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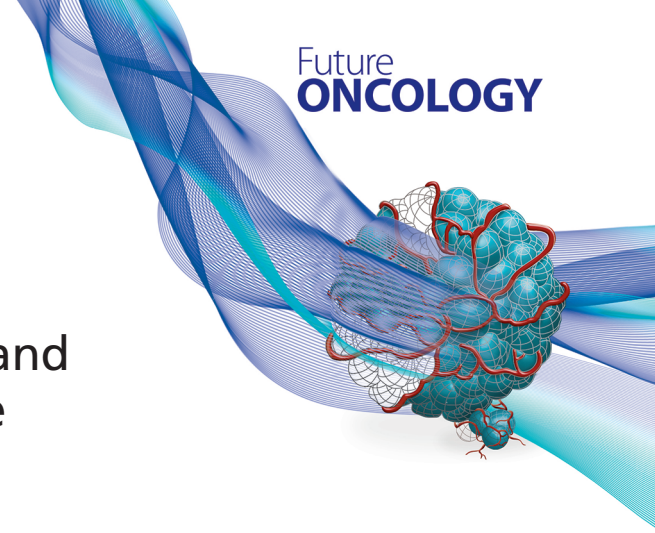

Indirect comparisons of brigatinib and alectinib for front-line *ALK*-positive non-small-cell lung cancer

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Aim: To conduct an indirect treatment comparison (ITC) of the relative efficacy of brigatinib and alectinib for progression-free survival in people with tyrosine kinase inhibitor (TKI)-naive *ALK*-positive non-small-cell lung cancer (NSCLC). **Methods:** Final aggregate and patient-level data from the ALTA-1L trial comparing brigatinib to crizotinib and published aggregate data from ALEX (comparing alectinib to crizotinib) were contrasted using Bucher ITC and matching-adjusted indirect comparisons (MAICs). **Results:** No statistically significant differences were identified between brigatinib and alectinib in reducing the risk of disease progression overall and in patients with baseline central nervous system metastases. **Conclusion:** Brigatinib appeared similar to alectinib in reducing risk of disease progression for people with TKI-naive *ALK*-positive NSCLC.

Plain language summary: Patients with advanced non-small-cell lung cancer (NSCLC) who have a genetic marker called rearrangement in the anaplastic lymphoma kinase, or *ALK*-positive disease, are treated with targeted medications taken by mouth. Two medications, alectinib and brigatinib, are both considered first-line treatment for these patients but have not been compared head-to-head. Recently, updated clinical trial results were published for these medications. The present study utilized these updated results and advanced statistical tests to indirectly compare the effectiveness of the two treatments to help guide clinical treatment choices. Results showed brigatinib and alectinib have a similar magnitude of effect in decreasing the risk of a patient with *ALK*-positive NSCLC developing worsening disease.

First draft submitted: 23 February 2022; Accepted for publication: 27 April 2022; Published online: 24 May 2022

Keywords: alectinib • ALK inhibitor • brigatinib • Bucher ITC • matching-adjusted indirect comparison • NSCLC • progression-free survival • systematic literature review

Lung cancer is the leading cause of cancer-related mortality worldwide. An estimated 2.2 million new cases were diagnosed in 2020 and about 1.8 million deaths occur every year [1]. Non-small-cell lung cancer (NSCLC) is the most common form of lung cancer (85% of patients), with up to 7% of patients with stage IIIB/IV NSCLC harboring rearrangements in the *ALK* gene [2] – making them sensitive to targeted molecular therapy.

Crizotinib is the first ALK-targeted tyrosine kinase inhibitor (TKI) that was approved by the US FDA for the treatment of patients with locally advanced or metastatic NSCLC in 2011 [3]. Second-generation ALK-targeted TKIs, alectinib and brigatinib, approved by the FDA as front-line treatments in 2017 and 2020 respectively, have

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been shown in randomized controlled trials (RCTs) to be superior to crizotinib [4,5]. The approval of alectinib was based on data from ALEX (NCT02075840), an RCT comparing alectinib to crizotinib conducted in 303 treatment-naive patients with advanced disease [4], whereas the approval of brigatinib was based on the second interim results of ALTA-1L (NCT02737501), an RCT comparing brigatinib to crizotinib in 275 locally advanced or metastatic patients naive to ALK-TKIs [5]. Most recent results of ALEX [6] and final results from ALTA-1L [7] (after a similar follow-up time) reaffirmed, respectively, alectinib's and brigatinib's superiority over crizotinib in this setting.

Although no head-to-head data comparing brigatinib and alectinib in the ALK-TKI-naive population are available, several studies [8–11] have estimated their relative efficacy using network meta-analysis (NMA) [12] or Bucher´s indirect treatment comparison (ITC) methodology [13] and found no significant differences in terms of progression-free survival (PFS). The present analysis provides updated estimates for the relative efficacy of brigatinib versus alectinib using the most recent PFS data of the ALEX (median follow-up in the alectinib arm 37.8 months [14]) and the final data cut from the ALTA-1L (median follow-up in the brigatinib arm 40.4 months [7]) clinical trials. Bucher ITC results are presented alongside, for the first time, results from matching-adjusted indirect comparison (MAIC) [15] methods, used to account for imbalances in treatment effect modifiers between the patient populations in these two trials.

