Editorial

Brigatinib entering the clinic for ALK rearranged metastatic NSCLC: editorial on a randomized multicenter phase II study with two brigatinib dose regimens

Adrianus J. de Langen

Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

Correspondence to: Adrianus J. de Langen, MD, PhD. Department of Thoracic Oncology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands. Email: j.d.langen@nki.nl.

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Introduction

In ~5% of patients with non-small-cell lung cancer (NSCLC), the disease is characterized by an anaplastic lymphoma kinase (ALK) rearrangement (1,2). In 2011 the Food and Drug Administration granted Crizotinib, an ALK tyrosine kinase inhibitor (TKI), accelerated approval based on durable objective response rates (ORR) of 50 percent and 61 percent in two single-arm open-label studies (3-5). A signal that was confirmed in a randomized phase III study where crizotinib showed superior outcome when compared to pemetrexed or docetaxel monotherapy in patients that progressed after platinum doublet chemotherapy (6).

Crizotinib moved to the first line based on a randomized phase III study that showed superior outcome with first line crizotinib treatment as compared with platinum-doublet chemotherapy (7). Crizotinib resulted in an ORR of 74% (*vs.* 45% with chemotherapy) and a progression-free survival (PFS) of 10.9 months (*vs.* 7.0 months with chemotherapy). Since then, the field of ALK TKI development moved quickly. Two ALK TKIs received approval by the FDA for the treatment of patients with ALK-rearrangement positive NSCLC that progressed on crizotinib. Ceritinib showed superior outcome when compared to pemetrexed or docetaxel monotherapy in patients that progressed after at least one line of chemotherapy and crizotinib (8). The majority of patients (82%) received crizotinib at the time of study enrollment. Ceritinib resulted in an ORR of 45% and a PFS of 5.4 months. Alectinib showed efficacy in two single arm studies in patients that progressed while receiving crizotinib (9,10). The majority of patients (80% and 74%) received one of more lines of prior chemotherapy. The ORR was 50% and 48% and the PFS 8.9 months and 8.1 months. Since then, both drugs received FDA approval for first line treatment as well. Ceritinib showed superior outcome when compared to platinum-doublet chemotherapy (11). Ceritinib resulted in an ORR of 73% (*vs.* 27% with chemotherapy) and a PFS of 16.6 months (*vs.* 8.1 months with chemotherapy). Alectinib showed superior outcome when compared with crizotinib (12). Alectinib resulted in an ORR of 83% (*vs.* 76% with crizotinib) and the median PFS was not yet reached with alectinib (95% CI: 17.7 months–not yet reached) *vs.* 11.1 months with crizotinib.

Central nervous system (CNS)

ALK positive NSCLC has a high probability to metastasize to the CNS. Up to 60% of patients develop CNS metastases during the course of their disease (6,13) and ~20% of patients present with CNS metastases at the time of diagnosis (6,14). With crizotinib treatment the CNS is a preferential site for progression of disease. In the crizotinib registration studies, 70% of the patients with brain

metastases prior to crizotinib initiation, had a new lesions or non-target progression in the CNS at the time of disease progression, while this was 20% for patients without CNS metastases at presentation (13). Besides drug resistance mechanisms, the limited CNS penetration of crizotinib is likely to play a role (15). Ceritinib and alectinib both demonstrated to be active in controlling and treating brain metastases, both in crizotinib naïve patients (11,12) and patients that progressed in the CNS after crizotinib failure (8-10). In patients that failed crizotinib and had active CNS metastases at study enrollment, ceritinib resulted in ORRs of 35% and 45% in the phase III and II trials, respectively (8,16). Alectinib resulted in ORRs of 57% and 75% in two single arm phase II studies (9,10).

