Review Article

Optimal first-line treatment for metastatic ALK+ non-small cell lung cancer—a narrative review

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Background and Objective: First-line treatment options for patients with advanced non-small cell lung cancer (aNSCLC) whose tumors harbour anaplastic lymphoma kinase (*ALK*) gene rearrangements have rapidly evolved from chemotherapy, to the first in class ALK-targeted tyrosine kinase inhibitor (TKI) crizotinib in 2011, and now include no fewer than five Food and Drug Administration (FDA)-approved ALK inhibitors. However, while superiority to crizotinib has been established, head-to-head clinical trials comparing newer generation ALK inhibitors are lacking, and decisions on optimal first-line treatment must be based on analysis of the relevant trials, with attention to systemic and intracranial efficacy, toxicity profile as well as consideration of patient factors and preferences. Here we aim to synthesise findings from review of these trials and to describe options for optimal first-line treatment for ALK+ NSCLC.

Methods: A literature review of relevant randomised clinical trials was undertaken using *Embase* database. There were no limitations to time frame or language applied.

Key Content and Findings: Crizotinib was established as the standard of care first-line treatment for patients with ALK+ aNSCLC in 2011. Since this time, alectinib, brigatinib, ensartinib and lorlatinib have all demonstrated superiority as first-line treatments compared to crizotinib, based on progression free survival, intra-cranial efficacy, and side-effect profiles.

Conclusions: Options for optimal first-line treatment for ALK+ aNSCLC include alectinib, brigatinib and lorlatinib. This review serves as a resource summarizing data from key clinical trials with ALK inhibitors to aid in decision making when tailoring treatment for patients. Future research in the field includes real world analysis of efficacy and toxicity of next-generation ALK-inhibitors, identification of mechanisms of tumor persistence and acquired resistance, development of novel ALK inhibitors, and use of ALK-TKIs in earlier stage disease.

Keywords: ALK+; non-small cell lung cancer (NSCLC); first-line

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Introduction

Background

Anaplastic lymphoma kinase (*ALK*) gene rearrangements were first identified as an oncogenic driver in a subset of non-small cell lung cancers in 2007 (1). A phase I study with the first in class ALK tyrosine kinase inhibitor (TKI) crizotinib, demonstrated that tumours harbouring *ALK* gene rearrangements were sensitive to ALK inhibition (2). The PROFILE1014 study comparing crizotinib to standard

of care platinum doublet chemotherapy established first-line ALK-TKI as a new standard of care and in turn created a requirement for testing of tumors from newly diagnosed non-small cell lung cancer (NSCLC) for *ALK* rearrangements (3). Although this represented a significant advance in the treatment of ALK+ aNSCLC, tumors eventually develop resistance to crizotinib. Additionally, crizotinib has limited penetration of the blood-brain barrier and central nervous system (CNS) progression on crizotinib is common (4,5). Thus, newer generation ALK-inhibitors, with improved activity against crizotinib resistance mutations, increased potency and improved CNS penetrance, continue to be developed. A phase III randomised controlled trial (RCT) investigating the second generation ALK inhibitor ceritinib demonstrated superiority of ceritinib over chemotherapy in the first-line setting (6). Subsequent RCTs with second generation ALK inhibitors alectinib, brigatinib, ensartinib and most recently third generation ALK inhibitor lorlatinib have demonstrated superiority over crizotinib on the basis of overall and CNS efficacy.

Rationale and knowledge gap

Despite the multitude of available therapies, there are no RCTs comparing next-generation ALK inhibitors to one another. Thus, selecting the optimal treatment in the first-line setting requires detailed analysis of available evidence, with attention to systemic and intracranial efficacy and to toxicity as well as patient factors and preferences. Previous reviews addressing this topic have included a Cochrane Review by Cameron *et al.*, which concluded that next-generation ALK-inhibitors improve PFS and likely OS when compared to crizotinib, but again this study did not compare next-generation ALK-inhibitors to one another (7). Additionally, the pace of drug development means that previous relevant narrative reviews do not discuss all of the currently available ALK-TKIs (8,9).

Objective

In this narrative review, we aim to analyse and summarise contemporary relevant evidence from clinical trials and to synthesise recommendations for first-line treatment for patients with ALK+ NSCLC. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-656/rc).

Methods

We conducted a literature review using the Embase database evaluating clinical trials for the first-line treatment of ALK rearranged NSCLC. The search strategy is shown in *Table 1*.

