**Article title: Comparative effectiveness from a single-arm trial and real-world data: alectinib versus ceritinib**

**Short running title:** **Comparative effectiveness of a single-arm trial**

**Figure number:** 5

**Table number:** 3

**Abstract**

**Aim:** To compare the overall survival of anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer patients who received alectinib with those who received ceritinib.

**Materials & Methods:**  Two treatment arms (alectinib [n = 183]; ceritinib [n = 67]) were extracted from clinical trials and an electronic health record database respectively. Propensity scores were applied to balance baseline characteristics. Kaplan–Meier and multivariate Cox regression were conducted.

**Results:** After propensity score adjustment, baseline characteristics were balanced. Alectinib had a prolonged median OS (alectinib = 24.3 months; ceritinib = 15.6 months) and lower risk of death (hazard ratio: 0.65, 95% confidence interval: 0.48, 0.88).

**Conclusions:** Alectinib was associated with prolonged OS versus ceritinib, which is consistent with efficacy evidence from clinical trials.

**Keywords:** real-world evidence •comparative effectiveness • non-small-cell lung cancer •

**Introduction**

In health technology assessments, it has become increasingly important to demonstrate comparative effectiveness for new therapies, in addition to the traditional licensing requirements of quality of manufacture, safety and efficacy [1]. However, the race to license new therapies, especially for rare biomarker-defined populations such as *anaplastic lymphoma kinase* (*ALK*)-positive non-small-cell lung cancer (*ALK*+ NSCLC), has meant that regulatory approval using single-arm phase II studies can precede the availability of traditional , comparative evidence using randomized controlled trials (RCTs), which can take time to recruit rare biomarker-defined populations [2, 3]. In addition, the highly segmented treatment landscape for ALK inhibitors (ALKi) has meant that it is not always possible to perform head-to-head comparison trials using the standard of care that can provide the best comparative evidence.

In the absence of comparative evidence from RCTs, external controls are often used to bridge the gap of providing comparative evidence using direct adjusted comparisons [4–7]. However, as these types of studies typically do not use individual patient-level data (IPD), they are susceptible to systematic variation or bias. Therefore, innovation in methods of gathering and assessing comparative evidence is needed in order to accelerate reimbursement decisions for new therapies in rarer cancers.

To overcome this problem, our study used U.S. IPD from the Flatiron Health electronic health record (EHR) database [8] to create an external real-world data (RWD) control arm that provides comparative evidence. The external RWD control and two single-arm phase II alectinib trials (NP28673 and NP28761) were retrospectively analyzed to compare overall survival (OS) in patients with *ALK*+ advanced NSCLC treated with alectinib versus ceritinib following crizotinib failure (CF).

**Materials & Methods**

Study population and data sources

The population was derived from IPD of adult patients (≥18 years) diagnosed with locally advanced (American Joint Committee on Cancer [AJCC] stage IIIB, not amenable to curative therapy) or metastatic (AJCC stage IV) NSCLC, with a documented *ALK* rearrangement, and who had experienced disease progression on crizotinib Two treatment arms were constructed: alectinib and ceritinib. The alectinib treatment arm was derived by pooling data from patients enrolled in two phase II studies (Global study NP28673 [NCT01801111] [9]; and North American study NP28761 [NCT01871805] [10]). To derive the ceritinib arm, IPD were extracted by applying inclusion and exclusion criteria from the NP28673 and NP28761 clinical trials to the EHR derived database (Flatiron Health). After blending the two treatment cohorts, additional exclusion criteria were applied to address the imbalances between the ceritinib and alectinib cohorts in stage of diagnosis and treatment with crizotinib post-progression (further details can be found in the supplementary section).

Statistical analysis

The primary endpoint was OS, defined as the time from the date of initiation of alectinib or ceritinib until death from any cause. Patients were censored on their date of last visit, if they were still on their previous treatment at the end of the study period or if their death could not be confirmed.

To reduce indication bias, a logit propensity score was estimated by regressing treatment assignment (alectinib vs ceritinib) on key prognostic factors that were previously identified and similarly defined across populations (age, gender, race, stage at initial diagnosis, prior lines of therapy [11,12]). The propensity score was applied via inverse probability treatment weighting (IPTW) with stabilized weights, the most general approach for the primary analysis. Trimming was applied pre-weighting to include only patients with an overlapping distribution of propensity scores [13,14]. Graphical display of the propensity score was used to assess the distribution pre- and post-weighting. Standardized mean differences (SMD) were computed for all covariates in the unadjusted (no propensity scores) and adjusted sample to assess the balance of the cohort. Any difference observed greater than 0.1 pooled standard deviation units indicated an imbalance [11,13].