Brigatinib in patients with crizotinib-refractory ALK-positive non-small-cell lung cancer: a randomized, multicenter phase II trial

In a randomized phase II trial Kim *et al*. evaluated two dose regimens of brigatinib, a second generation ALK TKI, in patients with ALK-rearrangement positive NSCLC that progressed on crizotinib at the time of study enrollment (17). Any number of prior chemotherapy regimens was allowed. The patients (n=222) were 1:1 randomized to oral brigatinib 90 mg once daily (arm A) or 180 mg once daily with a 7-day lead-in of 90 mg once daily (arm B) because of pulmonary toxicity that was encountered in the phase I/II trial with a starting dose of 180 mg (18). Patients were stratified by baseline brain metastases (present *vs.* absent) and best investigator-assessed response to crizotinib (response *vs.* other or unknown). Treatment was allowed to be continued at the investigator's discretion after progression. A contrast-enhanced MRI of the brain was required at screening and follow-up imaging was done every 8 weeks. The primary end-point was confirmed ORR per RECIST v1.1 (per investigator). Secondary end points included confirmed ORR [per central independent review committee (IRC)], CNS response, duration of response, PFS, overall survival (OS), safety, tolerability, and quality-of-life. A sample size of ≥109 patients in each arm was calculated to provide 90% power to rule out an ORR of 20% when the true ORR would be ≥35% with a two-sided alpha level of 0.025. The trial was not designed for statistical comparisons between the two dosing arms. 112 patients were allocated to arm A (90 mg arm) and 110 to arm B (180 mg). In arms A and B 71% and 67% had brain metastases at the time of study enrollment, respectively, and 74% received prior chemotherapy in both arms. Investigator-assessed confirmed ORR was 45% (97.5% CI, 34% to 56%) in arm A and 54% (97.5% CI, 43% to 65%) in arm B. Investigator-assessed median PFS was 9.2 months (95% CI, 7.4–15.6) and 12.9 months (11.1–not yet reached) in arms A and B, respectively. IRC-assessed intracranial ORR in patients with measurable baseline brain metastases was 42% (11 of 26 patients; 95% CI, 23% to 63%) in arm A and 67% (12 of 18 patients; 95% CI, 41% to 87%) in arm B.

The most common treatment-emergent adverse events (AEs) in arms A and B were nausea (33%/40%), diarrhea (19%/38%), headache (28%/27%) and cough (18%/34%). The most common grade ≥3 AEs were hypertension (6%/6%), increased blood creatine phosphokinase (3%/9%), pneumonitis (3%/5%) and increased lipase (4%/3%). Early onset pulmonary AEs [median time to onset, 2 days (range, 1 to 9 days)] occurred in 14 patients (6%) and included dyspnea, hypoxia, cough, pneumonia, or pneumonitis. These AEs occurred at 90 mg in both arms and no such events occurred after escalation to 180 mg. In seven patients (3%) this event was ≥ grade 3. They were managed with dose interruption and successful reintroduction of brigatinib was possible in 6 of 14 patients. One patient continued treatment with resolution of symptoms after dose reduction to 60 mg once daily without needing dose interruption. Seven patients discontinued treatment, including one patient who died on day 7, after experiencing dyspnea, cough, and pneumonia. This patient's autopsy revealed malignant pleural effusion, widespread lung scarring, and diffuse alveolar damage.

Dose reduction as the result of any AE occurred in 7% and 20% of treated patients in arms A and B, respectively. Dose interruption (≥3 days) for any reason occurred in 18% and 36% of patients in arms A and B, respectively. The most common reasons for dose reduction were increased blood creatine phosphokinase, pneumonitis, and rash.

Based on these results, the FDA granted brigatinib accelerated approval as a treatment for patients with ALK-rearranged NSCLC who are resistant to prior crizotinib.

Sequencing of ALK TKIs and the position of chemotherapy

With three drugs (alectinib, ceritinib and crizotinib) having FDA approval for the treatment of ALK TKI naïve ALK-rearranged metastatic NSCLC and three drugs having a label for the second line setting after crizotinib failure (alectinib, brigatinib and ceritinib), it is unclear what the

