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Real-world comparative effectiveness of 1L alectinib (ALC) vs crizotinib (CRZ) in patients (pts) with *ALK*+ advanced NSCLC with or without baseline CNS metastases (mets)

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Summary

1L real-world data (RWD) cohort comprised **364 patients**

141 **alectinib-treated patients**

223 **crizotinib-treated patients**

In patients with baseline CNS metastases, median real-world (rw)PFS and rwOS were **significantly improved** and development of further CNS metastases was **significantly delayed** with **alectinib** vs **crizotinib**

In an ALEX-like RWD cohort comprising **325 patients**, weighted HRs for rwPFS showed **similar benefit** for **alectinib** vs **crizotinib** as reported in ALEX, irrespective of the presence of CNS metastases at baseline

In patients without baseline CNS metastases, rwPFS was **significantly improved** and development of the first CNS metastases was **significantly delayed** with **alectinib** vs **crizotinib**

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Background

- Alectinib is recommended as a preferred first-line treatment option and standard of care for patients with advanced *ALK*+ NSCLC in key clinical practice guidelines (ESMO, NCCN and ASCO / Ontario Health).[1–3]
- The randomised, open-label, phase III ALEX study (NCT02075840) compared the efficacy and safety of alectinib vs crizotinib in treatment-naïve patients with advanced *ALK*+ NSCLC.[4]
  - Mature progression-free survival (PFS) data from ALEX confirmed significant improvement in PFS for alectinib vs crizotinib: stratified hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.32–0.58. Median PFS with alectinib was 34.8 months vs 10.9 months with crizotinib.[4]
  - Alectinib has also demonstrated a clinically meaningful improvement in overall survival (OS) (5-year survival rate: 62.5% with alectinib vs 45.5% with crizotinib); OS data remain immature.[5]
- Here, we present a retrospective analysis of real-world data (RWD) from an electronic health record database that compares the efficacy of first-line alectinib and crizotinib treatment in patients with advanced *ALK*+ NSCLC, with or without central nervous system (CNS) metastases at baseline, in US clinical practice.

Methods

- Adult patients with advanced *ALK*+ NSCLC who received first-line alectinib (from 11 December 2015) or crizotinib (from 1 January 2014) were included from the nationwide Flatiron Health electronic health record-derived de-identified database.
- Propensity scores were applied to balance baseline characteristics, and weighted HRs (wHR) of alectinib vs crizotinib were calculated for real-world (rw) outcomes, including PFS (rwPFS), OS (rwOS) and time to new CNS metastases (rwTTNCM; death was included as an event).
  - In patients with baseline brain scans, outcomes in patients with or without baseline CNS metastases were analysed.
- Sensitivity analyses were performed in patients with known Eastern Cooperative Oncology Group performance status (ECOG PS) or treated after 11 December 2015.
- To compare real-world comparative effectiveness with the ALEX study, a population filtered by ALEX laboratory values inclusion / exclusion criteria (ALEX-like RWD cohort) was analysed and wHRs compared with corresponding HRs from ALEX.

Patient populations

- The RWD cohort comprised 364 patients (141 alectinib; 223 crizotinib; **Table 1**).
  - A greater percentage of patients treated with alectinib compared with those treated with crizotinib had CNS metastases at baseline (38% vs 26%), were of Asian race (15% vs 5%), were non-smokers (62% vs 50%), had known programmed death-ligand 1 (PD-L1) status (72% vs 15%), and had known ECOG PS (65% vs 48%).
- The ALEX-like RWD cohort comprised 325 patients (120 alectinib; 205 crizotinib).

