First-line Brigatinib in Anaplastic Lymphoma Kinase-positive Non-small Cell Lung Cancer: A Network Meta-Analysis

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Disclosure

HML and YW are employees of Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and may own stock. ABC, BN, LV, and KF are employees of Evidera. KLR has served as a consultant to Amgen, AstraZeneca, Blueprint, Boehringer Ingelheim, Calithera, Euclises, Genentech, Guardant, Janssen, Lilly, Merck KGaA, Precision Health, Seattle Genetics, Takeda, and Tesaro.

Study Sponsorship

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Background

Lung cancer is the leading cause of cancer-related mortality worldwide.[1] An estimated 2.2 million new cases were diagnosed in 2020 and about 1.8 million deaths occurred worldwide.[1] Non-small cell lung cancer (NSCLC) characterized by anaplastic Lymphoma Kinase (ALK) rearrangements are diagnosed in 5% of patients with NSCLC, with up to 7% in advanced NSCLC (stage IIIB/IV).[2] ALK-targeted tyrosine kinase inhibitors (TKI) such as alectinib, brigatinib, and crizotinib have shown to be effective as first-line (1L) treatment of ALK-positive NSCLC. However, head-to-head comparisons between available ALK inhibitors are lacking.

Objectives

To conduct a systematic literature review (SLR) and network meta-analysis (NMA) to estimate the relative efficacy of brigatinib compared to other approved ALK inhibitors or chemotherapy in patients with locally advanced or metastatic ALK inhibitor-naïve ALK-positive NSCLC.

[1] World Health Organization, International Agency for Research on Cancer. Globocan 2020: Lung Cancer. Available at https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf.
[2] Hofman P. ALK in Non-Small Cell Lung Cancer (NSCLC) Pathobiology, Epidemiology, Detection from Tumor Tissue and Algorithm Diagnosis in a Daily Practice. *Cancers*. 2017. 9(8):107.

SLR Methodology

- The SLR was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[1]
- Systematic searches were conducted in MEDLINE, Embase, and the Cochrane databases to identify clinical trials published from database inception to August 1, 2019. Abstracts from the past three meetings (2017-2019) of select conferences were also reviewed.
- Abstracts and full texts were reviewed by two independent reviewers based on pre-specified selection criteria (Table 1) and disagreements were resolved by a third reviewer.

Inclusion Criteria		
Population	• Adults (≥18 years) with ALK+ histologically or cytologically confirmed stage IIIB (locally advanced) or stage IV (metastatic) NSCLC who are: ○ Previously untreated, ALK inhibitor-naïve ○ Have received one prior systemic therapy and are ALK inhibitor-naïve	
Intervention	• Alectinib; brigatinib; ceritinib; crizotinib; ensartinib; lorlatinib	
Comparator	• Any of the above interventions; chemotherapy; best supportive care or placebo	

Outcomes	**Efficacy**
	• OS
	• PFS or time to progression: overall; intracranial; CNS
	• Responses
	  • Objective (overall, partial, complete, time to response, DOR, DCR)
	  • Intracranial (overall, partial, complete, time to response, DOR, DCR)
	  • CNS (overall, partial, complete, time to response, DOR, DCR)
		Safety
		• AEs including grade 3+, grade 3 or 4, and SAEs (overall and treatment-emergent)
		• Treatment withdrawal/discontinuations (all cause, due to AEs)
		• Death (treatment-related and overall)

Table 1: PICOS Criteria

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; CNS = central nervous system; DCR = disease control rate; DOR = duration of response; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival

[1] Moher D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.

SLR Results

- The searches of the indexed databases yielded 834 unique records after de-duplication.
- Of these, 713 records were excluded following title/abstract screening.
- The full texts of 120 records were screened to determine their relevance to the review.
- Eight RCTs (reported in 33 publications) and 11 single-arm trials (reported in 17 publications) were included in the SLR.
- Five global* RCTs (ALEX, ALTA-1L, ASCEND-4, PROFILE 1007, PROFILE 1014) evaluating 4 ALK inhibitors (alectinib, brigatinib, ceritinib, crizotinib) as 1L treatment** in ALK+ NSCLC were included in the NMA.

