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COST-EFFECTIVENESS ANALYSIS OF ALECTINIB VERSUS CRIZOTINIB IN FIRST-LINE ALK-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER IN THE BRAZILIAN PRIVATE HEALTHCARE SYSTEM PERSPECTIVE

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INTRODUCTION

- Anaplastic lymphoma kinase (ALK) translocation in advanced non-small cell lung cancer (NSCLC) is a potential mechanism for target therapy with tyrosine kinase inhibitors (TKi).[1]
- ALK-positive patients are usually young and more than 90% are non-smokers. In this group, the risk of metastasis is higher than observed for other aberrations and the central nervous system (CNS) is one of the main sites.[2]
- CNS progression requires intensive monitoring and is associated with higher and faster mortality.[2]
- Crizotinib was the first TKi for first-line ALK-positive NSCLC treatment reimbursed on the Brazilian private healthcare system. However, patients usually present progressive disease in less than 12 months, mostly in the CNS.[3]
- Alectinib is a second generation TKi and demonstrated superior efficacy over crizotinib in ALEX, a phase III randomized-controlled trial.[4,5]
- Median progression-free survival (PFS) was increased from 10.9 months with crizotinib to 34.8 months with alectinib (hazard ratio [HR] 0.43; 95% confidence interval [CI] 0.32-0.58).[4,5]
- Time to CNS progression was longer with alectinib than crizotinib (HR 0.16; 95% CI 0.10-0.28) and 12-month incidence rates of CNS progression was 9.4% (95% CI 5.4-14.7) with alectinib *versus* 41.4% (95% CI 33.2-49.4) with crizotinib.[4,5]
- Alectinib also presented lower incidence rates of grade 3-5 adverse events than crizotinib (44.7% *versus* 51.0%, respectively).[4,5]

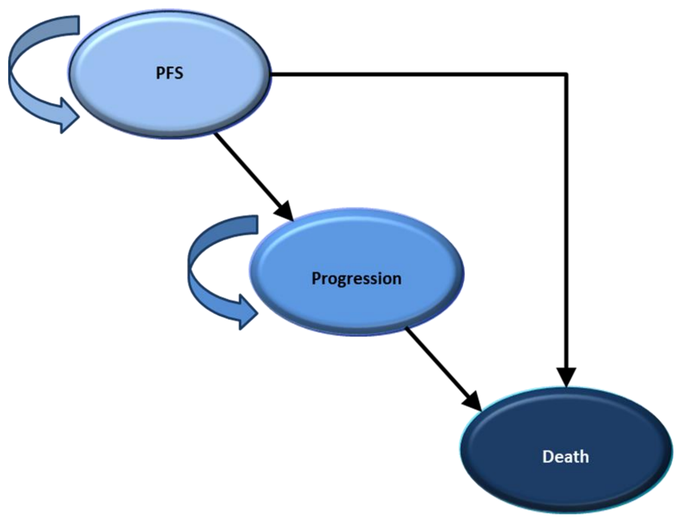
- **The use of precision medicine and target therapies in Oncology is usually associated with incremental costs, which is one of the main barriers for granting access to innovation.[6,7]**
- **In the Brazilian private healthcare system, sustainability and innovation have been massively discussed and data evaluating costs and health benefits are essential assets to guide decision making.[6,7]**
- **This study aimed to evaluate the cost-effectiveness of alectinib *versus* crizotinib for naïve ALK-positive advanced NSCLC treatment in the Brazilian private healthcare system.**

METHODS

Partitioned Survival Model

- An area under the curve (AUC) partitioned survival model was developed based on three mutually excluding health states: overall survival (OS), PFS and post-progression (PP) - Figure 1.
- All patients entered the model progression-free and alive and were allowed to stay within the same state or move to progression or death at the end of each cycle. At each time point, the proportion of patients in the PP state was assumed to be the difference between OS and PFS.
- Cycle length was one week and half-cycle correction was applied in order to account for mid-cycle transitions.
- Costs and effectiveness were discounted using a 5% rate.