Materials & methods

Systematic literature review & risk of bias assessment

To inform the ITC analyses, a systematic literature review (SLR) was conducted to identify all published RCTs and single-arm trials of alectinib and brigatinib used as front-line treatment of ALK-TKI-naive adults with locally-advanced or metastatic *ALK*-positive NSCLC. Patients were allowed to have received one prior systemic therapy regimen.

The SLR was conducted according to the methodology outlined in the NICE technology appraisal methods guide [16], the Cochrane Collaboration guidance [17], and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18].

The following electronic databases were searched (from inception to 1 August 2019) for publications relating to front-line treatment in *ALK*-positive NSCLC: Embase via Embase.com; MEDLINE and MEDLINE In-Process via PubMed; and the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effects (DARE; all via the Cochrane Library). The searches were limited to studies in humans and only English-language articles were included. The search strategies comprised terms for 'lung cancer', 'treatment-naive' and 'anaplastic lymphoma kinase' and are available on request. Abstracts from the past three meetings of selected conferences at the time the SLR was conducted (2017–2019) were also reviewed (specifically, American Society of Clinical Oncology [ASCO] Annual Meeting, European Society for Medical Oncology [ESMO], International Association for the Study of Lung Cancer/World Conference on Lung Cancer [IASLC WCLC], European Lung Cancer Conference [ELCC] and International Society for Pharmacoeconomics and Outcomes Research [ISPOR]).

Two independent researchers screened publication abstracts against the study inclusion criteria. Relevant publications were then dual-reviewed in full text. Disagreements were resolved by a third researcher. At the time of analysis, additional targeted searches were conducted through June 2020 to identify relevant publications reporting more recent data for the ALEX and ALTA-1L clinical trials.

Data were extracted and validated by two independent reviewers into a predefined template. The main outcome of interest was PFS, including both independent review committee (IRC)- and investigator (INV)-assessed PFS. A quality assessment of the included studies was undertaken using the Cochrane Risk of Bias tool for RCTs [19].

ITC considerations

Data sources for all ITC analyses included aggregate clinical results (identified by means of the SLR and the targeted searches or extracted from the final analysis of the ALTA-1L clinical study report) and for the MAICs, additionally, individual patient data (IPD) from the ALTA-1L clinical study report (date of last patient visit: 29 January 2021). This work was exempt from the need for institutional review or approvals as no primary data were collected.

The Bucher ITC [13] method is based on aggregate data and assumes that there is no difference between the trials in the distribution of effect-modifying variables. It is highly vulnerable to systematic variation (bias) resulting from imbalances in effect modifier distributions. Anchored MAICs preserve [15] intra-trial randomization benefits

in generating the contrast estimate between brigatinib and alectinib, and thus require matching only on treatment effect modifier variables that are imbalanced between the trials.

The proportion of patients with baseline CNS metastases was notably higher in ALEX for both treatment arms (alectinib: 42%, crizotinib: 38%) compared with ALTA-1L (brigatinib: 29%, crizotinib: 30%). Using the final data from ALTA-1L, baseline CNS metastases was identified as a significant treatment effect modifier in terms of IRC- and INV-assessed PFS, with brigatinib performing relatively better than crizotinib in patients with baseline CNS metastases. This finding was corroborated by the clinical community. Therefore, this imbalance warranted exploration of subgroup Bucher ITC analyses stratified by presence of baseline CNS metastases, as well as of population-adjusted ITC methods (i.e., MAICs).

A further difference in the clinical trial design was that ALEX did not permit prior systemic therapy. ALTA-1L did allow for this, and 26% in the brigatinib arm and 27% in the crizotinib arm received at least one full cycle of prior chemotherapy. Although this was not demonstrated to be a significant treatment effect modifier using the ALTA-1L data, this difference between trials was explored in subgroup analyses.

Bucher ITC statistical analysis approach

Bucher ITC analyses were conducted for IRC- and INV-assessed PFS. Subgroup analyses were conducted to explore the impact of differences in baseline CNS metastases and prior systemic therapy. Relative effects of the compared treatments were assumed to be independent of follow-up time, and results are presented as hazard ratios (HRs) with associated 95% CIs.

MAIC statistical analysis approach

The imbalance in the baseline CNS metastases across the ALTA-1L and ALEX clinical trials warranted the use of population adjustment methods, i.e., anchored MAICs [15]. Weights were estimated using a method of moments approach [20]. A Cox regression was then run between the MAIC-weighted crizotinib and brigatinib ALTA-1L arms. The resultant log-HR together with a 'robust/sandwich' variance estimate was extracted and inputted, along with the ALEX alectinib versus crizotinib log-HR and variance estimate, into the Bucher algorithm to produce the brigatinib versus alectinib contrast.

For completeness, unanchored MAICs were explored to examine the impact of removing any data for crizotinib, i.e., estimating the relative effect of brigatinib versus alectinib as if they were from two single arm trials. The unanchored MAIC assumes that all effect modifiers and prognostic factors are accounted for. These included: age, ever smoked, Asian ethnicity, baseline CNS metastases, Eastern Cooperative Oncology Group (ECOG) score and whether patients had previous systemic therapy. These factors were previously identified in the literature and were validated through clinician input [21–23]. A robust weighted Cox regression was run on this dataset with the coefficient on the treatment indicator representing the brigatinib versus alectinib log-HR contrast.