* RCTs focused on regional populations (i.e., J-ALEX, ALESIA, and PROFILE 1029) were not included. CROWN and Exalt3 were not available at the time of analysis.
** ≤1 prior chemotherapy regimen was allowed

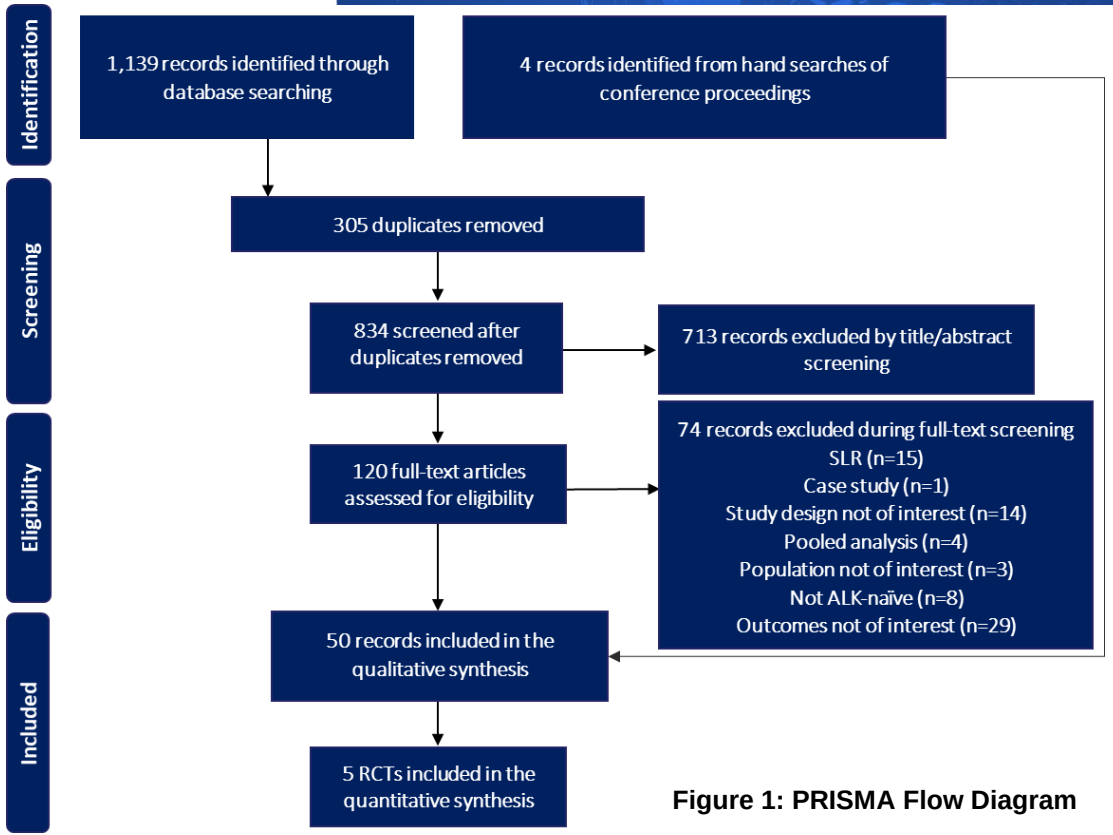

Figure 1: PRISMA Flow Diagram

Trial Name (Number)	N (%) of Patients Evaluated at Baseline per Intervention and Population		
	ITT	First Line (no prior chemotherapy)	Baseline CNS Metastases*
ALTA-1L (NCT02737501)	Brigatinib: 137 Crizotinib: 138	Brigatinib: 101 (73.7%) Crizotinib: 101 (73.2%)	Brigatinib: 40 (29.2%) Crizotinib: 41 (29.7%)
ALEX (NCT02075840)	Alectinib: 152 Crizotinib: 151	Alectinib: 152 (100%) Crizotinib: 151 (100%)	Alectinib: 64 (42.1%) Crizotinib: 58 (38.4%)
ASCEND-4 (NCT01828099)	Ceritinib: 189 Chemotherapy: 187	Ceritinib: 176 (93.1%) Chemotherapy: 163 (87.2%)	Ceritinib: 59 (31.2%) Chemotherapy: 62 (33.2%)
PROFILE 1007 (NCT00932893)	Crizotinib: 173 Chemotherapy: 174	NA	Crizotinib: 60 (34.7%) Chemotherapy: 60 (34.5%)
PROFILE 1014 (NCT01154140)	Crizotinib: 172 Chemotherapy: 171	Crizotinib: 172 (100%) Chemotherapy: 171 (100%)	Crizotinib: 45 (26.2%) Chemotherapy: 47 (27.5%)