Discussion/summary

Narrative

Discovery of ALK and crizotinib

Transforming chromosomal rearrangements resulting in the *EML4-ALK* gene fusion which resulted in aberrant expression and constitutive activity of the ALK kinase was first discovered in lung cancer in 2007 by Hiroyuki Mano and colleagues (1). Four years later, crizotinib, the first-in-class ALK-directed TKI, received accelerated FDA approval for the management of ALK+ aNSCLC after demonstrating activity in a phase I trial with a median progression free survival (mPFS) of 9.7 months (95% CI: 7.7–12.8) and objective response rate (ORR) of 60.8% (95% CI: 52.3–68.9%) (2). A global phase III study subsequently compared crizotinib to single agent chemotherapy in patients with ALK+ NSCLC who had already received platinum-pemetrexed combination and demonstrated superiority of crizotinib, with a mPFS of 7.0 months and ORR of 65% (10). Until this time, patients with ALK-rearranged NSCLC were managed with chemotherapy, as per wild-type patients, with a median overall survival (mOS) of less than 15 months (11). PROFILE 1014, a global phase III study showing superiority of crizotinib compared to platinum-pemetrexed, with mPFS of 10.9 months compared to 7.0 months (HR 0.45; 95% CI: 0.35–0.60, P<0.001) and ORR of 74% compared to 45%, P<0.001 (*Table 2*) established ALK inhibition with crizotinib as a new standard of care for patients with newly diagnosed *ALK* rearranged NSCLC (3). These findings were confirmed in a phase III study of first-line crizotinib versus chemotherapy in an East Asian population (*Table 2*) (12). Thus, crizotinib transformed initial management of aNSCLC harbouring *ALK* rearrangements and set the new benchmark for future comparative trials. The discovery of crizotinib also led to the requirement that all newly diagnosed patients with advanced adenocarcinoma of the lung undergo testing for *ALK* rearrangements. Subsequently, newer generation ALK-TKIs that are more potent against the ALK kinase, have activity against mutations that result in resistance to

Table 1 Search strategy summary

Items	Specification
Date of search	12/08/2022
Databases and other sources searched	Embase
Search terms used	Embase <1974 to 2022 August 12>
	1. ((anaplastic lymphoma kinase or ALK positive or ALK rearrang*) adj4 (non-small cell lung cancer* or nonsmall cell lung cancer* or NSCLC)).tw,kw. 2819
	2. ((anaplastic lymphoma kinase or ALK positive or ALK rearrang*) adj4 lung adj3 adenocarcinoma*).tw,kw. 436
	3. 1 or 2 3170
	4. exp randomized controlled trial/723233
	5. (random* or RCT or placebo).tw. 1943632
	6. 4 or 5 2041197
	7. 3 and 6 305
	8. 7 not (conference abstract.pt. or (systematic review or meta-analysis).ti.) 128
Timeframe	Unlimited
Inclusion criteria	Randomised controlled trials
Selection process	All abstracts reviewed by first author. Only randomised clinical trials including patients who were treatment naïve were included (8 studies in total). Updated analysis relating to these 8 studies were also included

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial.

crizotinib, and with increased CNS penetration have been developed, including the second generation inhibitors ceritinib, alectinib, brigatinib and ensartinib as well as the third generation inhibitor lorlatinib, all of which have been evaluated in the first-line setting.

Ceritinib

Ceritinib was studied in global phase III trial in comparison to chemotherapy in the first-line setting (ASCEND-4) (6). Between 2013–2015, 376 ALK+ treatment naïve patients were randomised to receive ceritinib or platinum-based chemotherapy. PFS was superior in the ceritinib group, with a HR for disease progression or death of 0.55 (95% CI: 0.42–0.73, P<0.001) (*Table 2*). Gastrointestinal toxicity was frequent in the ceritinib treated group and included diarrhoea in 85%, nausea in 69% and vomiting in 66%. This was mostly grade 1–2.