Effective sample sizes (ESS) were calculated following MAIC reweighting. This conservative estimate of the sample size assumes all patients received an equal weight of one (the more evenly distributed the weights, the closer the ESS is to the sample size). MAIC weights were programmed in R (v3.61 or above) using published code [20], while the Cox regressions with robust variance estimates were implemented using the R statistical package 'survival' [24].

Results

SLR results & availability of data for analyses

The database searches identified 837 unique records, from which 713 records were excluded following title/abstract screening. The full texts of 124 records were screened to determine their relevance to the review. Upon completion of the SLR, four RCTs (reported across 12 publications) met inclusion criteria for quantitative analyses. One additional publication related to the ALEX trial [6] was identified by the targeted searches (Supplementary Figure 1).

Two trials (J-ALEX [25] and ALESIA [26]) were excluded from quantitative analyses due to lack of generalizability; both RCTs were conducted exclusively in Asian populations. Additionally, patients in J-ALEX [25] received a different alectinib dose (300 mg twice daily [b.i.d]) than those in the ALEX trial (600 mg b.i.d, FDA marketing authorization dose). Ultimately, two global RCTs (ALEX [4,6,27–31] and ALTA-1L [32,33]) evaluating three ALK-TKIs (alectinib, brigatinib and crizotinib) as front-line ALK treatment (≤1 prior systemic therapy regimen was allowed) in *ALK*-positive NSCLC were included in quantitative analyses.

Anchored comparisons of brigatinib versus alectinib were available via their shared comparison with crizotinib. Bucher ITC analyses were feasible for IRC- and INV-assessed PFS for the intent-to-treat (ITT) populations and the systemic therapy-naive populations. Bucher ITC stratified by baseline CNS metastases were feasible for PFS-INV in the ITT population. MAIC analyses (anchored and unanchored) were conducted to compare brigatinib and alectinib in terms of IRC- and INV-assessed PFS in both the ALK-TKI-naive and the systemic therapy-naive populations.

Characteristics of the included studies

ALTA-1L and ALEX were international, industry-sponsored, open-label, phase III RCTs. ALTA-1L compared brigatinib 180 mg daily (after a 7-day lead-in at daily 90 mg) with crizotinib 250 mg b.i.d. ALEX evaluated alectinib 600 mg b.i.d versus crizotinib 250 mg b.i.d. Median (range) follow-up in the brigatinib arm was 40.4 (0–52.4) months in ALTA-1L for all analyses. Both studies reported IRC- and INV-assessed PFS. ALTA-1L used IRC-assessed PFS as a primary outcome and ALEX used INV-assessed PFS instead. For ALEX, two publications and two different median follow-up times contributed data to the analyses (Table 1) [4,14]. The later publication [14] did not present results for IRC-assessed PFS, as it fell beyond the mandated IRC assessment period.

The risk of bias for ALTA-1L and ALEX was mostly driven by their open-label design. However, for the PFS outcome the risk was considered low in the ALTA-1L trial, as it was assessed by IRC.

Patient characteristics for both trials are presented in Table 2. As shown, baseline characteristics were generally well balanced between the intervention and comparator groups within and across both RCTs, with the exception of baseline CNS metastases and the proportion of patients who had received prior systemic therapy. Of note, baseline CNS metastases were defined as brain metastases in the ALTA-1L trial and no further specified in the ALEX trial, where asymptomatic brain or leptomeningeal metastases were allowed at study baseline.

Table 1. Characteristics of the ALTA-1L and ALEX trials.

Trial	Study design	Stratification factors for the randomization	Population	Treatment arms (number randomized)	Median follow-up in the ALK-TKI arm presented stratified by analysis and outcome (months)	Crossover allowed?	Ref.
ALTA-1L (NCT02737501)	International, open-label, phase III, RCT	Baseline brain metastases (present or absent) and completion of at least one full cycle of previous chemotherapy for locally advanced or metastatic disease (yes or no)	**Inclusion criteria:** Stage IIIB/IV *ALK*-positive NSCLC **Exclusion criteria:** Prior ALK-TKI; >1 prior systemic anticancer therapy	Brigatinib 7-day lead-in at 90 mg q.d. then 180 mg q.d. (137) Crizotinib 250 mg b.i.d (138)	**All analyses:** IRC-assessed PFS: 40.4 INV-assessed PFS: 40.4	Yes, upon disease progression (from crizotinib to brigatinib)	[7]
ALEX (NCT02075840)	International, open-label, phase III, RCT	ECOG performance status (0 or 1 vs 2), race (Asian vs non-Asian), baseline CNS metastases (present or absent)	**Inclusion criteria:** Stage IIIB/IV *ALK*-positive NSCLC; Life expectancy ≥12 weeks **Exclusion criteria:** Prior ALK-TKI; Any prior systemic anticancer therapy	Alectinib 600 mg b.i.d (152) Crizotinib 250 mg b.i.d (151)	**Bucher ITC:** IRC-assessed PFS: 18.6 INV-assessed PFS: 37.8 **MAIC unanchored:** IRC-assessed PFS: 18.6 INV-assessed PFS: 37.8 **MAIC anchored:** IRC-assessed PFS: 18.6 INV-assessed PFS: 37.8	No†	[4,14]

†Patients assigned to crizotinib may have received alectinib after disease progression (in countries where alectinib was already approved or available).
b.i.d: Twice a day; ECOG: Eastern Oncology Cooperative Group; INV: Investigator; IRC: Independent review committee; ITC: Indirect treatment comparison; MAIC: Matching-adjusted indirect comparison; NSCLC: Non-small-cell lung cancer; PFS: Progression-free survival; q.d.: Daily; RCT: Randomized controlled trial; TKI: Tyrosine kinase inhibitor.

