Optimizing Treatment Sequencing to Maximize Survival in ALK+ Advanced Non-Small Cell Lung Cancer: A Modeling Study

H. Le[1*], **N. Rifi[2]**, T. Williams[3], L. Bloudek[3], S. Ramsey[3]
[1]Pfizer Inc, New York/NY/USA, [2]Pfizer Inc, Paris/FR, [3]Curta Inc, Seattle/WA/USA
**At the time of study conduct*
Correspondence: *Nada.Rifi@pfizer.com*

INTRODUCTION

- The European Society for Medical Oncology (ESMO) guidelines recommend either alectinib, brigatinib or lorlatinib anaplastic lymphoma kinase inhibitors (ALKis) as first-line (1L) treatment options for ALK-positive advanced non-small-cell lung cancer (aNSCLC).
  - Guidelines do not specify a first preference from among these three ALKis.[1]
- Lorlatinib is approved by the European Medicines Agency (EMA) for patients without prior treatment with other ALKis and when disease has worsened after treatment with other ALKis, including alectinib, brigatinib, ceritinib, and crizotinib.[2]
- Currently, there are no head-to-head comparisons to aid in selection of different sequences of ALKis.
- Real-world evidence comparing observed treatment sequences has not had sufficient follow-up time to interpret findings.
- This study uses modeling methods to identify the longest likely progression-free survival (PFS) across sequencing strategies for recommended ALKis.
- Analyses were conducted for the overall trial populations and in subgroups of patients with and without central nervous system (CNS) metastases at the start of 1L treatment.

METHODS

- Disease state models were developed across lines of therapy (LoT), informed from clinical trials of recommended therapies for ALK+ aNSCLC.
  - Three 1L treatment options were compared: alectinib, brigatinib or lorlatinib.
  - Time to progression was based on published Phase 2 and 3 clinical trial data for alectinib and brigatinib and patient-level data for lorlatinib.
  - Patients experiencing progression initiated second line ALKi or chemotherapy. Those who progressed after 2 ALKis received chemotherapy.
  - An area under the curve (AUC) approach was used to account the plateauing of observed PFS to estimate cumulative progression-free life years across all LoTs.
- Parametric survival curves for overall survival (OS) and progression-free survival (PFS) were fit using the *flexsurv* package in R.
- Patient-level data from the CROWN global, randomized, Phase 3 trial of lorlatinib vs crizotinib was used for OS and PFS.
- All other survival curves in the overall population were based on pseudo patient-level data derived from digitized Kaplan-Meier plots and the Guyot algorithm.[3]
- For CNS subgroups, the ALESIA Phase 3 trial of alectinib vs crizotinib in Asian patients was used due to data availability.
- Total projected time in progression-free state was calculated for each treatment sequence across all LoTs.

DATA SOURCE

Table 1. Data Source

Population	LoT	Alectinib	Brigatinib	Lorlatinib
Overall Trial Population	1L	ALEX[4]	ALTA-1L[5]	CROWN[6]
	2L	ALUR[7]	ALTA[8]	NCT04362072 & NCT01970865 cohort EXP2-3A[9]
	3L	Real-world Data[10]	N/A	N/A
With CNS Metastases at Start of 1L	1L	ALESIA[11]	ALTA-1L[5]	CROWN[6]
	2L and 3L	Assumed same as overall population		
Without CNS Metastases at Start of 1L	1L	ALESIA[11]	Data gap	CROWN[6]
	2L and 3L	Assumed same as overall population		

LIMITATIONS

- Results are sensitive to choice of survival distribution.
- Potential differences in baseline population characteristics across the different studies could influence survival outcomes.
- Data were limited for OS in patients in the subgroups with and without CNS metastases at start of 1L.
  - 2L PFS, 1L OS, and 2L OS for the CNS subgroups were assumed to be the same as the overall population for each treatment.
- Sparse data are presently available for alectinib and brigatinib after progression on lorlatinib.
  - 2L data for alectinib and brigatinib are derived from trials of patients previously treated with crizotinib.
  - As lorlatinib failure frequently involves compound ALK mutations that confer cross-resistance to earlier-generation TKIs, 2L survival for alectinib and brigatinib post-lorlatinib may be shorter than assumed in this model.
- This analysis does not replace head-to-head comparator trials and/or indirect treatment comparisons which adjust for potential differences across trials.

CONCLUSION

- **Several ALKis are available for 1L treatment among patients with advanced ALK+ NSCLC.**
- **Based on currently available clinical evidence, these models predict that therapy pathways beginning with lorlatinib may yield the longest PFS (estimated at 10.5 to 12.3 years).**
- **Based on these modeling approaches, survival advantages with 1L lorlatinib are predicted in patients with and without brain metastases at presentation.**

RESULTS

Table 2. Projected Survival for Treatment Sequence – Overall Population

Sequence (1L → 2L → 3L)	1L Median PFS, Months (Source)	2L Median PFS, Months (Source)	3L Median PFS, Months (Source)	Cumulative Progression-Free Years Across LoTs *Based on AUC Approach*
Lorlatinib → alectinib → chemotherapy	93.6 (projected based on CROWN)	10.9 (ALUR)	4.3 (Lin 2020)	**12.3 years**
Lorlatinib → brigatinib → chemotherapy		12.9 (ALTA)		**11.8 years**
Lorlatinib → chemotherapy		4.3 (Lin 2020)	N/A	**10.5 years**
Alectinib → lorlatinib → chemotherapy	34.8 (ALEX)	12.2 (NCT01970865 [1027 Study]	4.3 (Lin 2020)	**7.4 years**
Brigatinib → lorlatinib → chemotherapy	30.8 (ALTA-1L)			**6.7 years**

Table 3. Projected Survival for Treatment Sequence – Without Baseline CNS Metastases

Sequence (1L → 2L → 3L)	1L Median PFS, Months (Source)	2L Median PFS, Months (Source)	3L Median PFS, Months (Source)	Cumulative Progression-Free Years Across LoTs *Based on AUC Approach*
Lorlatinib → alectinib → chemotherapy	100 (projected based on CROWN)	10.9 (ALUR)	4.3 (Lin 2020)	**12.8 years**
Lorlatinib → brigatinib → chemotherapy		12.9 (ALTA)		**12.3 years**
Lorlatinib → chemotherapy		4.3 (Lin 2020)	N/A	**11.2 years**
Alectinib → lorlatinib → chemotherapy	41.6 (ALESIA)	12.2 (NCT01970865 [1027 Study])	4.3 (Lin 2020)	**7.4 years**
Brigatinib → lorlatinib → chemotherapy	Data gap			**N/A**

Table 4. Projected Survival for Treatment Sequence – With Baseline CNS Metastases

Sequence (1L → 2L → 3L)	1L Median PFS, Months (Source)	2L Median PFS, Months (Source)	3L Median PFS, Months (Source)	Cumulative Progression-Free Years Across LoTs *Based on AUC Approach*
Lorlatinib → alectinib → chemotherapy	65 (projected based on CROWN)	10.9 (ALUR)	4.3 (Lin 2020)	**10.3 years**
Lorlatinib → brigatinib → chemotherapy		12.9 (ALTA)		**10.7 years**
Lorlatinib → chemotherapy		4.3 (Lin 2020)	N/A	**9.4 years**
Alectinib → lorlatinib → chemotherapy	42.3 (ALESIA)	12.2 (NCT01970865 [1027 Study] EXP2-3A)	4.3 (Lin 2020)	**7.3 years**
Brigatinib → lorlatinib → chemotherapy	24 (ALTA-1L)			**5.6 years**

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