Median OS and corresponding 95% confidence intervals (CIs) were provided for each of the treatment arms and compared with a log-rank test. A doubly robust approach was taken with a multivariate Cox proportional hazard model to estimate the average treatment effect of alectinib on the re-weighted cohort.

Sensitivity and secondary analyses

Multiple sensitivity analyses were conducted to assess the robustness of the primary analysis. The following cohorts were used: patients with follow-up time in the top 10th percentile excluded; missing covariates imputed (race and stage at diagnosis); central nervous system (CNS) metastases as a prognostic factor; patients with 1–3 lines of prior treatment (patients with more than three lines of treatment were excluded); and age as a continuous variable. A secondary matched analysis was performed through Genetic Matching (GenMatch), by applying an evolutionary search algorithm that maximized the balance of observed confounders across the alectinib and ceritinib treatment arms [15]. A naïve comparison with an independent ceritinib clinical trial cohort (ASCEND-2, NCT01685060 [16]) was also conducted to evaluate the generalizability of the RWD outcomes to a clinical trial cohort [17]. Further description can be found in the supplementary section.

**Results**

The primary analysis included a pooled cohort of 183 patients who received alectinib from the two phase II studies, and 67 patients who received ceritinib from the Flatiron database (Figure 1).

Demographic and clinical characteristics

Prior to adjustment, patients in the alectinib arm were younger, more heavily pre-treated and had a higher prevalence of CNS metastases than the ceritinib arm. Both treatment cohorts were more likely to be female, Caucasian, have adenocarcinoma (ACA) histology, have an initial diagnosis of stage IV and no history of smoking (Table 1). After re-weighting, all covariates were balanced with SMD below the 10% threshold. The highest difference that remained was prior lines of treatment (6.4%) (Table 2). The balance was further confirmed upon visual graphical inspection; the distribution of the propensity score by treatment arm was comparable after re-weighting (Figure 2).

Treatment effectiveness

The median follow-up was 23 months for the alectinib arm and 12 months for the ceritinib arm.The crude median OS of the un-weighted alectinib arm (n = 183) was 26 months (95% CI: 21–not reached [NR]) and 16 months (n = 67; 95% CI: 12–NR) for the un-weighted ceritinib arm. Median OS of the re-weighted cohorts was 24 months (95% CI: 21–NR) for alectinib (n = 183) and 16 months (n = 64; 95% CI: 16–19) for ceritinib (Figure 3). The multivariate Cox model showed that alectinib was associated with a significantly lower risk of death compared with ceritinib (hazard ratio [HR]: 0.65; 95% CI: 0.48–0.88; p= 0.006) (Figure 4). Female, non-white race, younger age and one prior treatment were also associated with longer survival (Figure 4). The estimated comparative effectiveness of alectinib versus ceritinib was consistent across the sensitivity analyses with an adjusted HR ranging from 0.53 (95% CI: 0.40–0.70) to 0.67 (95% CI: 0.49–0.92; Table 3).

Naïve comparison with ceritinib trial

Similar imbalances observed between the alectinib arm and ceritinib arm were also observed between patients enrolled in a ceritinib trial group (ASCEND-2) and the ceritinib RWD arm (Supplementary Table 1). Median OS was consistent between ceritinib (RWD) (16 months, 95% CI: 12–NR) and ceritinib (trial) (15 months, 95% CI: 14–NR; Figure 5A). Prolonged OS compared with ceritinib (trial) was observed in the un-weighted alectinib cohort (median 26 months, 95% CI: 21–NR; Figure 5B).

Subsequent treatments

Subsequent therapies were allowed for both treatment groups. At data cut-off, 56 patients in the alectinib arm were still receiving alectinib treatment and four patients in the ceritinib arm were still receiving ceritinib treatment. In total, 53 patients (42%) in the alectinib arm received at least one subsequent therapy; 32 patients (25%) received ceritinib and three patients (2%) were retreated with crizotinib. In the ceritinib arm, 34 patients (54%) received at least one subsequent therapy; eight patients (12%) received alectinib and two patients (3%) were retreated with crizotinib.