Table 1. Baseline characteristics of RWD cohort

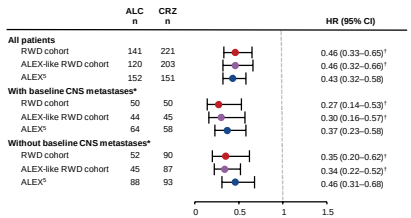
n (%)		Alectinib (n=141)	Crizotinib (n=223)
Age at diagnosis	Mean (SD)	63.1 (12.8)	62.2 (13.3)
Gender	Female	75 (53.2)	121 (54.3)
	Male	66 (46.8)	102 (45.7)
Race	Hispanic or Latino	5 (3.5)	13 (5.8)
	Asian	21 (14.9)	12 (5.4)
	Black	6 (4.3)	14 (6.3)
	White	85 (60.3)	147 (65.9)
	Other	24 (17.0)	37 (16.6)
ECOG PS	0 / 1	76 (53.9)	80 (35.9)
	2	13 (9.2)	18 (8.1)
	3	3 (2.1)	7 (3.1)
	4	0	1 (0.4)
	Missing	49 (34.8)	117 (52.5)
Stage at initial diagnosis*	I	12 (8.5)	12 (5.4)
	II	8 (5.7)	10 (4.5)
	III	9 (6.4)	24 (10.8)
	IV	111 (78.7)	176 (78.9)
	Other	1 (0.7)	1 (0.4)
Histology	Non-squamous cell carcinoma	136 (96.5)	212 (95.1)
	Squamous cell carcinoma	4 (2.8)	4 (1.8)
	NSCLC histology NOS	1 (0.7)	7 (3.1)
CNS metastases	Yes	53 (37.6)	58 (26.0)
	No	88 (62.4)	165 (74.0)
Smoking status	Smoking history	54 (38.3)	111 (49.8)
	No smoking history	87 (61.7)	112 (50.2)
Index period	01 Jan 2014 to 10 Dec 2015	0	125 (56.1)
	11 Dec 2015 to 5 Nov 2017	26 (18.4)	90 (40.4)
	6 Nov 2017 to 31 Aug 2019	115 (81.6)	8 (3.6)
***ALK* testing method**	FISH	78 (55.3)	165 (74.0)
	IHC	8 (5.7)	12 (5.4)
	NGS	38 (27.0)	21 (9.4)
	PCR	0	2 (0.9)
	Other	2 (1.4)	0
	Unknown	15 (10.6)	23 (10.3)
PD-L1 status	High (≥50%)	37 (6.2)	10 (4.5)
	Low (1–<9%)	43 (29.1)	14 (6.3)
	Negative (<1%)	23 (16.3)	10 (4.5)
	Unknown	40 (28.4)	189 (84.8)

*American Joint Committee on Cancer – Cancer Staging Manual, 8th edition. NOS, not otherwise specified; SD, standard deviation.

Progression-free survival

- The median duration of PFS follow-up in the RWD cohort (calculated by reverse Kaplan-Meier method) was 15.2 months with alectinib and 19.5 months with crizotinib.
- In the RWD cohort, median rwPFS was significantly improved with alectinib (24.5 months; 95% CI 15.8–NA) vs crizotinib (12.0 months; 95% CI 9.3–14.4) (**Figure 1**).
- In patients with baseline brain scans, a significant rwPFS benefit was seen irrespective of the presence of baseline CNS metastases (**Figure 1**).
  - With baseline CNS metastases: alectinib 21.0 months (95% CI 15.0–NA) and crizotinib 5.9 months (95% CI 3.9–12.9).
  - Without baseline CNS metastases: alectinib 25.3 months (95% CI 16.8–NA) and crizotinib 10.2 months (95% CI 9.0–16.9).
- In the ALEX-like RWD cohort, similar rwPFS benefit of alectinib vs crizotinib to that seen for PFS in the ALEX study was observed[5] (**Figure 1**).

Figure 1. PFS in the RWD cohort, ALEX-like RWD cohort and ALEX study

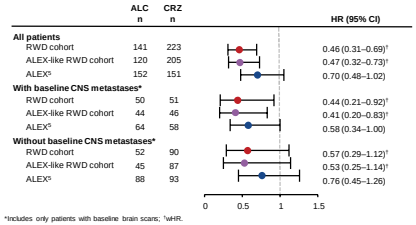


*Includes only patients with baseline brain scans; †wHR.