Alectinib

In a global study of 303 patients randomised to alectinib or crizotinib (ALEX), those receiving alectinib had an improved PFS (HR 0.47, 95% CI: 0.45–0.65) (*Table 2*) (13). An updated analysis in 2020 showed the mPFS by investigator review for the alectinib group was 34.8 months compared to 10.9 months for those receiving crizotinib (19). Although overall survival data remained immature at the time of this report, 5-year OS rate was 62.5% for alectinib, with a HR of 0.67 (95% CI: 0.46–0.98, P=0.0376) when compared to crizotinib (19). Improvement in CNS penetration was reflected by improved 12-month cumulative incidence of CNS progression, with a rate of 41.4% (95% CI: 33.2–49.4) for crizotinib compared to 9.4% (95% CI: 5.4–14.7) for alectinib (*Table 2*) (13). Grade 3 to 5 adverse events (AEs) occurred in 41% of those on alectinib and 50% of those on crizotinib (median duration of treatment 17.9 and 10.7 months respectively). Nausea, vomiting and diarrhoea all occurred less frequently for those on alectinib (13). The ALESIA trial randomised 187 patients from Eastern Asia 2:1 to receive alectinib or crizotinib (15). A PFS benefit was also seen in this cohort with the use of alectinib (15). J-ALEX enrolled 207 patients in Japan specifically and randomised patients 1:1 to receive alectinib or crizotinib (14). Unlike

Table 2 Summary of randomised controlled trials investigating first-line treatment of ALK+ aNSCLC, as of August 2022

ALK inhibitor	Study, year of publication	Treatments being compared	Hazard ratio for disease progression or death [95% CI]	Intracranial activity (variable endpoints)	Objective response rates % [95% CI]	1st line approval	Ref
Crizotinib (1st generation)	PROFILE 1014, 2014	Crizotinib *vs.* chemotherapy	0.45 [0.35–0.60], P<0.001**	*All patients:* IC disease progression 5% *vs.* 15%;	74 [67-81] *vs.* 45 [37–53], P<0.001	US: 2011; Europe: 2015	(3)
	PROFILE 1029, 2018	Crizotinib *vs.* chemotherapy	0.40 [0.29–0.56]; P<0.001**	median IC TTP NR (95% CI, 20.8–NR) *vs.* 16.0 months (95% CI, 12.6–NR)	87.5 [79.6–93.2] *vs.* 45.6 [35.8–55.7], P<0.001		(12)
Ceritinib (2nd generation)	ASCEND-4, 2017	Ceritinib *vs.* chemotherapy	0.55 [0.42–0.73], P<0.00001**	*For those with measurable baseline brain metastases*: IC ORR 72.7% (95% CI, 49.8–89.3) *vs.* 27.3% (95% CI, 10.7–50.2); IC CR 9.1% *vs.* 9.1%	72.5 [65.5–78.7] *vs.* 26.7 [20.5–33.7]	US: 2017; Europe: 2017	(6)
Alectinib (2nd generation)	ALEX, 2017	Alectinib *vs.* crizotinib	0.47 [0.34–0.65], log-rank P<0.001*	*For those with measurable baseline brain metastases*: IC ORR 81% (95% CI, 58–95) *vs.* 50% (95% CI, 28–72); IC CR 38% *vs.* 5%	82.9 [76.0–88.5] *vs.* 75.5 [67.8–82.1], P=0.09	US: 2017; Europe: 2017	(13)
	J-ALEX, 2017#	Alectinib *vs.* crizotinib	0.34 [0.17–0.71], log-rank P<0.0001**	*For those with baseline brain metastases*: HR for TTP of brain metastatic lesion or death 0.16 (95% CI, 0.02–1.28); No baseline brain metastases: HR for time to onset of new brain metastases or death 0.41 (95% CI, 0.17–1.01)	92 [85.6–97.5] *vs.* 79 [70.5–87.3]		(14)
	ALESIA, 2018	Alectinib *vs.* crizotinib	0.37 [0.22–0.61], P<0.0001*	Time to CNS progression cause-specific HR 0.14	91 *vs.* 77 (HR 0.22, 95% CI: 0.12–0.40; P<0.0001)		(15)
Brigatinib (2nd generation)	ALTA-1L, 2018#	Brigatinib *vs.* crizotinib	0.49 [0.33–0.74], log-rank P<0.001**	*For those with measurable baseline brain metastases*: IC ORR 78% (95% CI, 52–94) *vs.* 29% (95% CI, 11–52); IC CR 11% *vs.* 0%	71 [62–78] *vs.* 60 [51–68]	US: 2020; Europe: 2020	(16)
Lorlatinib (3rd generation)	CROWN, 2020	Lorlatinib *vs.* crizotinib	0.28 [0.19–0.41], P<0.001**	*For those with measurable baseline brain metastases*: IC ORR 82% (95% CI, 57–96) *vs.* 23% (95% CI, 5–54); IC CR 71% *vs.* 8%	76 [68–83] *vs.* 58 [49–66]	US: 2021; Europe: 2022	(17)
Ensartinib (2nd generation)	eXalt3, 2021#	Ensartinib *vs.* crizotinib	0.51 [0.35–0.72], log-rank P<0.001**	*For those without baseline brain metastases in mITTgroup:* ^ Development of new brain metastases rate: 4.2% *vs.* 23.9%; cause specific HR 0.32 (95% CI, 0.16–0.63), P=0.001	74 [66–81] *vs.* 67 [58–74]	China: 2022	(18)