Table 2. Baseline patient population characteristics of the ALTA-1L and ALEX trials.

Trial name	ALTA-1L		ALEX	
Intervention/comparator	Brigatinib	Crizotinib	Alectinib	Crizotinib
Patients randomized, n	137	138	152	151
Prior therapy status, n (%)				
STN	101 (73.7)	101 (73.2)	152 (100)	151 (100)
1–prior	36 (26.3)	37 (26.8)	0 (0)	0 (0))
Baseline CNS metastases n (%)	40 (29.2)	41 (29.7)	64 (42)	58 (38)
Mean age, years	57.9	58.6	56.3	53.8
Median (range) age, years	58.0 (27–86)	60.0 (29–89)	58 (25–88)	54 (18–91)
Male sex, n (%)	68 (49.6)	57 (41.3)	68 (45)	64 (42)
Ethnicity, n (%)				
Asian	29 (43.1)	49 (35.5)	69 (45)	69 (46)
Black	0 (0)	2 (1.4)	NR	NR
White	76 (55.5)	86 (62.3)	NR	NR
Unknown/other	2 (1.5)	1 (0.7)	NR	NR
Non-Asian	NR	NR	83 (55)	82 (54)
Smoking status, n (%)				
Never	84 (61.3)	75 (54.3)	92 (61)	98 (65)
Current	4 (2.9)	7 (5.1)	12 (8)	5 (3)
Former	49 (35.8)	56 (40.6)	48 (32)	48 (32)
ECOG performance status, n (%)				
0	54 (39.4)	53 (38.4)	NR	NR
1	76 (55.5)	78 (56.5)	NR	NR
0 or 1	NR	NR	142 (93)	141 (93)
2	7 (5.1)	7 (5.1)	10 (7)	10 (7)
Disease stage at entry, n (%)				
IIIb	8 (5.8)	12 (8.7)	NR	NR
IV	129 (94.2)	126 (91.3)	NR	NR
Histology, n (%)				
Adenocarcinoma	126 (92.0)	137 (99.3)	137 (90)	142 (94)
Adenosquamous	3 (2.2)	1 (0.7)	NR	NR
Large cell	2 (1.5)	0 (0)	0 (0)	3 (2)
Squamous	4 (2.9)	0 (0)	5 (3)	2 (1)
Other	2 (1.5)	0 (0)	6 (4)	4 (3)
Undifferentiated	NR	NR	4 (3)	0 (0)

ECOG: Eastern Oncology Cooperative Group; NR: Not reported; STN: Systemic therapy-naive.

ITC results

All ITC analyses indicated similar IRC- and INV-assessed PFS outcomes for brigatinib versus alectinib for the ALK-TKI-naive ITT population, resulting in HRs close to parity. The Bucher ITC estimated HRs of 0.96 (95% Cl: 0.61, 1.52) for IRC-assessed PFS and 0.99 (95% Cl: 0.64, 1.52) for INV-assessed PFS (Figure 1).

Cox proportional hazard models were run using final data from ALTA-1L for IRC- and INV-assessed PFS to investigate potential treatment effect modifiers, including age (>65 years old), ever smoked, Asian ethnicity, presence of baseline CNS metastases, ECOG score and whether patients had previous chemotherapy treatment. Baseline CNS metastases was shown to be the only significant effect modifier (p-values of 0.04 and 0.05, respectively) in the ALK-TKI naive population. This finding was corroborated by the clinical community.

Adjusting for differences in baseline CNS metastases in the anchored MAICs rendered similar results (HRs: 0.98 and 0.99 for IRC- and INV-assessed PFS, respectively; Figure 2). The unanchored MAIC further corroborated results (HRs: 0.95 and 1.02 for both IRC- and INV-assessed PFS, respectively). This alignment across methods supports the assumption that all treatment effect modifiers (relevant to all approaches) and prognostic factors (relevant to the unanchored approach) are likely accounted for in the analyses. Furthermore, subgroup analyses