**Discussion**

Although not a substitute for RCTs, comparisons with RWD can bridge evidence gaps when the standard of care has shifted quickly, or when RCT evidence is not available, as in the case of the CF setting in patients with *ALK*+ NSCLC. Our analysis provides insight into the treatment effect among second generation ALK-inhibitors in the CF setting.

Prior to re-weighting, patient characteristics were imbalanced. The ceritinib arm had a higher median age compared to the ceritinib trial arm, most likely due to the difference in patient selection for clinical trials versus treatment in clinical practice. Patients in the ceritinib arm were similar to a previous cohort of CF patients that had a median age of 67 years [18]. Patients in the alectinib arm had a higher proportion of pre-treatment, mainly comprising chemotherapy (platinum-doublet) regimens. This may be due to the fact that many patients in the alectinib arm were diagnosed before crizotinib was approved for first-line treatment. Patients receiving alectinib also reported a higher prevalence of CNS metastases at baseline than in the ceritinib (RWD) arm, possibly due to under-reporting in clinical practice compared with the more rigorous clinical trial assessment. The prevalence of CNS metastases observed in the ceritinib (RWD) arm was similar to a CF population from a global real-world cohort, which reported a range of CNS prevalence after CF of 23% in the US to 54% in Europe [19].

As this study is a comparison of a non-randomized sample, similarity of baseline characteristics was essential. To address any potential bias, the study cohort was re-weighted using IPTW, based on a calculated propensity score to harmonize the two treatment arms. This is a robust method to reduce bias and estimate average treatment effects across groups after balancing observed confounders [13, 20–23]. After re-weighting, balance in baseline covariates between the two treatment arms was achieved based on SMD <10%, which is considered negligible [11].

Alectinib was associated with lower risk of death in the primary analysis and sensitivity analyses compared with ceritinib. The lower risk of death associated with alectinib is aligned when examining the efficacy evidence from the phase II and III trials for alectinib. In the two phase II studies of alectinib in the CF setting median duration of response with alectinib was 11.2 and 13.5 months) [9,10]. A lower duration of response to ceritinib of 9.7 months was reported in a similar phase II trial (ASCEND-2) [16]. A randomized phase III study (ALUR) of CF patients treated with alectinib versus chemotherapy confirmed alectinib’s superiority over chemotherapy with a median PFS of 9.6 months compared to 1.4 months in patients that received chemotherapy (HR: 0.15, (95% CI: 0.08-0.29) [24]. The differentiated profile of alectinib compared to other ALK inhibitors is further supported by data from the phase III randomized study (ALEX), which compared the treatment of alectinib to crizotinib in previously untreated patients with ALK rearrangement. This trial showed the positive treatment effect of alectinib over crizotinib in terms of PFS (HR for disease progression or death, 0.47; 95% CI, 0.34 to 0.65; median PFS, not estimable [95% CI, 17.7 months to not estimable] with alectinib vs. 11.1 months (95% CI, 9.1 to 13.1) with crizotinib) [25].

There are potential limitations to this analysis. Unobserved confounding may have impacted the results which propensity score-based approaches cannot address. Eastern Cooperative Oncology Group performance status (ECOG PS) is a key prognostic factor and criterion of the alectinib trials, but it was not available consistently in the Flatiron database as it is not generally collected in clinical practice. When ECOG PS was available, any patient in the ceritinib (RWD) cohort with an ECOG PS >2 was excluded. However, this information was not available for more than 60% of patients. Given the high rate of missing data, imputation methods were not used as they would not be meaningful. A recent systematic review of cohorts initiating second-line and third-line treatment in clinical practice reported that most patients had a Karnofsky performance status ≥70, or an ECOG PS <2 [26]. Thus, it is plausible that many of the patients in the ceritinib arm had an ECOG PS <2, given that the treatment setting was second and third line, aligning to patients in the alectinib arm.

Propensity-based approaches can also be at risk of model misspecification. To evaluate the potential impact of misspecification on the treatment effect, we conducted a sensitivity analysis with a non-biased propensity score approach, GenMatch [27]. The treatment effect stayed consistent in the GenMatch analysis, which suggests little impact of this potential bias on the observed treatment effect.

