

# ALK Inhibitors in ALK-positive NSCLC with Central Nervous System Metastases

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DOI: <https://doi.org/10.17925/EOH.2020.16.1.18>

In anaplastic lymphoma kinase (ALK)-rearranged non-small-cell lung cancer, brain metastases occur in 22–33% of cases at diagnosis and could reach up to 70% after crizotinib failure. Next-generation ALK inhibitors (ngALKi) have superior intracranial activity and prolonged responses compared with crizotinib and chemotherapy, as was shown in treatment-naïve or crizotinib pre-treated patients, irrespective of prior brain irradiation. Nevertheless, central nervous system relapse is also seen with ngALKi. Tailored treatment is necessary to obtain long-term survival without detrimental effects on cognition. Possible options include profiling secondary mutations to select sequential ngALKi, stereotactic radiotherapy and/or surgery, with the aim to avoid/deter whole brain irradiation.

## Keywords

Non-small cell-lung cancer, anaplastic lymphoma kinase, brain metastases, personalised treatment

**Disclosures:** Benjamin Besse declares the following: research sponsored at Gustave Roussy Cancer Center by AbbVie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, Bristol Myers Squibb, Celgene, Eli Lilly, GlaxoSmithKline, Ignyta, Ipsen, Merck KGaA, Merck Sharp & Dohme, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda and Tiziana Pharma; investigator or co-investigator of trials sponsored by Nerviano, GlaxoSmithKline, Pfizer, Roche-Genentech, Eli Lilly, OSE Pharma, Merck Sharp & Dohme, Celgene, Stemcentrx, Ignyta, AbbVie, Loxo Oncology, AstraZeneca and Blueprint Medicines. Lizza EL Hendriks declares the following: research funding at Maastricht University Medical Center from Roche-Genentech, Boehringer Ingelheim and AstraZeneca; advisory boards for Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Roche-Genentech, Pfizer, Takeda and Merck Sharp & Dohme (all institution); speaker for Merck Sharp & Dohme; travel/conference reimbursement from Roche-Genentech, Bristol Myers Squibb (self); mentorship programme with key opinion leaders funded by AstraZeneca; fees for educational webinars from Quadia (self); interview sessions funded by Roche-Genentech (institution); local principal investigator of clinical trials sponsored by AstraZeneca, Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Takeda, Blueprint Medicines and Roche Genentech. Mihaela Aldea has no financial or non-financial relationships or activities to declare in relation to this article.

**Review Process:** Double-blind peer review.

**Compliance with Ethics:** This article is an opinion piece and does not report on new clinical data, or any studies with human or animal subjects performed by any of the authors.

**Authorship:** The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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**Received:** 13 April 2020