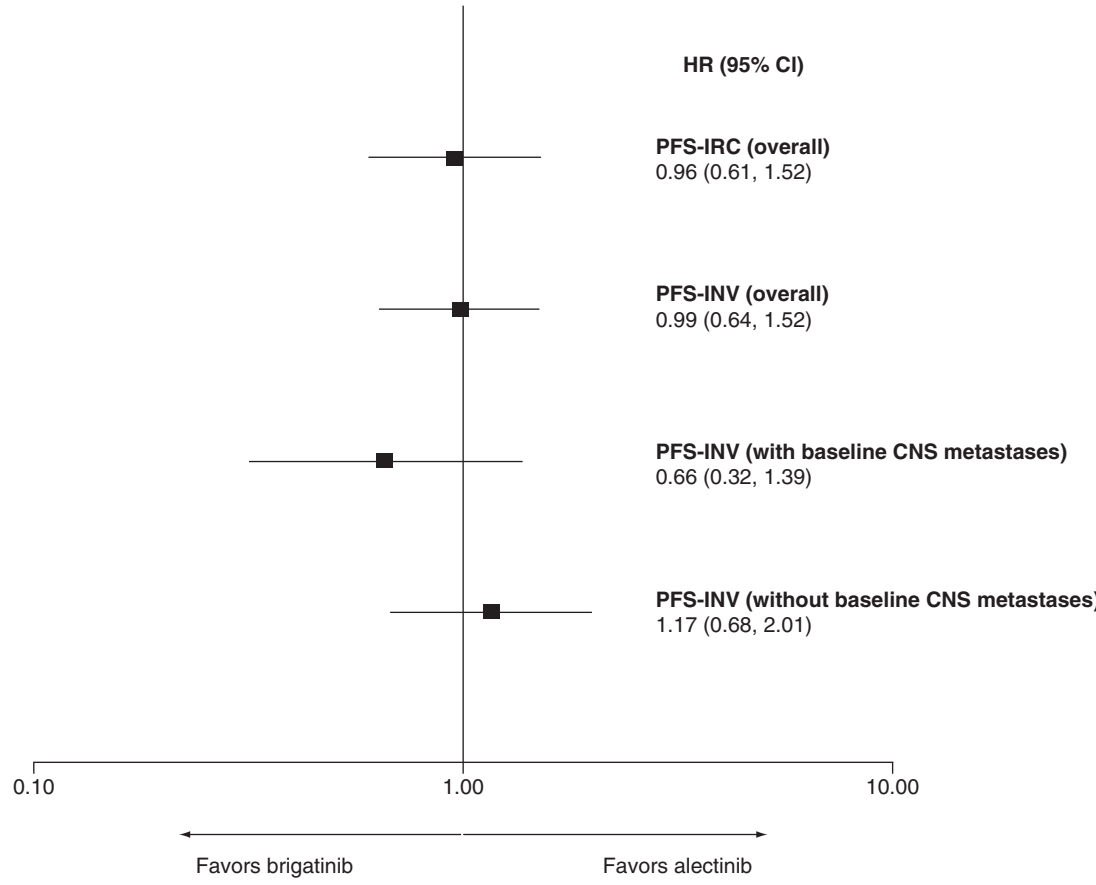

Figure 1. Bucher indirect treatment comparison hazard ratio (95% CI) results for brigatinib versus alectinib for independent review committee- and investigator-assessed progression-free survival, for the intent-to-treat population and for patients with and without baseline CNS metastases.
HR: Hazard ratio; INV: Investigator; IRC: Independent review committee; PFS: Progression-free survival.

conducted to explore the impact of differences in the use of prior systemic therapy across trials showed results for patients without prior systemic therapy were similar to those observed for the ALK-TKI-naive ITT population, i.e., no significant differences were identified between brigatinib and alectinib in reducing the risk of disease progression (Table 3). The ESS was not substantially reduced in any of the MAIC analyses (Figure 2), indicating that a large proportion of the ALTA-1L patients contributed to the results. Tables 4 and 5 present the weights applied both for ALK-naive ITT and for systemic therapy-naive populations, as well as the comparison of baseline characteristics pre- and post-MAIC weighting for the anchored and unanchored approaches, which show that the MAIC process was successful in balancing inter-trial arms on included treatment effect-modifying and prognostic variables. No statistically significant differences were observed between brigatinib and alectinib for INV-assessed PFS in patients with (HR: 0.66 [95% CI: 0.32, 1.39]) or without (HR: 1.17 [95% CI: 0.68, 2.01]) baseline CNS metastases (Figure 1).

Discussion

Brigatinib and alectinib are both oral, second-generation TKIs with similar mechanisms of action, which involve the inhibition of ALK. Both have demonstrated an increased potency in inhibiting ALK compared with crizotinib in their respective head-to-head trials in the front-line setting. Brigatinib and alectinib were both designed to penetrate the blood–brain barrier effectively and have demonstrated this through improved intracranial efficacy compared with crizotinib. Both have good activity against *ALK* mutations that confer resistance to crizotinib. Although a substantial proportion of patients with *ALK*-positive NSCLC present with CNS metastases before the start of ALK-TKI therapy [4,34–38], this is not always known in the real-world care setting at the time of treatment initiation. Because brigatinib and alectinib are highly efficacious regardless of CNS metastases when compared