*, as assessed by investigators; **, as assessed by blinded independent committee review or independent radiology review; #, patients may have had up to one prior line of treatment, excluding ALK-directed tyrosine kinase inhibitors; ^, mITT population in eXalt3 study was used to describe the efficacy among patients with central laboratory-confirmed ALK-positive status. ALK, anaplastic lymphoma kinase; aNSCLC, advanced non-small cell lung cancer; DoR, duration of response; CR, complete response; IC, intracranial; ORR, overall response rate; NE, not evaluable; NR, not reached; RR, response rate; TTP, time to progression; US, United States; mITT, modified intention to treat.

ALEX and ALESIA, patients may have received up to one line of previous anticancer therapy (excluding ALK-directed TKI) for advanced disease, and a lower dose of alectinib was used (600 mg per day compared to 1,200 mg per day) (14). This lower dose was utilised for regulatory reasons following a phase I/II study in Japanese patients and did not appear to impact efficacy, with a HR 0.34 (99.7% CI: 0.17–0.71, stratified log-rank test P<0.0001) in favour of alectinib (*Table 2*) (14,20). There was no difference in overall survival (HR 1.03, 95% CI: 0.67–1.58, P=0.9105), noting that cross-over was allowed in this study (21).

Brigatinib

Brigatinib demonstrated superior efficacy compared to crizotinib in a global phase III study of 275 patients, the ALTA-1L study (16). Of note, this trial also included patients who had received up to one prior line of systemic therapy for locally advanced or metastatic disease (26% in brigatinib arm and 27% in crizotinib arm). Patients receiving brigatinib had a HR for disease progression or death of 0.48 (95% CI: 0.25–0.66) (*Table 2*). Again, improved CNS activity was demonstrated compared to crizotinib, with a 12-month cumulative incidence of CNS progression rate of 22.4% for those on crizotinib compared to 7.8% for those on brigatinib (HR 0.30, 95% CI: 0.17–0.53) (22). Interstitial lung disease or pneumonitis occurring within 14 days of starting treatment was observed in 3% of those on brigatinib and 0% of those receiving crizotinib. Survival data from this trial remains immature.

Ensartinib

Ensartinib demonstrated superior efficacy compared to crizotinib in a phase III global study of 290 patients, the eXalt3 trial (18). Patients could be included if they had received up to one previous line of chemotherapy for metastatic disease (23.8% of those receiving ensartinib and 28.6% of those receiving crizotinib) and this was included as a stratification factor. Patients receiving ensartinib had a HR for disease progression or death of 0.51 (95% CI: 0.35–0.72). Although this study was not powered to detect significant difference between subgroups, the HR for disease progression or death was numerically smaller for Asian patients (HR 0.32, 95% CI: 0.19–0.55). The incidence of rash in the ensartinib group was 67.8% (grade 3 in 11%) and pruritis in 26.6%. On the basis of this study, ensartinib was approved for use in the first-line setting by the National Medical Products Administration (NMPA) in China.