Table 2: Summary of Trials Included in the NMA

* Various definitions of baseline brain or CNS metastases across trials were assumed to be equivalent.

Abbreviations: CNS = central nervous system; ITT = intention-to-treat; NA = not applicable

NMA Methodology

- Bayesian NMAs were performed to assess the comparative efficacy (progression-free survival [PFS]) of brigatinib with other ALK inhibitors or chemotherapy as 1L treatment.
- The NMA assumed that there were no important effect modifiers and that common comparators could be assumed identical across studies.
- Only fixed-effects model results are presented given that most comparisons in the network (Figure 2), with the exception of crizotinib vs. chemotherapy, contain a single study per node. Random-effects model results were similar (data not shown).
- Below, we use the frequentist language of 'statistically significant' to indicate 95% credible intervals that did not overlap 1.0.

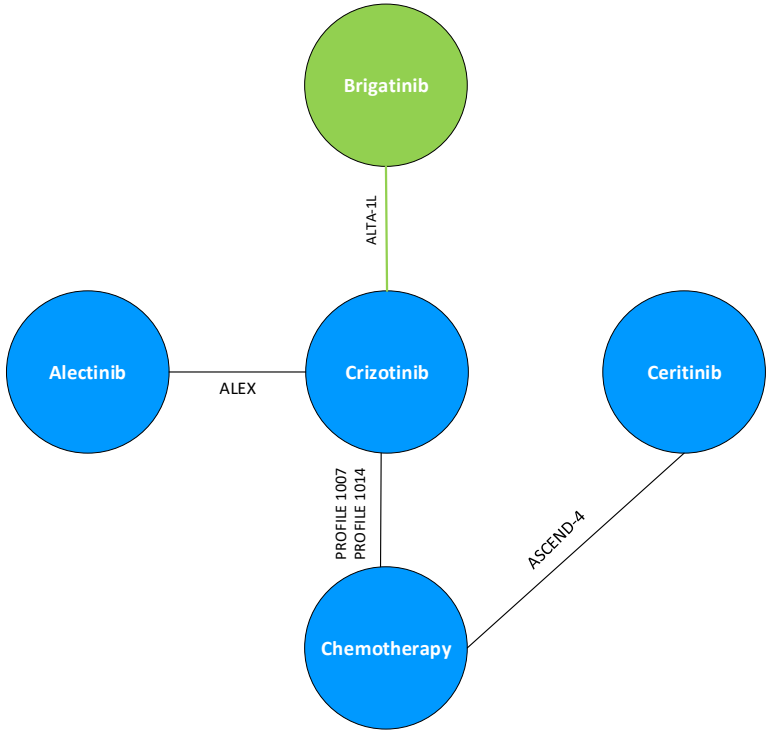

Figure 2: Overall Base-case Network Diagram

NMA Results

Brigatinib significantly reduced the risk of disease progression or death (IRC-assessed PFS) compared with ceritinib, crizotinib, and chemotherapy.

- No significant differences were observed between brigatinib and alectinib.