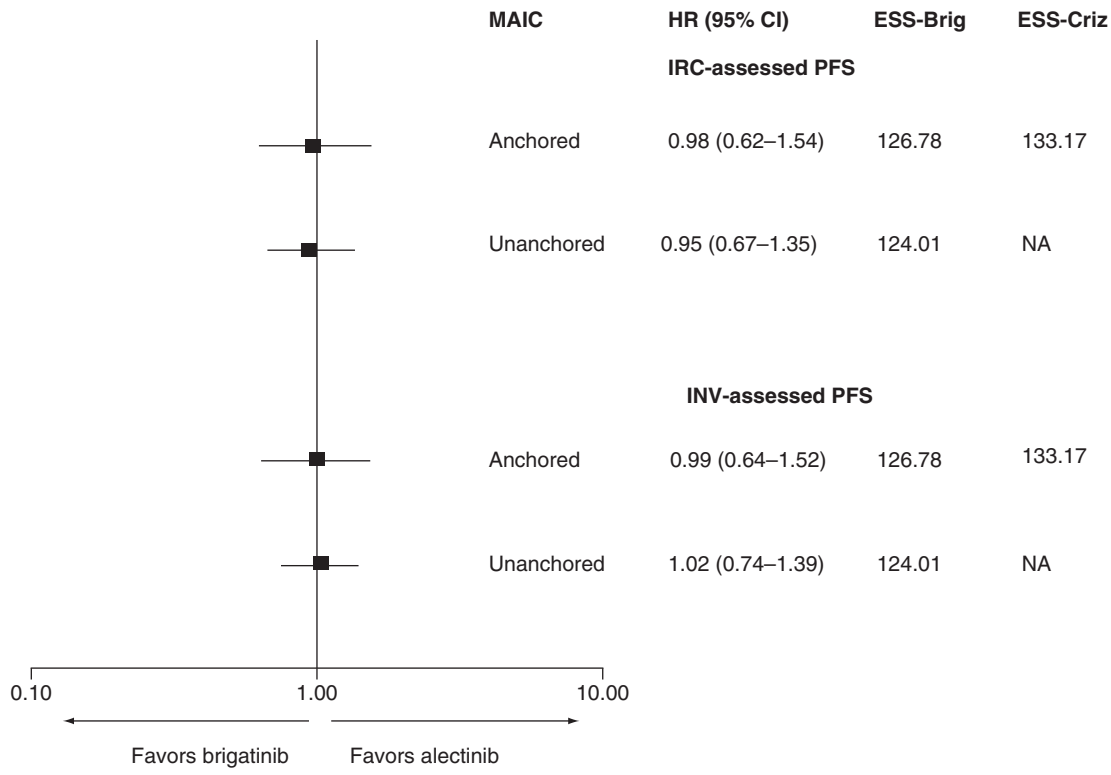

Figure 2. Anchored and unanchored matching-adjusted indirect treatment comparison hazard ratio (95% CI) progression-free survival results for brigatinib versus alectinib for the overall adjusted population.
Brig: Brigatinib; Criz: Crizotinib; ESS: Effective sample size; HR: Hazard ratio; INV: Investigator; IRC: Independent review committee; MAIC: Matching-adjusted indirect treatment comparison; NA: Not applicable; PFS: Progression-free survival.

Table 3. Brigatinib versus alectinib indirect treatment comparisons for progression-free survival outcomes in the systemic therapy-naive population.

Outcome	Method	HR (95% CI)
IRC-assessed PFS	Bucher ITC	1.00 (0.61, 1.65)
	Anchored MAIC	1.04 (0.64, 1.69)
	Unanchored MAIC	1.03 (0.70, 1.50)
INV-assessed PFS	Bucher ITC	0.89 (0.55, 1.43)
	Anchored MAIC	0.92 (0.58, 1.48)
	Unanchored MAIC	1.06 (0.75, 1.51)

HR: Hazard ratio; ITC: Indirect treatment comparison; INV: Investigator; IRC: Independent review committee; MAIC: Matching-adjusted indirect comparison; PFS: Progression-free survival.

Table 4. Covariate balance and weight checks in brigatinib anchored matching-adjusted indirect comparison to alectinib.

ALTA-1L population	ALTA-1L treatment	Unadjusted proportion	Adjusted proportion	ALEX target	n	ESS
ALK-TKI-naive	Crizotinib	0.2971	0.3841	0.3841	138	133.1724
	Brigatinib	0.2920	0.4211	0.4211	137	126.7807
Systemic therapy-naive	Crizotinib	0.2673	0.3841	0.3841	101	94.4255
	Brigatinib	0.2475	0.4211	0.4211	101	86.9439

ESS: Effective sample size; TKI: Tyrosine kinase inhibitor.

Table 5. Covariate balance and weight checks in brigatinib unanchored matching-adjusted indirect treatment comparison to alectinib.

Covariate	Population	ALTA-1L (brigatinib unweighted)	ALEX (alectinib)	ALTA-1L (brigatinib weighted)
Age	ALK-TKI-naive	57.8759	56.3000	56.3000
	Systemic therapy-naive	58.6337	56.3000	56.3000
Male	ALK-TKI-naive	0.4964	0.4474	0.4474
	Systemic therapy-naive	0.5050	0.4474	0.4474
Ever smoked	ALK-TKI-naive	0.3869	0.3947	0.3947
	Systemic therapy-naive	0.3267	0.3947	0.3947
Asian	ALK-TKI-naive	0.4307	0.4539	0.4539
	Systemic therapy-naive	0.3960	0.4539	0.4539
Baseline CNS metastases	ALK-TKI-naive	0.2920	0.4211	0.4211
	Systemic therapy-naive	0.2475	0.4211	0.4211
ECOG2	ALK-TKI-naive	0.0511	0.0658	0.0658
	Systemic therapy-naive	0.0594	0.0658	0.0658

Results are identical for each end point within a stated population. ALK-TKI-naive: n = 137; ESS = 124.01. Systemic therapy-naive n = 101; ESS = 81.43.
ECOG2: Eastern Cooperative Oncology Group performance scale score of 2 (not 0 or 1); TKI: Tyrosine kinase inhibitor.

with crizotinib, these next-generation ALK-TKIs are the natural treatment choice over crizotinib (first in class) in *ALK*-positive NSCLC. While both brigatinib and alectinib have demonstrated efficacy versus crizotinib, there are no head-to-head data for brigatinib compared with alectinib in the frontline setting.

We conducted an SLR and supplemental searches and performed ITCs using various methodological approaches (Bucher ITC, anchored and unanchored MAICs) to compare the efficacy of brigatinib with alectinib as front-line treatments for *ALK*-positive NSCLC. No differences were observed between brigatinib and alectinib in delaying progression in these populations. Subgroup analyses for patients with and without baseline CNS metastases and no prior systemic therapy also showed no statistically significant differences for brigatinib compared with alectinib.