**Accepted:** 18 May 2020

**Published Online:** 27 August 2020

**Citation:** *European Oncology & Haematology*. 2020;16(1):18–21

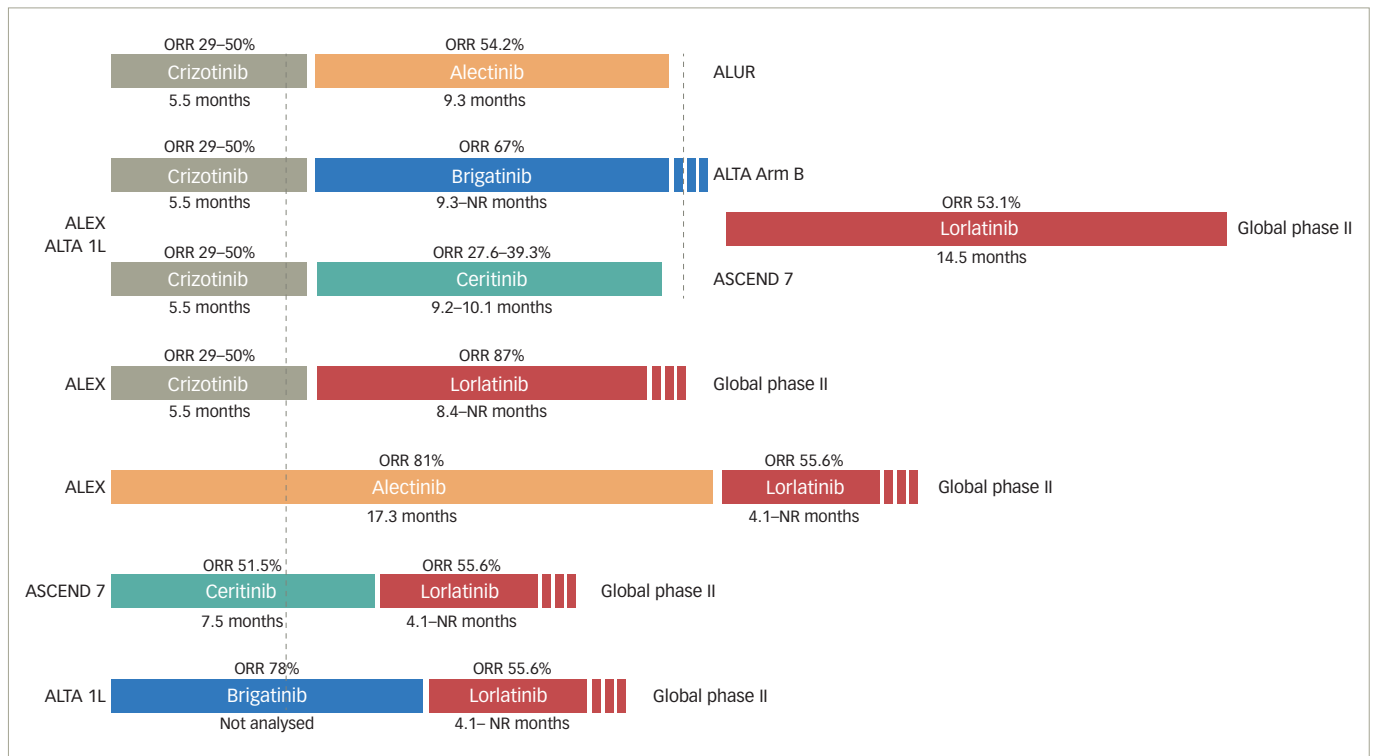
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**Support:** No funding was received in the publication of this article.

At initial diagnosis of metastatic disease, central nervous system (CNS) metastases are present in 22–33% of patients with anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small-cell lung cancer (NSCLC). After crizotinib failure, the incidence can reach up to 70%, compared with 40% in all comers.<sup>1</sup> The presence of CNS disease is an indicator of poor prognosis in NSCLC and is associated with a lower quality of life compared with metastasis in other organs. Therefore, optimal treatment, or even prevention of CNS disease, is important. Next-generation ALK inhibitors (ngALKi), including second-generation ALKi (alectinib, ceritinib, brigatinib) and the third-generation ALKi (lorlatinib), have increased potency and higher CNS activity compared with the first-generation ALKi, crizotinib.<sup>1</sup> In this editorial, we will discuss the management of patients with ALK+ NSCLC with CNS metastases, with a special focus on the activity of ngALKi.