Lorlatinib

Lorlatinib is the first 3rd generation ALK inhibitor to be approved for use by the FDA, following evidence of superior efficacy compared to crizotinib in the global phase III CROWN trial (17). This study randomised 296 patients to receive either crizotinib or lorlatinib. Patients receiving lorlatinib had a HR for disease progression or death of 0.28 (95% CI: 0.19–0.41) (*Table 2*) (17). Of particular interest was the marked CNS benefits; for those with pre-existing brain metastases the HR for disease progression or death was 0.20 (95% CI: 0.10–0.43) for those receiving lorlatinib compared to crizotinib (17). Among those with measurable brain metastases in the lorlatinib group the overall response rate was 82% with a complete intracranial response in 71% of patients (*Table 2*). Lorlatinib also improved time to intracranial progression. In the entire intention to treat population, median time to intracranial progression was not reached (95% CI: NR–NR) in the lorlatinib group compared to 16.6 months (95% CI: 11.1–NR) in the crizotinib group, HR 0.08 (0.040–0.174) (23). The 12-month cumulative incidence of intracranial progression as first event (i.e., intracranial progression without non-CNS progression) was 2.8% in the lorlatinib group (95% CI: 1.0–8.1) compared to 33.2% in the crizotinib group (95% CI: 24.6–44.7), HR 0.06 (95% CI: 0.02–0.18) (17). For those with baseline brain metastases, the median time to intracranial progression was not reached (95% CI: NR–NR) in the lorlatinib group compared to 7.3 months (95% CI: 3.7–9.3) in the crizotinib group, HR 0.10 (0.04–0.27) (23). For those without baseline brain metastases, the median time to intracranial progression was not reached (95% CI: NR–NR) in the lorlatinib group compared to 30.8 months (95% CI: 18.4–NR) in the crizotinib-treated group, HR 0.02 (95% CI: 0.002–0.14) (23). This improved CNS penetrance was also associated with increased CNS toxicity in the lorlatinib group, with 21% experiencing cognitive side-effects (of any grade) compared to 6% in the crizotinib group. Mood side effects were reported 16% of those receiving lorlatinib compared to 5% of those receiving crizotinib.

Efficacy endpoints

The progression free survival achieved by ALK+ patients

receiving TKI in the phase III studies discussed ranges from around 11 months for those receiving crizotinib to 21.0 months for those receiving brigatinib in the ALTA-1L study (by BICR), to 34.8 months in alectinib arm of ALEX study (investigator assessed), to beyond 36 months in the lorlatinib arm of CROWN study (by BICR), where median PFS has not yet been reached) (19,23,24). These substantial PFS gains are the best reported with any targeted therapies across all of the known molecular subtypes of aNSCLC, and are best contextualised when considering the median survival for patients with wild-type aNSCLC remains in the order of 10–22 months in recent phase III studies (25,26). It should be noted that patient cohorts differed across trials; patients may have had up to one prior line of anticancer therapy excluding ALK-directed TKI in ALTA-1L, eXalt3 and J-ALEX whilst others were in the first-line setting only, some were national or regional (J-ALEX, ALESIA) whilst others were global, and patient eligibility criteria differed across trials (14-16,18). Patients with brain metastases were included in all of the above-mentioned trials however PROFILE 1014 and 1029 required brain metastases to be treated where other trials allowed treated or asymptomatic brain metastases (3,12). Patients with asymptomatic or treated leptomeningeal disease were included in some trials (ALEX, J-ALEX, ALESIA, ALTA-1L, CROWN) but exclude from others (14,15,17,18). Furthermore, most studies reported PFS as assessed by BICR as the primary endpoint, whilst the updated results of the global ALEX study reported investigator assessed PFS (*Table 2*) (13,16). Additionally, cross-over was variably permitted on protocol (permitted in PROFILE 1014, PROFILE 1029, J-ALEX, ALTA-1L and ASCEND-4 and not permitted in CROWN or in ALEX) (3,6,12-14,16,17).