OS estimates in the ceritinib RWD arm may have been immature given the limited follow-up time, and the small sample size which may have biased results. However, the median OS estimates from the ASCEND-2 trial, which had a longer follow-up and larger sample size, were similar to the ceritinib RWD cohort, providing evidence that the OS estimates from the ceritinib RWD arm are generalizable. In a sensitivity analysis excluding patients with >10% of follow-up to evaluate if the longer follow-up in the alectinib was driving the HR, the HR of alectinib versus ceritinib of 0.65 (95% CI: 0.47-0.89) stayed consistent with the primary result of 0.65 (95% CI: 0.48-0.88), which suggests the higher proportion of patients with longer follow-up time in the alectinib arm had a minimal impact on the estimated treatment effect.

Finally, there are inherent differences in the data collection between the two treatment arms by nature of design of the clinical trial and RWD, which could potentially lead to surveillance bias. We believe if this did exist, it would be bias towards the null, because data from the alectinib arm were collected for the purpose of the clinical trial. Moreover, collection of the outcome (date of death) from the Flatiron Health database we believe matches that of a clinical trial, with a sensitivity of 91% and specificity of 96% of capturing death events of the advanced NSCLC EHR-derived database [28].

To our knowledge, this is the first comparative effectiveness analysis to evaluate OS among patients with *ALK*+ advanced NSCLC who received treatment with alectinib or ceritinib following CF. Alectinib has a clearly differentiated profile compared to other ALK inhibitors and this has been demonstrated in phase II and phase III randomized studies in both the CF setting as well as in the treatment naïve setting [24,25,29]. Therefore, our results from this analysis are consistent with the observations from the two randomized phase 3 studies that have been conducted until now (ALUR and ALEX). In addition, a similar median OS was observed among ceritinib treated patients in the real world (median OS: 15.6 months) and in a clinical trial setting (median OS: 14.9 months) thereby increasing the credibility of the results observed with the RWD ceritinib. It is therefore, the totality of evidence which in this case includes real world data as well as trial data that is being used to demonstrate the clinical effectiveness of alectinib.

**Conclusion**

In this adjusted comparison, alectinib was associated with a lower risk of death compared with ceritinib, which aligns with the totality of clinical trial evidence that has been used to license and reimburse alectinib. Median survival estimates were similar between the ceritinib (RWD) and ceritinib (trial) cohorts, supporting the generalizability of the ceritinib RWD and the plausibility of the results reported in this analysis. In conclusion, we propose that the utility of RWD in providing external controls should be evaluated further with more case studies and validated with IPD from a trial control arm. This will be especially useful in cases where novel medicines are being licensed in rare populations, where is more difficult to perform large RCTs to generate comparative evidence.

**Summary points**

* Due to the small proportion of patients with *anaplastic lymphoma kinase*-positive non-small-cell lung cancer (*ALK*+ NSCLC), development of new tyrosine kinase inhibitors has been based on single-arm trials, and therefore, generating comparative evidence in this setting has been challenging.
* This study specifically looked at how newly emerging areas, such as electronic health records (EHR) systems, can help identify a rare molecularly defined population (such as *ALK*+ NSCLC), and how this can be used to generate comparative evidence within the setting of single-arm studies.
* EHR data collected from January 1, 2011 and February 28, 2016 (certinib) was combined with individual patient data (IPD) from two single-arm phase II studies (alectinib) to estimate treatment effectiveness.
* Data were harmonized by applying inclusion and exclusion criteria from the trials to the EHR database. Propensity score and GenMatch modelling were used to address imbalances of measured confounders. Overall survival (OS) was then compared with a multivariate Cox proportional hazards model.
* A sensitivity analysis evaluating OS of the control cohort from EHR was conducted with a naïve comparison between the EHR cohort and digitized trial data from the control treatment.
* Alectinib was associated with a significantly lower risk of death compared with ceritinib (hazard ratio: 0.65, 95% confidence interval [CI]: 0.48–0.88, *P* = 0.006), in line with efficacy data from the single-arm trials. Alectinib also achieved a longer median OS compared with ceritinib (24.3 vs 15.6 months, respectively).
* Median OS estimates were similar between the ceritinib ASCEND-2 trial and RWD populations (ASCEND-2 15 months, 95% CI: 14–not reached, RWD 16 months, 95% CI: 12–not reached). In our comparison, alectinib was associated with prolonged OS versus ceritinib.
* This study is a proof of concept study to test whether a comparator arm could be generated from RWD and average treatment effect could be estimated in a rare molecularly defined population, where a phase III study may not be feasible. More case studies are needed to validate the approach.