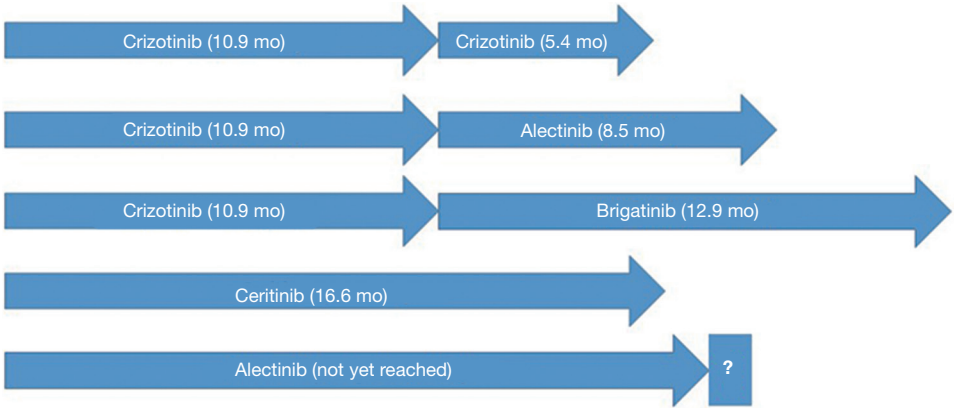

Figure 1 Graphic showing the relative progression-free survival times of the individual ALK TKIs, taking the sequence into account. The reader should bear in mind that these results were not obtained from head-to-head studies and that differences in study populations and design prohibit formal comparisons.

best strategy is to sequence the available ALK TKIs. In this trial brigatinib showed an ORR that is similar to that of alectinib and ceritinib in patients that progressed on crizotinib. Although the trial was not powered to compare the two dosing arms, efficacy outcomes favored the higher dose, most notably in PFS and intracranial response. At a dose of 180 mg, the intracranial ORR was 67%. Although formal comparisons are not available this seems to be equivocal to what can be seen with alectinib (9,10). The median PFS of 9.2 and 12.9 months compare favorably to that of what can be obtained with ceritinib or alectinib after crizotinib failure, although again, formal comparisons are not available (*Figure 1*). It remains an open question what strategy leads to the longest OS; start with a second generation ALK TKI or start with crizotinib and a second generation ALK TKI upon crizotinib failure, of which brigatinib may be the winner, based on PFS. The best way to answer this question is by performing head-to-head studies with a cross-over design. Unfortunately the recent ALEX study with first line alectinib *vs.* crizotinib did not allow for cross-over and therefore it remains unanswered what strategy results in the longest (combined) PFS (first line alectinib or sequential crizotinib and alectinib). The ongoing ALTA-1L study with first line brigatinib *vs.* crizotinib does allow for cross-over to brigatinib in patients that are randomized to crizotinib and hopefully this will answer the sequencing question of crizotinib and brigatinib (19).

Another open question is the efficacy of second generation ALK TKIs after progression on treatment with another second generation ALK TKI. Especially now that two second generation ALK TKIs (alectinib and ceritinib) received FDA approval for first line treatment of ALK-rearranged NSCLC. The emergence of ALK mutations is more common after second generation ALK TKI treatment than crizotinib and the individual ALK TKIs show different ALK mutation profiles at the time of disease progression, possibly resulting in cross-sensitivity (20). A publication by Shaw *et al.* showed that monitoring ALK mutation status can guide sequencing of ALK TKIs in a case where the emergence of a L1198F mutation resensitized ALK-rearranged NSCLC to crizotinib after lorlatinib failure, a next generation ALK TKI (21). Analogous to the EGFR setting, mutation testing both in plasma and tissue enables to monitor resistance and might guide treatment.

Adding to the complexity, (platinum doublet) chemotherapy remains a treatment option with clinical efficacy with an ORR of 27–45% and a PFS of 7.0–8.1 months (7,11). As an 'off-ALK' treatment it targets ALK-rearranged NSCLC through a different mechanism and offers an ALK TKI drug holiday and might sensitize the tumor to retreatment with ALK TKIs (22).

Conclusions

Brigatinib showed an excellent response rate in patients with ALK-rearrangement positive NSCLC that failed crizotinib. Once daily 180 mg with a 7-day lead-in of 90 mg once daily is the preferred dose with a high overall and CNS response rate and a manageable toxicity profile. PFS compares favorably with that of alectinib and ceritinib after crizotinib failure. Questions that remain unanswered are

the best way to sequence ALK TKIs (first line crizotinib followed by a second generation ALK TKI or first line treatment with a second generation ALK TKI) and the efficacy of second generation ALK TKIs after progression on another second generation ALK TKI.

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