Despite impressive gains in PFS and survival benefits compared to wild-type groups, the phase III trials discussed above have not yet demonstrated statistically significant improvements in overall survival. This is likely in part due to effects of cross-over in some trials and utilisation of effective post-study treatment. A caveat is that survival data remains immature for recent studies with newer-generation ALK inhibitors. Despite this, updated results from the ALEX study have demonstrated new landmark survival for patients with aNSCLC, with mOS of 56.4 months in the crizotinib group (*vs.* not reached in the alectinib group), and with 62.5% of patients in the alectinib group alive at 5 years (19). Signals of improved OS have emerged from the updated analysis of ALTA-1, which found an improvement in mOS on post-hoc analysis for those with baseline brain metastases who received brigatinib compared to those receiving crizotinib (HR 0.43, 95% CI: 0.21–0.89) (24). Additionally, following statistical adjustment for cross-over, improvement in OS was demonstrated for the overall cohort receiving brigatinib compared to crizotinib (HR 0.54, 95% CI: 0.31–0.92, P=0.023 by marginal structured model and HR 0.50, 95% CI: 0.28–0.87, P=0.014 by inverse probability of censoring weight approach) (24). Similarly, when statistical adjustment (rank-preserving structural failure time model) was applied to account for the effect of cross-over in an updated survival analysis from PROFILE 1014, Solomon *et al.* reported an improvement in OS favouring crizotinib over chemotherapy (HR 0.0346, 95% bootstrap CI: 0.081–0.718) (27). Limitations to this method of analysis are acknowledged (27). A Cochrane review by Cameron *et al.* demonstrated a likely survival benefit of crizotinib over chemotherapy (HR 0.84, 95% CI: 0.72–0.97) and a likely survival benefit of next-generation ALK inhibitors over crizotinib (HR 0.71, 95% CI: 0.56–0.90) despite cross-over in the included trials (7). Importantly, when considering the impact of treatment on survival, first-line treatment cannot be considered in isolation; first-line treatment choice may impact the PFS of subsequent treatments and a particular sequence of treatments may confer improved survival overall. This has not been studied in RCTs. However, small retrospective cohort studies have investigated the impact of treatment sequence on PFS and OS (28-30). Important limitations to such observational studies include selection bias, where patients with favourable biology are more likely to receive second and subsequent lines of therapy, in addition to potential lack of data on the rate and type of treatments received subsequently.

Intracranial activity is another important endpoint to be considered when selecting optimal first-line therapy given the functional consequences and morbidity related to brain metastases. It is known that CNS metastases are common in patients with ALK+ lung tumours at diagnosis and develop cumulatively, and that CNS penetration of crizotinib is limited (31,32). As newer generation ALK inhibitors have been created, on target potency and CNS penetration have also increased. In patients with one or more measurable brain metastases at baseline, alectinib has shown an intracranial ORR of 81% and a complete intracranial response in 38%; brigatinib an intracranial ORR of 78% and complete intracranial response in 28%; and lorlatinib an intracranial ORR of 83% and complete intracranial response in 72% (*Table 2*) (16,17,19). In the CROWN trial, the 12-month cumulative incidence of

intracranial progression as first event was significantly lower in the lorlatinib group, HR 0.06 (95% CI: 0.02–0.18) (17). Lorlatinib was also effective at preventing the development of brain metastases in those without baseline CNS disease, with an improved median intracranial PFS compared to crizotinib, HR 0.02 (95% CI: 0.002–0.14) (23).

Management of toxicity

Although ALK inhibitors are generally well tolerated, management of side-effects forms an important component of optimal overall management. The toxicity profiles of the 5 FDA-approved ALK-TKIs vary, and this may be a consideration when selecting the best first-line treatment for an individual patient. Gastrointestinal toxicity is common with both crizotinib and ceritinib but can be more severe with ceritinib. A reduced dose of 450 mg and administration with food has been found to ameliorate gastrointestinal toxicity (33). Pulmonary toxicity can be observed with any of the ALK inhibitors, but may be more common with brigatinib, occurring in 4% of those receiving brigatinib *vs.* 2% of those receiving crizotinib (grade 3–4 in 3% and 0.7% respectively) (16). Additionally, brigatinib has demonstrated a unique early pulmonary toxicity as discussed above (16). This risk can be reduced by commencing brigatinib at a lower dose 90 mg for 7 days before increasing to 180 mg daily if tolerated (34). If symptomatic pulmonary toxicity is suspected, brigatinib should be withheld pending prompt investigation and management. Pneumonitis also occurred in some patients receiving other next-generation ALK-inhibitors; 2% of those receiving ceritinib *vs.* 1% of those receiving chemotherapy in the ASCEND-4 study, 1% of those receiving lorlatinib *vs.* 1% of those receiving crizotinib in the CROWN trial, 1% of those receiving ensartinib requiring treatment discontinuation *vs.* not reported in those receiving crizotinib in the eXalt3 trial, and 0% of those in the alectinib group of the ALEX study *vs.* 2% of those receiving crizotinib (6,13,17,18). Grade 1–2 myalgias are relatively common with alectinib, occurring in 16% of patients (compared to 2% in crizotinib group). Myalgias often dissipate despite treatment continuation but may in some cases necessitate dose reduction. Hypercholesterolaemia and hypertriglyceridemia are common with lorlatinib, occurring at any grade in 70% and 64% respectively (17). These should be managed with beta-hydroxy beta-methylglutaeyl-CoA reductase inhibitors (e.g., rosuvastatin) and fibrates, respectively (35). The increased CNS-penetration of lorlatinib correlates with increased CNS toxicity, as discussed above. It is important to proactively discuss potential cognitive and mood side-effects with patients and their family members and to reassure that this toxicity usually resolves or improves with dose reduction or interruption. Furthermore, in the phase III CROWN trial, dose reduction did not appear to impact 12-month progression free survival (36). Additionally, CNS AEs may resolve spontaneously; of 86 CNS AEs reported in the CROWN trial, 53 were managed without intervention and 28 of these (53%) resolved (36).