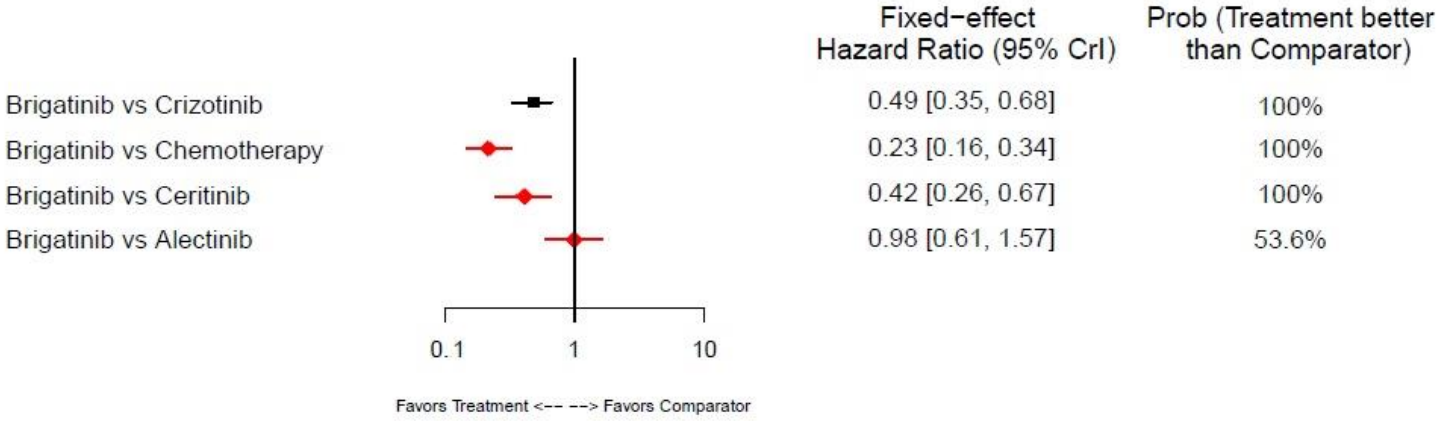

Figure 3: Bayesian NMA Fixed-Effects Results for Brigatinib versus Comparators for IRC-assessed PFS
IRC-assessed PFS was the primary outcome for all included trials except ALEX.
Abbreviations: CrI = credible interval; INV = investigator; IRC = independent review committee; PFS = progression-free survival
Black = direct evidence from ALTA-1L; Red = indirect comparison to ALTA-1L

No significant differences were observed between brigatinib and alectinib in INV-assessed PFS.

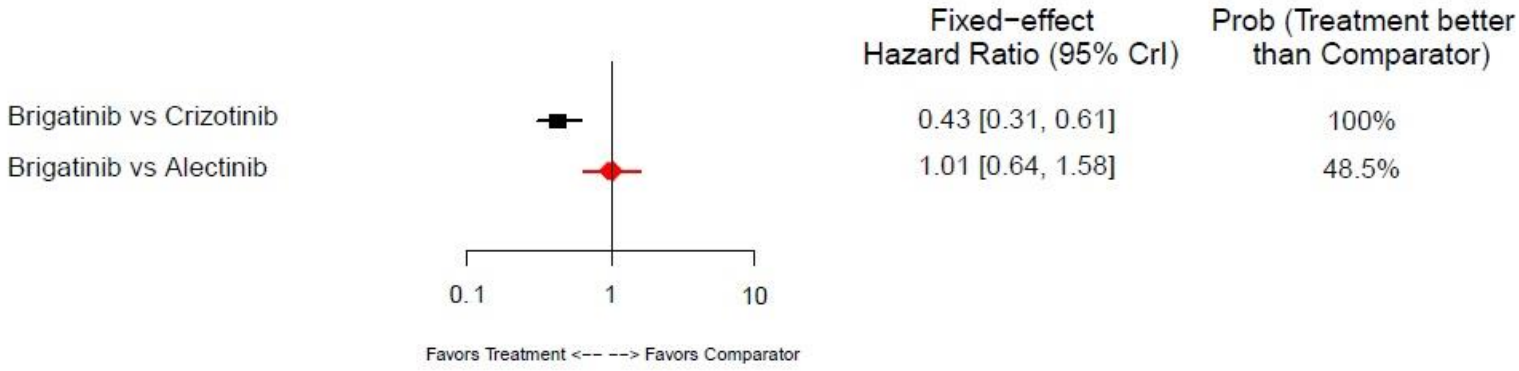

Figure 4: Bayesian NMA Fixed-Effects Results for Brigatinib versus Comparators for INV-assessed PFS
INV-assessed PFS was the primary outcome of the ALEX trial.
Abbreviations: CrI = credible interval; INV = investigator; IRC = independent review committee; PFS = progression-free survival
Black = direct evidence from ALTA-1L; Red = indirect comparison to ALTA-1L

The risk of disease progression or death among patients without prior receipt of chemotherapy and those with baseline CNS metastases was similar to that in the main analyses, but brigatinib may provide further benefit in patients with CNS metastases vs. comparators.