## First-generation versus ngALKi in the prevention of CNS disease

Crizotinib, the first approved ALKi, has superior intracranial disease control rates compared with standard chemotherapy (85% versus 45%, respectively, at 12 weeks). However, the intracranial time to tumour progression (TTP) was not significantly different between the two treatment arms, probably because of the insufficient CNS penetration of crizotinib (cerebrospinal fluid [CSF]/plasma ratio 0.0026).<sup>2,3</sup> NgALKi can largely overcome this problem. Interestingly, when used in the first-line setting, alectinib and crizotinib had similar efficacy in controlling extra-CNS disease. The progression-free survival (PFS) advantage of alectinib could be mainly attributed to its lower rates of CNS progression.<sup>1</sup> CNS progression under first-line crizotinib occurred in 45% of cases compared with 12% with alectinib in the ALEX trial (ClinicalTrials.gov identifier: NCT02075840),<sup>4</sup> with a cause-specific hazard ratio (HR) for intracranial TTP of 0.18 in favour of alectinib for patients with baseline brain metastases and 0.14 for patients without brain metastases. These results indicate a preventive effect of alectinib on brain metastasis development and progression.<sup>5</sup> Similar results were found with brigatinib in the first-line ALTA-1L trial (NCT02737501). CNS progression, as the first site of disease progression, was lower with brigatinib compared with crizotinib (9% versus 19%, respectively, in patients with baseline brain metastases; 1% versus 5%, respectively, in patients without baseline brain metastases).<sup>6</sup> These results show that the upfront use of ngALKi, instead of crizotinib, is able to decrease the incidence of brain metastases.

**Figure 1: Most common treatment sequences and outcomes based on clinical trials<sup>4,6,8,9,12,14</sup>**


Intracranial overall response rate (%) in ALK+ patients with measurable brain metastases and intracranial median duration of response (months) in the intention-to-treat population.

ALK = anaplastic lymphoma kinase; NR = not reached; ORR = overall response rate.

In the ASCEND-4 trial (NCT01828099), which evaluated ceritinib in comparison with chemotherapy, CNS progression in patients without baseline brain metastases occurred in 31% of patients; of these patients 30% had an isolated CNS progression.<sup>7</sup>

### How to proceed with treatment in the case of CNS progression on an ALK inhibitor

NgALKi have higher intracranial activity compared with chemotherapy or crizotinib.<sup>4–6,8–12</sup> CNS responses occur early, starting from the first evaluation scan,<sup>13</sup> and are durable. The duration of response under ngALKi can reach more than 1 year in crizotinib-naïve patients. Importantly, ngALKi are effective also after crizotinib failure, with intracranial overall response rates (ORR) ranging from 27–87% and a median duration of response of several months (Figure 1). After failing at least two lines of ALKi, the third-generation ALKi, lorlatinib, achieved an intracranial ORR of 53% and an intracranial median duration of response of 14.5 months.<sup>14</sup> This impressive activity in heavily pre-treated patients is due to the retained potency of lorlatinib to acquired resistant mutations under prior ALKi (including ALK G1202) and because of its better capacity to penetrate into the CNS (CSF drug concentrations of 75% of plasma levels).<sup>14,15</sup> The ASCEND-7 study (NCT02336451), which has been specifically designed to assess the CNS response under ceritinib, has also evaluated leptomeningeal disease. This cohort of patients (n=18) was crizotinib pre-treated in 89% of cases and had prior radiotherapy in 61% of cases. The median PFS was 5.2 months and the median overall survival 7.2 months, longer than that established in patients with historical NSCLC (1–3 months).<sup>16</sup>

Importantly, data from the above-mentioned clinical trials are not comparable because of different inclusion/evaluation criteria (Table 1).

### Patients with CNS relapse might benefit from a molecularly guided treatment sequence

Despite an increase in intracranial activity of ngALKi, CNS disease will often eventually relapse. The sequential use of the third-generation ALKi, lorlatinib, after second-generation ALKi, was successful in a global phase II trial (NCT01970865).<sup>14</sup> There are currently no clinical trials evaluating a sequential approach between different second-generation ALKi. This might be justified, considering that second-generation ALKi have different 'sensitivity' profiles, according to resistance mutations.<sup>1</sup> Thus, a molecularly guided approach tailored to secondary mutations could earn additional treatment lines and also increase the chance of obtaining a CNS response. Another situation that could be encountered is the development of isolated CNS progression, a frequent phenomenon with crizotinib, that could also occur with ngALKi.<sup>17</sup> For example, in the ASCEND-4 study evaluating first-line ceritinib versus chemotherapy, 48% of patients failing ceritinib developed isolated CNS progression.<sup>7</sup> Isolated CNS progression occurs as either a consequence of resistance alterations or insufficient drug penetration. In the latter case, there may be a retention of sensitising alterations.<sup>17</sup>