Previous studies estimating the relative efficacy of brigatinib and alectinib in the ALK-TKI-naive NSCLC population have been published [9–11,39,40]. However, this work presents new data and has several key strengths compared with existing studies. First, the latest available data from ALTA-1L (final analysis) have been utilized. Second, a MAIC approach was used to account for imbalances in baseline CNS metastases across the ALTA-1L and ALEX trials. Baseline CNS metastases are highly prognostic for patients treated with crizotinib [4,5]. The treatment effect of brigatinib versus crizotinib and alectinib versus crizotinib would be expected to improve as the proportion of patients with baseline CNS metastases increases. MAIC analyses re-weighted ALTA-1L's brigatinib IPD such that the baseline CNS metastases population reflected those in the ALEX trial, which improved the treatment effect of brigatinib versus crizotinib in a population with a higher proportion of baseline CNS metastases. To our knowledge, this is the first study to explore the impact of these differences in an assessment of brigatinib versus alectinib for the front-line therapy of *ALK*-positive NSCLC. The inputs underpinning the methods have been extensively validated through clinician feedback at multiple advisory boards and through alignment with published ITCs in the *ALK*-positive NSCLC space. Furthermore, the trials included in our analyses are international. Therefore, the results are considered generalizable to different settings; this was not always accounted for in previous studies [8,11,40]. Finally, we analyzed IRC- and INV-assessed PFS independently.

While this manuscript focuses on PFS outcomes, in a previous study we estimated the relative efficacy for brigatinib versus alectinib in terms of overall survival (OS) using the final data from ALTA-1L and the most recent data available for ALEX and concluded that also for OS brigatinib was at least as effective as alectinib in reducing the risk [41]. Of note, unlike ALEX, ALTA-1L allowed a protocol-defined crossover upon disease progression in the crizotinib arm. Therefore, a substantially higher proportion of patients subsequently received brigatinib in the crizotinib arm of the ALTA-1L study than received alectinib in the crizotinib arm of the ALEX study. This bias was further exacerbated by higher overall proportions of subsequent ALK-TKI use in the ALTA-1L trial (both brigatinib and crizotinib arms) compared with the ALEX trial (both alectinib and crizotinib arms). This imbalance in post-progression treatment was addressed in the OS analyses but with the limitation that some differences in subsequent ALK-TKI use could not be accounted for, which may have led to biases that could not be quantified [41]. Nevertheless, given that brigatinib and alectinib have similar mechanisms of action and a similar increase in PFS, it

is plausible that a similar increase in survival would be expected between the two agents. This notion was discussed and supported by clinicians involved in a recent health technology appraisal for brigatinib [42].

This study highlights the similarities in outcomes between brigatinib and alectinib. However, there are some differences that are not reflected through the ITCs presented here but may be relevant in clinical practice. Brigatinib demonstrated clinically relevant and statistically significant health-related quality-of-life (HRQOL) improvements compared with crizotinib in the ALTA-1L trial [5]. In contrast, no statistically significant differences in HRQOL outcomes were observed between alectinib and crizotinib in the ALEX trial [43]. Brigatinib and alectinib are both administered orally. However, they have slightly different dosing regimens; brigatinib is given initially at 90 mg dose once daily for a week followed by a 180 mg dose taken in one tablet once daily thereafter with or without food, whereas alectinib is four capsules taken b.i.d with food.

Limitations associated with the analyses mainly relate to the data available. Only one trial provided information for each of the interventions included. Moreover, some variables that may have impacted outcomes could not be assessed for balance, for example, the exact number of baseline CNS metastases and whether patients had received prior treatment with stereotactic radiosurgery or whole-brain radiation therapy. In addition, the necessity for conducting indirect anchored comparisons in the absence of head-to-head data unavoidably increases contrast variances and thereby confidence intervals: the indirect treatment contrast variance estimate is based on the sum of the two independent trial contrast variances. Given that the individual trials were powered to detect statistically significant differences only between their included study arms and not future indirect comparisons, it is unsurprising that the ITC HR contrast estimates straddle both sides of parity to a wider extent than one wished.

In addition, the definitions of PFS varied across the trials. Therefore, there may be some inherent bias from an inability to exactly align with outcome definitions. Important limitations relating to the methodologies include: the Bucher ITC assumes that there are no differences between the trials in the distribution of effect-modifying variables. The anchored MAICs relax this assumption and adjust for differences in treatment effect modifiers, but require that all effect modifiers are included – an assumption which was tested using a list of candidate variables (informed by clinical experts and the literature) and the ALTA-1L data. The unanchored MAICs were explored to examine the impact of removing any data for crizotinib. This methodology is often perceived with skepticism given that it does not exploit intra-trial randomization in forming contrast estimates. However, in the current analyses, the unanchored MAIC end points replicate closely the contrast results produced by their anchored MAIC equivalents (that do leverage intra-trial randomization) indicating that the unanchored MAIC was correctly specified and accounted for the relevant prognostic factors.

This work focused on efficacy outcomes only. The safety profile of brigatinib [5] and alectinib [4] is not similar. Some toxicities are more prevalent with brigatinib and others are more frequent with alectinib, limiting the value of any comparison. However, both treatments have been shown to be well-tolerated as front-line therapy.