Figure 1. Partitioned Survival Model Outline

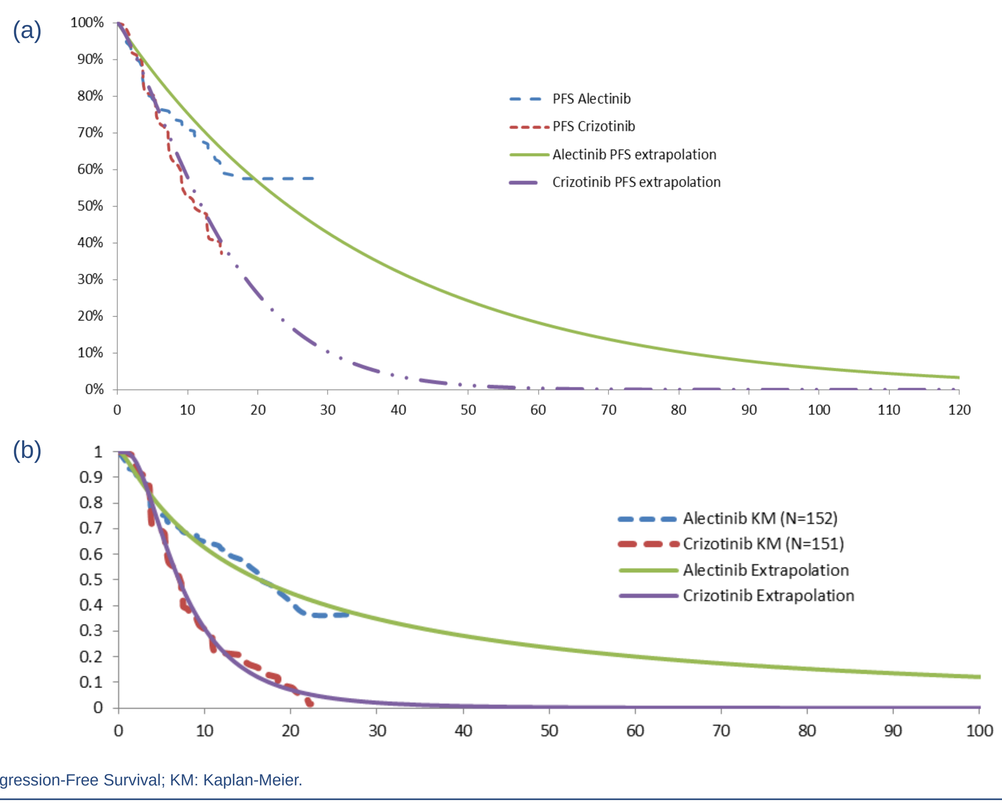


PFS: Progression-Free Survival

Clinical Inputs

- ALEX trial Kaplan-Meier curves were used to estimate the probability of disease progression and survival. Estimated for alectinib and crizotinib were extrapolated to the lifetime horizons using parametric distributions.[4,5]
- The best goodness-of-fit was defined based on Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and conformity to the original survival curves, validated by a lung cancer advisory board.
- For PFS, the most plausible models for alectinib and crizotinib were exponential and Weibull, respectively (Figure 2a). For OS, Weibull curves were considered the best fit for both treatment arms.
- A time to event approach was adopted to estimate the proportion of patients who will have CNS progression. CNS PFS was extracted from ALEX trial and extrapolated to a lifetime horizon using exponential and lognormal curves for alectinib and crizotinib, respectively (Figure 2b).[4,5]

Figure 2. Extrapolation of (a) Progression-Free Survival and (b) Central Nervous System Progression Free-Survival Kaplan-Meier Estimates



PFS: Progression-Free Survival; KM: Kaplan-Meier.

Health State Utilities

- Health state utilities for PFS and PP, were collected on ALEX trial using EuroQoL Group's five dimensional (EQ-5D) generic health-related quality-of-life instrument.[4,5]
- On PP health state, for second non-TKi treatment was considered, for further lines, all patients were fully allocated on best supportive care (BSC). Non TKI and BSC utilities were obtained from published literature.[3,8]
- PFS utility was 0.814, PP non-TKi was 0.660 and PP BSC was 0.470.

Resource Use and Costs

- Direct medical costs of drugs, management of adverse events, supportive care, procedures related to CNS metastasis management and end-of-life care were included in the model, estimated on 2019 Brazilian reais (BRL) and converted to US dollars (USD) using a 0.27 conversion rate.
- Drug usage was defined as per label. For both alectinib and crizotinib, treatment duration was considered equal to PFS observed in ALEX trial.[4]
- A micro-costing approach was used to estimate health state costs by a multi-disciplinary team composed by healthcare professionals with experience in Oncology at the Brazilian private healthcare system.
- Drugs, procedures and material costs were extracted from Drug Market Regulation Chamber (CMED), Brasíndice guide and the Hierarchical Brazilian Classification of Medical Procedures (CBHPM) official prices.

