
Approval status for this indication: positive CHMP in 02/2020 **Other indications**: ❖ Brigatinib is indicated as monotherapy for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib ✓ **Medicine under additional monitoring**	**Approval status for this indication**: not approved **Other indications**: approved (04/2017) for the treatment of patients with ALK-positive metastatic 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.

Costs [5]

Induction treatment (lead-in): brigatinib 90 mg/daily for 7 days: € 1,355.90 (ex-factory price)
Maintenance phase: brigatinib 180 mg/daily for 28 days: € 4,400.00 (ex-factory price)

Study characteristics

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ALTA-1L NCT02737501	275	brigatinib at a dose of 180 mg once daily (with a 7-day lead-in period at 90 mg)	crizotinib at a dose of 250 mg twice daily	PFS	open-label, multicenter, randomized, international, phase 3 trial	ALK	Ariad Pharmaceuticals	Link

Efficacy (brigatinib vs. crizotinib)

PFS: estimated 12-month PFS, 67% (95% CI, 56-75) vs. 43% (95% CI, 32-53); HR for disease progression or death, 0.49 (95% CI, 0.33-0.74); p<0.001
PFS (BIRC), median, months (95% CI): 24 (18.5-NE) vs. 11 (9.2-12.9), HR 0.49 (95%CI, 0.35-0.68), p<0.0001
ORR: was 71% (95% CI, 62-78) with brigatinib and 60% (95% CI, 51-68) with crizotinib;
Confirmed ORR (BIRC), responders: 73.7% vs. 61.6%
Intracranial response: the confirmed rate of intracranial response among patients with measurable lesions was 78% (95% CI, 52-94) and 29% (95% CI, 11-52). The overall rate of intracranial objective response (objective response at one or more assessments was 83% (95% CI, 59-96) with brigatinib and 33% (95% CI, 15-57) with crizotinib
Intracranial PFS, median (95%CI)): 24 months (13-NE) vs. 5.6 (3.7-7.5), HR 0.31 (0.17-0.56), log-rank p-value <0.0001
QoL: secondary endpoint, results not available
OS: At data cutoff, in the ITT-population 12% of patients in the brigatinib group and 12% of patients in the crizotinib group had died. The 1-year rate of OS was 85% (95% CI, 76-91) with brigatinib and 86% (95% CI, 77-91) with crizotinib. The median OS was not reached in both groups.
Number of events: 33 (24.1%) vs. 37 (26.8%); HR (95% CI): 0.92 (0.57-1.47), log-rank p-value 0.7710

Safety (brigatinib vs. crizotinib)

Any AE grade ≥3: n=83/136 (61%) vs. n=76/137 (55%)
Grade 3 to 5 AEs: 61% vs. 55%
Death: n=7/136 (5%) vs. n=7/137 (5%) → AE(s) leading to death within 30 days after the last dose of the trial drug; none of the events were deemed by the investigators to be related to trial treatment
Discontinuation (discontinuation due to AEs): 12% (brigatinib group) vs. 9% (crizotinib group)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
An ESMO-MCBS assessment was not applicable since the neither median OS nor median PFS have been reached.											

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**

unclear	no	no (open-label)	unclear[1]	yes[2]	high
					First published: 02/2020 **Last updated:** 072020

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, BIRC=Blinded Independent Review Committee, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=U.S. Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, Int.=intention, ITT=intention-to-treat, MG=median gain, n=number, NE=not estimable, NSCLC=non-small-cell lung cancer, ORR=objective response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, ST=standard treatment.

References:

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3. European Medicines Agency (EMA). Medicines. Alunbrig. [2020-03-24]; Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/alunbrig.
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5. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [2020-03-24]; Available from: https://warenverzeichnis.apoverlag.at/.

[1] not all results of secondary endpoints available, trial is ongoing until 07/2020

2 industry-funded; limitation of analysis is that OS data will be confounded by crossover of patients in the crizotinib group to brigatinib during the trial and subsequent use of other tyrosine kinase inhibitors after discontinuation of the trial by patients from either group.