Conclusion

Final aggregate and patient-level data from ALTA-1L and published aggregate data from ALEX were contrasted to compare the efficacy of brigatinib with alectinib in patients with ALK-TKI-naive locally-advanced or metastatic *ALK*-positive NSCLC. Bucher ITC and anchored and unanchored MAICs were used. Brigatinib appeared similar to alectinib in reducing the risk of disease progression in patients with ALK-TKI-naive NSCLC.

Summary points

- Brigatinib and alectinib are ALK-targeted tyrosine kinase inhibitors (TKIs) for which randomized, global clinical trials have demonstrated improved efficacy over crizotinib in ALK-TKI-naive, *ALK*-positive non-small-cell lung cancer.
- Amid lack of head-to-head comparisons between these ALK-TKIs and to guide clinical decision-making, we indirectly compared their efficacies in terms of independent and investigator-assessed progression-free survival.
- Bucher indirect treatment comparisons and matching-adjusted indirect comparisons were used.
- No statistically significant differences were identified between brigatinib and alectinib in reducing the risk of disease progression.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0194

Author contributions

KL Reckamp: conceptualization, formal analysis, methodology, project administration, supervision, writing – review and editing. HM Lin: conceptualization, formal analysis, methodology, project administration, supervision, writing – review and editing. H Cranmer: conceptualization, formal analysis, methodology, project administration, supervision, writing – review and editing. Y Wu: formal analysis, methodology, project administration, supervision, writing – review and editing. P Zhang: formal analysis, methodology, writing – review and editing. LJ Walton: formal analysis, methodology, writing – review and editing. S Kay: data curation, formal analysis, methodology, software, writing – review and editing. A Cichewicz: data curation, formal analysis, methodology, software, writing – review and editing. B Neupane: data curation, formal analysis, methodology, software, writing – review and editing. K Fahrbach: data curation, formal analysis, methodology, software, writing – review and editing. S Popat: formal analysis, methodology, writing – review and editing. DR Camidge: conceptualization, formal analysis, methodology, supervision, writing – review and editing.

Financial & competing interests disclosure

This study was sponsored by ARIAD Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. The sponsor of this study was involved in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript, and in the decision to submit the article for publication. KL Reckamp, S Popat and DR Camidge received consulting fees from ARIAD Pharmaceuticals, Inc. KL Reckamp reports having received consulting fees from Amgen, AstraZeneca, Blueprint, Daiichi Sankyo, EMD Serono, Genentech, GlaxoSmithKline, Janssen, Lilly, Merck KGA, Mirati, Seattle Genetics, Takeda and Tesaro, as well as research funding to institution from Genentech, Blueprint, Calithera, Daiichi Sankyo, Elevation Oncology and Janssen. HM Lin, Y Wu and P Zhang are employed by Takeda Pharmaceutical Company Limited. H Cranmer is employed by Takeda Pharmaceuticals International Co. LJ Walton is employed by Takeda Pharmaceuticals International AG. S Kay is an employee of Model Outcomes Ltd, a consulting firm which provides data modeling services to pharmaceutical and related organizations. Model Outcomes received funding from ARIAD Pharmaceuticals, Inc. to conduct statistical modeling in this study. A Cichewicz, B Neupane and K Fahrbach are employees of Evidera, a consultancy which provides consulting and other research services to pharmaceutical, medical device, and other organizations. In their salaried positions, they work with a variety of companies and are precluded from receiving payment or honoraria directly from these organizations for services rendered. Evidera received funding from ARIAD Pharmaceuticals, Inc. to conduct the systematic literature review and statistical modeling in this study. S Popat reports having received consulting fees from Amgen, AstraZeneca, Bayer, Beigene, Blueprint, BMS, Boehringer Ingelheim, Daiichi Sankyo, Guardant Health, Incyte, Janssen, Lilly, Merck Serono, MSD, Novartis, Roche, Takeda, Pfizer, Seattle Genetics, Turning Point Therapeutics and Xcovery, as well as honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Bayer, Guardant Health, Janssen, Merck Serono, Roche, Takeda and Pfizer and payment for expert testimony from Merck Serono. DR Camidge reports the following ad hoc advisory board presence/consultations in years 2020 to 2022: Abbvie, Amgen, Anchiarno, Anheart, Apollomics, Appolomics, AstraZeneca, AstraZeneca/Daiichi, Beigene, BioThera, Blueprint, BMS, Daiichi-Sankyo, Dizal, Eisai, Elevation, Eli Lilly, EMD Serono, GSK, Helssin, Hengrui, Hummingbird, Janssen, Kestrel, Medtronic, Mersana, Mirati, Nalo Therapeutics, Nuvalent, Onkure, Pfizer, Puma, Qilu, Ribon, Roche, Roche/Genentech, Sanofi, Seattle Genetics, Shares, Takeda and Turning Point. DR Camidge reports having received research funding from Inivata in years 2020 to 2022. DR Camidge reports the following company sponsored trials at institution in years 2020 to 2022: Abbvie, AstraZeneca, Blueprint, Dizal, Inhibrx, Karyopharm, Pfizer, Phosplatin, Psioxus, Rain, Roche/Genentech, Seattle Genetics, Takeda, Turning Point and Verastem. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Professional medical writing assistance was provided by M Arregui (employee of Xcenda GmbH), E Wissinger and R Sugarman (employees of Xcenda LLC) and funded by Millennium Pharmaceuticals, Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

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