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\* Of interest for the disease area or methodology used. To conduct this study, the results and interpretation of alectinib and ceritinib trials were vital to providing the data and insights for the results. Diamond and Sekhon’s publication provided the background to a novel non-propensity scoring based approach to achieving covariate balance in GenMatch; Guyot et al., provided the methodology to re-digitize patient-level data from summary characteristics.

**Shaw AT et al. *Lancet Oncol*. 17(2), 234–242 (2016).**

This was a phase II study of alectinib in patients with *ALK*+ NSCLC who progressed on crizotinib in North America. Alectinib showed clinical activity and was well tolerated, providing evidence for alectinib as a suitable treatment in this patient population.

**Ou SHI et al. *J. Clin. Oncol.* 34(7), 661–668 (2016).**

This was a global phase II study of alectinib in crizotinib-refractory *ALK*+ NSCLC. Alectinib was active and well tolerated, including in patients with CNS metastases.

**Crino L, et al. *J. Clin. Oncol*. 34(24), 2866–2873 (2016).**

The phase II ASCEND-2 trial evaluated efficacy and safety of certinib in patients with *ALK*+ NSCLC previously treated with chemotherapy and who had progressed on crizotinib. Certinib treatment showed clinically meaningful responses, including in patients with CNS metastases.

**Diamond A, Sekhon JS. *Rev. Econ. Stat.* 95(3), 932–945 (2013).**

This paper describes genetic matching, a type of multivariate matching that uses an evolutionary search algorithm to determine the weight of each covariate.

**Guyot P,** **Ades AE, Ouwens MJ, et al. *BMC Med Res Methodol*. 2, 12:9 (2012).**

This paper describes a method that derives a close approximation to the original individual patient time-to-event data from the published Kaplan-Meier survival curves from which they were generated.

\*\*Of considerable interest for methodology used in the study. Austin et al.’s publications on propensity scores were essential to outlining best practices.

**Austin PC, Stuart EA. *Stat. Med.* 34(28), 3661–3679 (2015).**

This review describes methods to allow assessment of whether measured baseline covariates are balanced between treatment groups in a weighted sample in inverse probability treatment weighting.

**Austin PC. *Multivariate Behav. Res.* 46(3), 399–424 (2011).**

This article describes different propensity score methods and balance diagnostics for examining whether the propensity score model has been adequately specified.

**Figure legends**

**Figure 1.** **Cohort attrition.**

ALKi: ALK inhibitors; RWD: Real-world data.

**Figure 2.** **(A) SMD in pre- and post-matched weighted samples, (B) Pre- and post-matched weighted distribution of propensity score.**

IPTW: Inverse probability treatment weighting; RWD: Real-world data; SMD: Standardized mean differences.

**Figure 3.** **Kaplan–Meier curves of OS in the re-weighted analysis of the alectinib and ceritinib populations.**

OS: Overall survival; RWD: Real-world data.

**Figure 4.** **Multivariate Cox model analyses of OS.**

The first group listed for each variable is the reference group.

OS: Overall survival.

**Figure 5.** **Kaplan–Meier analysis of (A) real-world and clinical trial OS data for ceritinib and (B) alectinib pooled data versus re-digitized ASCEND-2.**

All populations are unweighted.

OS: Overall survival; RWD: Real-world data.