Optimal first-line treatment selection

As discussed, there are now a broad array of options available for the initial management of ALK+ aNSCLC. Phase III trials have established that alectinib, brigatinib, ensartinib and lorlatinib are superior to crizotinib on the basis of PFS and intracranial activity. Additional evidence comes from the Cochrane Review which concluded that next-generation ALK inhibitors including alectinib, brigatinib and lorlatinib achieve a superior PFS and OS compared to crizotinib as first-line treatment (7). Based on systemic and intracranial efficacy and on toxicity profiles, alectinib, brigatinib and lorlatinib are the preferred choices. Ceritinib is also a reasonable choice but has not been compared to crizotinib and thus is not preferred. Ensartinib is not available through the FDA or European Medicines Agency (EMA) where available it may be a reasonable choice compared with crizotinib.

Beyond first-line

Despite advances in first-line therapy, ALK+ lung cancers eventually develop resistance and patients experience disease progression. For those patients who receive crizotinib in the first-line, second-line therapy may be with either alectinib, brigatinib or lorlatinib (if available) (37-39). For those who receive first-line 2nd generation ALK inhibitor, second-line therapy with lorlatinib remains an option, with response rates of approximately 40% (or higher if ALK mutation confirmed in plasma or DNA sampling at the time of progression) (39,40). For those receiving first-line lorlatinib, the question of what to do at the time of progression is more challenging. Regardless of first-line treatment, biopsy of progressing tumour may shed light on resistance mechanisms, which are discussed in detail in a separate review within this special series. Around one third of tumours with acquired crizotinib resistance

will have a new mutation in the ALK-kinase domain. In particular, the G1202R mutation confers resistance to alectinib and ceritinib, but tumours may remain sensitive to lorlatinib (17,41). When plasma and tumour samples from 198 patients enrolled in the phase II registrational study of lorlatinib, the ORR to lorlatinib was 57% for those harbouring G1202R mutations/deletions alone (40). Response rates were less when compound mutations were also present (40). Resistance can also occur via ALK-independent mechanisms including MET amplification or phenotypic changes (42-44). Thus, repeat biopsy may identify a new targetable genetic abnormality or signalling pathway alteration. Treatment beyond progression is at times indicated when patients continue to gain clinical benefit or, in the case of mixed responses, where progressing tumours can be treated with local therapy (although this approach is experimental and generally only recommended as part of a clinical trial). Further studies of resistance mechanisms on next-generation inhibitors and trials using fourth generation ALK-directed TKIs are currently underway.

Limitations of this review

This review summarizes all randomized controlled trials comparing treatments for ALK+ aNSCLC in the first-line setting. As discussed, these trials were heterogenous on many levels and did not include head-to-head comparisons of newer generation ALK-TKIs limiting the ability to accurately compare between ALK-inhibitors. Furthermore, due to the summative nature of a review, extensive discussion of toxicity for each agent has not been included.

Conclusions

The management of ALK+ aNSCLC has been transformed over the past decade and unprecedented improvements in PFS and survival have been observed. Optimal first-line treatment may be with alectinib, brigatinib or lorlatinib. In the absence of phase III trials comparing these agents, selection will be based on factors such as informed patient preference, CNS disease, availability, pricing, and toxicity profile. As the benchmark standard of care for these patients is rapidly evolving, comparator arms in clinical trials may continue to be outdated by the time trials are complete. Thus, evidence from the real-world on comparative efficacy may aid in decision making into the future. This calls to attention to importance of shared registries and thorough and systematic documentation processes in order to study post-market efficacy of these drugs (45).

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