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

### General information [1]
- **Drug description**: next-generation ALK-inhibitor
- **Indication**: 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

<table>
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<tbody>
<tr>
<td>Approval status for this indication: positive CHMP in 02/2020</td>
<td>Approval status for this indication: not approved</td>
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<tr>
<td>Other indications:</td>
<td>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.</td>
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<tr>
<td>Brigitinib is indicated as monotherapy for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib</td>
<td>Medicine under additional monitoring</td>
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### 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

<table>
<thead>
<tr>
<th>Trial name</th>
<th>n</th>
<th>Intervention (I)</th>
<th>Comparator (C)</th>
<th>PE</th>
<th>Characteristics</th>
<th>Biomarker</th>
<th>Funding</th>
<th>Publication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALTA-1L NCT02737501</td>
<td>275</td>
<td>brigatinib at a dose of 180 mg once daily (with a 7-day lead-in period at 90 mg)</td>
<td>crizotinib at a dose of 250 mg twice daily</td>
<td>PFS</td>
<td>open-label, multicenter, randomized, international, phase 3 trial</td>
<td>ALK</td>
<td>Ariad Pharmaceuticals</td>
<td>Link</td>
</tr>
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### 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
- **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, 51-77) and 29% (95% CI, 11-52). The overall rate of intracranial objective response (objective response at one or more assessments was 83% (95% CI, 59-95) 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
- **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.
- **QoL**: secondary endpoint, results not available

### 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

<table>
<thead>
<tr>
<th>Scale</th>
<th>Int.</th>
<th>Form</th>
<th>MG ST</th>
<th>MG</th>
<th>HR (95% CI)</th>
<th>Score calculation</th>
<th>PM</th>
<th>Toxicity</th>
<th>QoL</th>
<th>AJ</th>
<th>FM</th>
</tr>
</thead>
</table>
| Risk of bias (study level)

An ESMO-MCBS assessment was not applicable since the neither median OS nor median PFS have been reached.
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=no 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:


unclear  no  no (open-label)  unclear  yes  high

First published: 02/2020
Last updated: 07/2020

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.