The distinction between these two causes of isolated CNS progression would better guide the treatment sequence between alternate second-generation drugs and third-generation drugs or the use of local therapies, such as cranial irradiation. However, performing a molecular profile in patients with isolated CNS progression is challenging, as it should be performed in CSF rather than in plasma. Plasma circulating tumour DNA is negative in ≥50% of cases of isolated CNS progression, depending on the performance of the technique.<sup>17</sup> In the absence of resistance alterations, an insufficient drug concentration in the brain might be responsible. However, currently there are only scarce data in

**Table 1: Clinical trials of anaplastic lymphoma kinase inhibitors – inclusion criteria, evaluation and follow-up of central nervous system disease**

Drug/clinical trial	Line of treatment	Type of CNS metastases	CNS screening mandatory	FU CNS imaging mandatory/frequency	CNS imaging	CNS evaluation criteria	Brain prespecified endpoint
Crizotinib 250 mg BID PROFILE 1014 <sup>2</sup> NCT01154140	First-line	BM: Stable; Treated	Yes	Yes; Every 6 weeks if baseline BM; 12 weeks otherwise	CT/MRI	RECIST 1.1.	IC-TTP IC-DCR
Alectinib 600 mg BID ALEX <sup>4</sup> NCT02075840	First-line	BM: Asymptomatic; Treated/untreated	Yes	Yes; Every 8 weeks	CT/MRI	RANO-BM	PFS IC-TTP IC-ORR IC-DOR
Alectinib 600 mg BID ALUR <sup>12</sup> NCT02604342	Post-crizotinib and platinum-based CT	BM: Asymptomatic; Symptomatic and ineligible for radiotherapy	Yes	Yes; Every 6 weeks	CT/MRI	RECIST 1.1.	IC-ORR IC-TTP IC-DCR IC-DOR
Ceritinib 750 mg QD fasted ASCEND-4 <sup>7</sup> NCT01828099	First-line	BM: Asymptomatic; 60% active BM	Yes	Yes; Every 6 weeks through cycle 33, then every 9 weeks	CT/MRI	Modified RECIST 1.1.	IC-ORR IC-DCR IC-DOR IC-clinical benefit rate
Ceritinib 750 mg QD fasted ASCEND-7 <sup>9</sup> NCT02336451	Crizotinib-naïve/ post-crizotinib	BM: Active; LM (arm 5)	Yes	Yes; Every 8 weeks	MRI	RECIST 1.1.	IC-ORR IC-DCR IC-TTR IC-DOR
Brigatinib 180 mg QD ALTA-1L <sup>6</sup> NCT02737501	First ALKi	BM: Asymptomatic; Untreated	Yes	Yes; Every 8 weeks through cycle 14, then every 12 weeks	MRI	RECIST 1.1.	IC-ORR IC-PFS
Brigatinib 180 mg QD ALTA Arm B <sup>8</sup> NCT02094573	Post-crizotinib and/or chemotherapy	BM: Asymptomatic; Active, in the absence of neurological instability and high doses of corticosteroids; LM	Yes	No – only in patients with baseline BM (every 8 weeks through cycle 15, then every 12 weeks)	MRI	RECIST 1.1.	IC-ORR IC-DOR IC-PFS
Lorlatinib 100 mg QD Global phase II <sup>14</sup> NCT01970865	Crizotinib-naïve, post-crizotinib, post-second- generation ALKi	BM: Asymptomatic; Treated/untreated	Yes	Yes; Every 6 weeks through cycle 30, then every 12 weeks	MRI	RECIST 1.1.	IC-ORR IC-DOR Median time to first IC response