**Table 1. Patient characteristics by treatment cohort.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Alectinib**  **(n = 183)** | **Ceritinib RWD**  **(n = 67)** | **Total**  **(n = 250)** | **p-value** |
| Mean age (SD)a,b | 52.5 (±11.2) | 59.8 (±11.4) | 54.5 (±11.7) | <0.0001 |
| Age group, n (%)a,c | | | | |
| <65 years | 160 (87) | 41 (61) | 201 (80) | <0.0001 |
| ≥65 years | 23 (13) | 26 (39) | 49 (20) |
| Gender, n (%)c | | | | |
| Male | 85 (47) | 30 (45) | 115 (46) | 0.89 |
| Female | 98 (54) | 37 (55) | 135 (54) |
| Race, n (%)c | | | | |
| White | 133 (73) | 49 (73) | 182 (73) | 1 |
| Other | 50 (27) | 18 (27) | 68 (27) |
| ACA histology, n (%)c | 175 (96) | 61 (91) | 236 (94) | 0.029 |
| ECOG PS, n (%)c | | | | |
| 0 | 64 (35) | 8 (12) | 72 (29) | 0.11 |
| 1 | 101 (55) | 8 (12) | 109 (44) |
| 2 | 18 (10) | 5 (7) | 23 (9) |
| Missing | 0 | 46 (69) | 46 (18) |
| Stage at diagnosis, n (%)a,c | | | | |
| IIIB | 13 (7) | 8 (12) | 21 (8) | 0.3 |
| IV | 170 (93) | 59 (88) | 229 (92) |
| CNS metastasis, n (%)a,c | | | | |
| Yes | 112 (61) | 23 (34) | 135 (54) | 0.0002 |
| No | 71 (39) | 44 (66) | 115 (46) |
| History of smoking, n (%)c | | | | |
| Yes | 62 (34) | 30 (45) | 92 (37) | 0.14 |
| No | 121 (66) | 37 (55) | 158 (63) |
| Prior chemotherapy, n (%) | 136 (74) | 19 (28) | 155 (62) | <0.0001 |
| Prior radiation, n (%) | 84 (46) | 21 (31) | 105 (42) | 0.043 |
| Prior lines of treatment, n (%) | | | | |
| 1 | 52 (28) | 38 (57) | 90 (36) | <0.0001 |
| 2 | 66 (36) | 20 (30) | 86 (34) |
| ≥3 | 65 (36) | 9 (13) | 74 (30) |
| Range of prior lines | (1–8) | (1–5) | (1–8) |  |

ACA: Adenocarcinoma; CNS: Central nervous system; ECOG PS: Eastern Cooperative Oncology Group performance status; RWD: Real-world data; SD: Standard deviation.

aSignificant difference (SD) between treatment cohorts (p < 0.05).

bWilcoxon rank-sum test.

cChi-squared test.

**Table 2. Baseline characteristics pre- and post-weighting.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Pre-weighting** | | | **Post-weighting** | | |
| **Alectinib** | **Ceritinib** | **SMD, %** | **Alectinib** | **Ceritinib** | **SMD, %** |
| Patients, n | 183 | 64a |  | 251b | 236b |  |
| ≥65 years, n (%) | 23 (13) | 23 (36) | 56.7 | 51 (20) | 48 (21) | 0.9 |
| Female, n (%) | 98 (54) | 34 (53) | 0.9 | 134 (53) | 121 (51) | 3.7 |
| White, n (%) | 133 (73) | 48 (75) | 5.3 | 184 (73) | 171 (72) | 1.8 |
| Stage IV at diagnosis, n (%) | 170 (93) | 57 (89) | 13.4 | 231 (92) | 218 (92) | 2.2 |
| Prior lines of treatment, n (%)  1  2  ≥3 | 52 (28)  66 (36)  65 (36) | 35 (55)  20 (31)  9 (14) | 62.8 | 91 (36)  86 (34)  74 (29) | 89 (38)  85 (36)  63 (27) | 6.4 |

SMD: Standardized mean difference.

aThree patients removed after applying trimming.

bPopulation sizes are larger due to weighting. Stabilized weights were used in order to have an average weight close to 1 (and pseudo sample size close to original sample size).