Outcomes	Comparison	Overall (all patients)	Subgroup with no prior chemotherapy	Subgroup with baseline CNS metastases*
		HR (95% CrI)	HR (95% CrI)	HR (95% CrI)
PFS (IRC-assessed)	Brigatinib vs Chemotherapy	0.23 (0.16, 0.34)	0.23 (0.15, 0.38)	0.10 (0.04, 0.22)
	Brigatinib vs Crizotinib	0.49 (0.35, 0.68)	0.52 (0.35, 0.77)	0.25 (0.14, 0.45)
	Brigatinib vs Ceritinib	0.42 (0.26, 0.67)	0.42 (0.24, 0.74)	0.14 (0.06, 0.36)
	Brigatinib vs Alectinib	0.98 (0.61, 1.57)	1.04 (0.62, 1.74)	NA
PFS (INV-assessed)	Brigatinib vs Crizotinib	0.43 (0.31, 0.61)	0.41 (0.27, 0.61)	0.24 (0.12, 0.45)
	Brigatinib vs Alectinib	1.01 (0.64, 1.58)	0.95 (0.57, 1.57)	0.63 (0.28, 1.42)

Table 3: The Comparative Efficacy of Brigatinib and Other ALK Inhibitors or Chemotherapy

* Various definitions of baseline brain or CNS metastases across trials were assumed to be equivalent.

HR <1 indicates reduced risk of disease progression or death with brigatinib vs. comparator

Abbreviations: ALK = anaplastic lymphoma kinase; CrI = credible interval; CNS = central nervous system; HR = hazard ratio; INV = investigator; IRC = independent review committee; NA = not available; PFS = progression-free survival

Limitations and Additional Analyses

- Definitions of PFS varied slightly across included RCTs.
- The assumption around lack of evidence of effect modification may not hold due to differences in the proportion of baseline CNS metastases across studies. Anchored matching-adjusted indirect comparisons (MAICs) is being conducted to better control for the differences in baseline CNS metastases across the trial population.
- Overall survival results were not presented due to the bias caused by the differences in subsequent therapies across studies, driven by protocol-offered treatment crossover in ALTA-1L and timing of the clinical trials. The unadjusted OS data from the ALTA-1L trial do not reflect an isolated treatment effect of brigatinib vs. crizotinib. Cranmer 2020[1] demonstrated that treatment switching adjustment has a large impact on the estimated treatment effect of brigatinib vs. crizotinib. Unanchored MAICs are also being conducted to remove the 'noise' associated with treatment crossover.
- A manuscript is in development to incorporate the findings of these additional analyses.

[1] Cranmer H. Overall Survival Estimates Adjusting for Treatment Crossover in Patients Previously Untreated with an ALK Inhibitor with ALK+ NSCLC Using DATA from the Alta-1L Clinical Trial. *Value Health*. 2020;23(2):S424-5.

Conclusions

- Brigatinib significantly prolonged PFS in ALK inhibitor-naïve patients with ALK-positive NSCLC compared with ceritinib, crizotinib, and chemotherapy and was at least as effective as alectinib in reducing the risk of progression.
- These results also suggest strong efficacy of brigatinib in patients with CNS metastases at baseline.
- In addition to the efficacy described here, brigatinib is also well tolerated and significantly improves health-related quality of life compared with crizotinib[1], making it a promising first-line treatment option for patients with ALK-positive NSCLC.

[1] Camidge DR. Brigatinib Versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non-Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial. *J Clin Oncol*. 2020 Nov 1;38(31):3592-3603.