ALKi = anaplastic lymphoma kinase inhibitor; BID = twice a day; BM = brain metastases; CNS = central nervous system; CT = computed tomography; FU = follow-up; IC = intracranial; IC-DCR = intracranial disease control rate; IC-DOR = intracranial duration of response; IC-ORR = intracranial objective response rate; IC-TTP = intracranial time to tumour progression; IC-TTR = intracranial time to treatment response; LM = leptomeningeal carcinomatosis; MRI = magnetic resonance imaging; PD = progression; QD = once a day; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases; RECIST = Response Evaluation Criteria in Solid Tumors.

several patients that investigate ALKi concentrations in the CSF, and there are no CSF penetration data on ALKi dose escalation.<sup>9,15,18</sup> For alectinib dose escalation (900 mg twice daily), intracranial responses have been described in two patients with leptomeningeal disease progression under standard dose of alectinib.<sup>19</sup>

### Switching to another ngALKi might avoid or defer cranial irradiation

In crizotinib-naïve and crizotinib-resistant patients, second- and third-generation ALKi have CNS activity regardless of brain irradiation history. In patients with NSCLC with asymptomatic brain metastases, there were similar intracranial ORRs in irradiated versus non-irradiated patients, as shown by trials of brigatinib (phase I/II trials) or alectinib.<sup>5,8</sup> In the ALEX trial, there was a HR for disease progression or death favouring alectinib over crizotinib of 0.34 for previously irradiated patients and 0.44 for patients without prior irradiation.<sup>5</sup> Also, patients with active brain

metastases had similar intracranial ORR and intracranial median duration of response in irradiated versus non-irradiated tumours in the ASCEND-7 trial, in both crizotinib-naïve or pre-treated patients.<sup>9</sup>

The availability of effective systemic treatments for sequential use could thus lead to deferring, or even avoiding, whole brain irradiation, which would spare patients the long-term neurocognitive radio-induced side effects. ALK+ patients are usually young, with a long median overall survival of 6.8 years from diagnosis of stage IV disease.<sup>20</sup> Similarly, long-term effects of stereotactic radiotherapy, such as radionecrosis, could be seen more frequently. Therefore, anticancer strategies should aim to prolong each line of treatment, without adding significant toxicity. For this purpose, when isolated CNS progression relapse is amenable to local treatment, stereotactic radiotherapy or surgery are usually employed, while continuing the same ALKi. As the incidence of radionecrosis is related to the tumour

size, stereotactic radiotherapy should not be delayed too much. It may be interesting to identify patients who will eventually develop early subsequent extra-CNS progression and who might benefit more from a tyrosine kinase inhibitor switch rather than a local treatment. In isolated CNS progression, a positive liquid biopsy might predict subsequent extra-CNS progression, but these data should be validated in prospective studies.<sup>17</sup>

Due to the availability and performance of ngALKi, patients can have long-term survival despite the presence of brain metastases.<sup>20,21</sup> We hope to witness even more rapid improvement in their management as other promising options are being investigated. These include the addition of bevacizumab in the NCT02521051 trial, novel drugs with promising early CNS efficacy data such as entrectinib (NCT03994796, NCT02568267) or

ensartinib (NCT03753685), proof of principle studies in patients who will undergo surgery (e.g., NCT02605746), a new lorlatinib trial in patients without measurable extra-CNS lesions (NCT02927340), trials evaluating upfront radiotherapy and ALKi (e.g., NCT04193007), or radiotherapy concurrent with continuation of the ALKi upon isolated CNS progression during ALKi (e.g., the Dutch multicentre platform trial NL6518/NTR6707).

In conclusion, patients with ALK+ NSCLC with brain metastases greatly benefit from ngALKi, irrespective of prior brain irradiation or the presence of brain involvement at baseline, in the first-line, or after failing crizotinib. The sequential ALKi approach is effective in terms of CNS activity and in obtaining long-term survival. Importantly, whole-brain irradiation can often be deferred or avoided, and patients are spared long-term radio-induced toxicity. □

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