**Table 3. Sensitivity analyses of OS.**

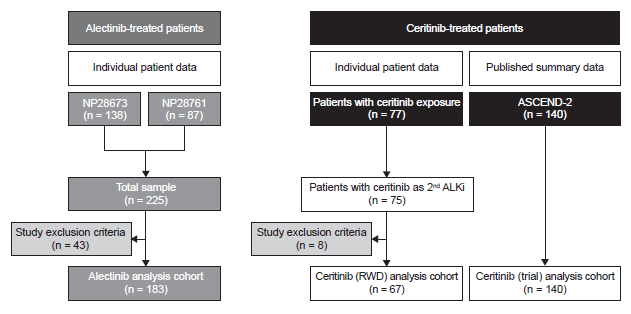
|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Alectinib patients** | | **Ceritinib patients** | |  |  |
| **Cohort** | **N** | **Median OS (95% CI)** | **N** | **Median OS (95% CI)** | **Adjusted HR (95% CI)** | **p–value** |
| Exclude patients with follow-up time in top 10th percentile | 164 | 24 (21–NR) | 57 | 16 (16–19) | 0.65  (0.47–0.89) | 0.007 |
| Exclude patients initiating treatment <12 weeks prior to data cut-off | 183 | 24 (20–NR) | 63 | 16 (16–19) | 0.65 (0.48–0.88) | 0.006 |
| Impute missing covariates (race and stage at diagnosis) | 208 | 24  (20–NR) | 70 | 16  (12–19) | 0.58  (0.44–0.76) | <0.001 |
| Include CNS metastases as prognostic factor | 152 |  | 64 |  | 0.67  (0.49–0.92) | 0.01 |
| Not including stage at diagnosis as a prognostic factor | 225 | 26  (21–NR) | 68 | 16  (12–19) | 0.53  (0.40–0.70) | <0.001 |
| Patients with 1–3 lines of treatmenta | 148 | 24  (20–NR) | 63 | 16  (14–19) | 0.66  (0.48–0.90) | 0.009 |
| Age as continuousb | 170 | 23  (20–NR) | 64 | 18  (16–19) | 0.66  (0.49–0.89) | 0.006 |
| Include Asian race category | 174 |  | 64 |  | 0.67  (0.49–0.91) | 0.01 |
| GenMatch | 183 | 26  (24–NR) | 67 | 16  (16–16) | 0.57  (0.50–0.65) | <0.001 |

CI: Confidence interval; CNS: Central nervous system; GenMatch: Genetic Matching; HR: Hazard ratio; NR: Not reached; OS: Overall survival.

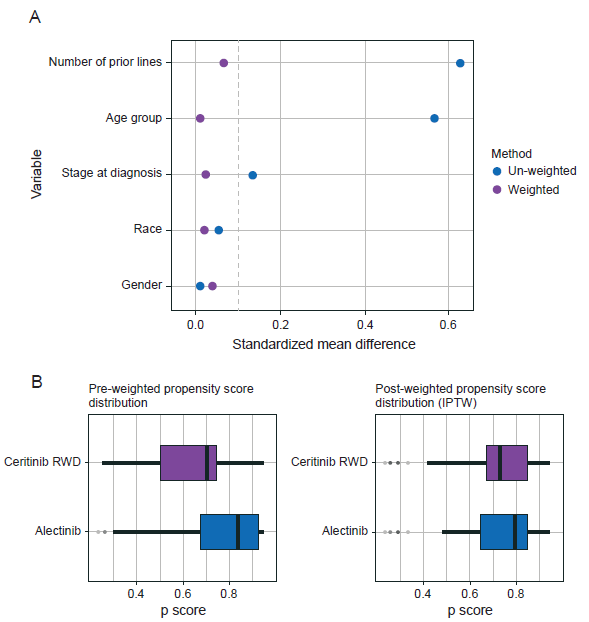
aThe sensitivity analysis was conducted including patients that had 1–3 lines of prior treatment. Patients with >3 lines of treatment were excluded.

bAdjusted for gender, race, age, stage at diagnosis and prior treatment.

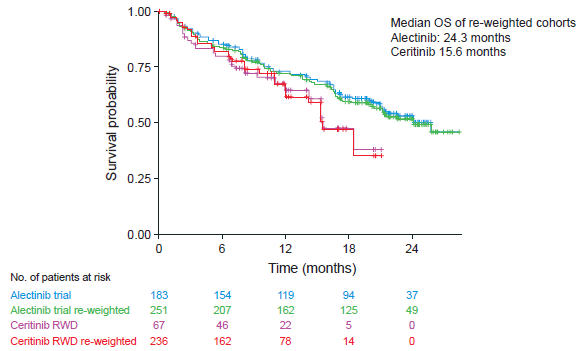
**Figure 1.**



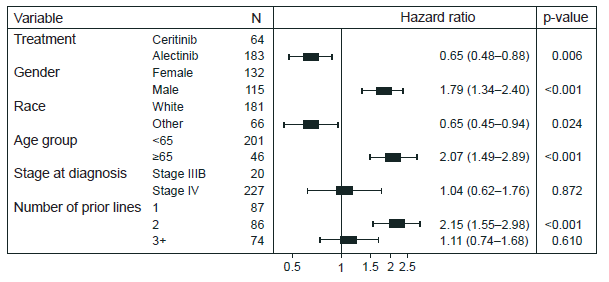
**Figure 2.**



**Figure 3.**



**Figure 4.**



**Figure 5.**