Overall survival

- The median duration of OS follow-up in the RWD cohort (calculated by reverse Kaplan-Meier method) was 19.1 months with alectinib and 44.2 months with crizotinib.
- In the RWD cohort, median rwOS was significantly improved with alectinib (not reached [NR]; 95% CI 29.2–NA) vs crizotinib (23.0 months; 95% CI 17.0–33.5) (**Figure 2**).
- In patients with baseline brain scans, a rwOS benefit was seen irrespective of the presence of baseline CNS metastases (**Figure 2**).
  - With baseline CNS metastases: alectinib 29.2 months (95% CI 26.7–NA) and crizotinib 7.6 months (95% CI 5.3–18.5).
  - Without baseline CNS metastases: alectinib NR (95% CI 25.1–NA) and crizotinib 30.9 months (95% CI 21.8–NA).
- In all patients, the rwOS benefit of alectinib vs crizotinib was greater in the ALEX-like RWD cohort than that seen for OS in the ALEX study[5] (**Figure 2**).

Figure 2. OS in the RWD cohort, ALEX-like RWD cohort and ALEX study

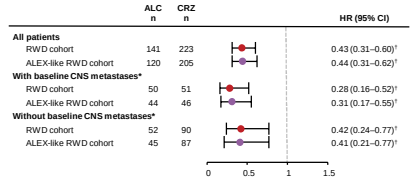


*Includes only patients with baseline brain scans; †wHR.

Time to new CNS metastases

- In the RWD cohort, median rwTTNCM was significantly improved with alectinib (29.2 months; 95% CI 23.5–NA) vs crizotinib (12.5 months; 95% CI 9.2–15.9; **Figure 3**).
- In patients with baseline brain scans, a significant rwTTNCM benefit was seen irrespective of the presence of baseline CNS metastases (**Figure 3**).
  - With baseline CNS metastases: alectinib 16.7 months (95% CI 14.8–NA) and crizotinib 4.6 months (95% CI 2.6–5.8).
  - Without baseline CNS metastases: alectinib NR (95% CI 23.5–NA) and crizotinib 16.5 months (95% CI 13.3–23.3).
- A similar rwTTNCM benefit of alectinib vs crizotinib was observed in the RWD and ALEX-like RWD cohorts (**Figure 3**).

Figure 3. Analyses of rwTTNCM in the RWD and ALEX-like RWD cohorts



*Includes only patients with baseline brain scans; data were analysed by inverse probability weighting using propensity scores in patients with baseline brain scans; †wHR.

Sensitivity analyses of the RWD cohort

- In the sensitivity analyses (known ECOG PS or more contemporaneous crizotinib-treated patients [treated after 11 December 2015]) of rwPFS in all patients or patients without baseline CNS metastases, significant beneficial HRs were observed for alectinib (**Table 2**).

Table 2. Sensitivity analyses of rwPFS in the RWD cohort

	Known ECOG PS		Treatment after 11 December 2015	
All patients	Alectinib n=92	Crizotinib n=104	Alectinib n=141	Crizotinib n=98
	HR 0.40 (95% CI 0.24–0.64)		HR 0.38 (95% CI 0.26–0.57)	
With baseline CNS metastases	Alectinib n=30	Crizotinib n=24	Alectinib n=53	Crizotinib n=24
	HR 0.26 (95% CI 0.10–0.67)		Cohorts could not be balanced*	
Without baseline CNS metastases	Alectinib n=62	Crizotinib n=80	Alectinib n=88	Crizotinib n=74
	HR 0.50 (95% CI 0.28–0.90)		HR 0.45 (95% CI 0.28–0.72)	

*The number of patients was too low to allow sufficient balancing.

Conclusions

Alectinib showed significant benefit over crizotinib in a real-world assessment of first-line treatment of advanced *ALK*+ NSCLC, including rwPFS, rwOS and rwTTNCM. The benefit of alectinib was observed irrespective of baseline CNS metastases.

In the RWD population that was filtered by the ALEX study laboratory values inclusion and exclusion criteria (ALEX-like RWD cohort), the weighted HR for rwPFS was consistent with the HR in ALEX. However, the adjusted HR for rwOS appeared to outperform the HR for OS in ALEX.

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