Sensitivity Analysis

- A one-way deterministic sensitivity analysis (DSA) was performed to determine which variables would impact costs and effectiveness outcomes. Costs and utilities were varied in ± 10% and results are presented in a tornado diagram.
- A probabilistic sensitivity analysis (PSA) was conducted using 1,000 Monte Carlo iterations to further test the model robustness.

RESULTS

Health States and Treatment Costs

- Monthly cost of alectinib and crizotinib was 26,720 BRL (7,214 USD) and 30,622 BRL (8,268 USD).
- CNS progression management was composed by radiotherapy (48%), surgery (28%), diagnostic procedures (17%), hospitalizations and emergency care (7%) and medical honorariums (1%).
- The estimated cost of a CNS progression event was estimated on 29,029 BRL (7,838 USD), with additional 61,819 BRL (16,691 USD) annual follow-up costs.

Base Case Analysis

- Alectinib increased progression-free life years (PFLY), life years (LY) and quality-adjusted life years (QALY) in 1.436, 0.87 and 0.87 *versus* crizotinib, respectively.
- On PFS health state, alectinib costs were 820,695 BRL (221,588 USD) and crizotinib costs were 528,614 BRL (142,726 USD). On PP health state, alectinib costs were 789,214 BRL (213,087 USD) and crizotinib 1,123,037 BRL (303,220 USD), which represent a 30% decrease on costs with alectinib.
- Within the PP health state, alectinib decreased 315,595 BRL (85,211 USD) related to CNS progression costs (699,432 BRL *versus* 1,015,027 BRL with crizotinib).
- Overall, total costs for alectinib was 1,609,909 BRL (434,675 USD) and for crizotinib 1,651,651 BRL (445,946 USD).
- Hence, alectinib was dominant over crizotinib, with higher efficacy and lower costs. Cost offsets were estimated on 41,742 BRL (11,270 USD) per patient, on a lifetime horizon – Table 1.

Table 1. Cost-Effectiveness Analysis Results

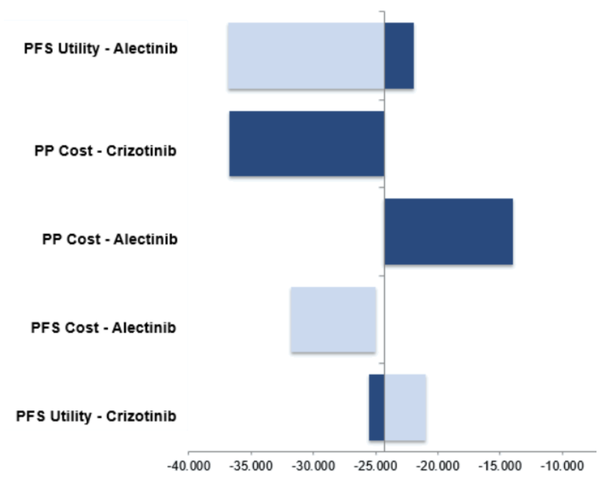
Parameter	Alectinib	Crizotinib	Incremental
Mean Progression-Free Life Years (PFLY)	**2.631**	**1.196**	**1.436**
Mean Life Years (LY)	**5.40**	**4.52**	**0.87**
Mean Quality-Adjusted Life Years (QALY)	**3.37**	**2.50**	**0.87**
Costs in PFS	820,695 BRL (221,558 USD)	528,614 BRL (142,726 USD)	292,081 BRL (78,862 USD)
Costs in PP	789,214 BRL (213,087 USD)	1,123,037 BRL (303,220 USD)	-333,823 BRL (90,132 USD)
CNS related costs (within PP health state)	699,432 BRL (188,844 USD)	1,051,027 BRL (283,777 USD)	-315,595 BRL (-82,211 USD)
Total Costs	**1,609,909 BRL (434,675 USD)**	**1,651,651 BRL (445,946 USD)**	**-41,742 BRL (-11,270 USD)**
ICER (Cost/PFLY gained)		**Dominant**	
ICER (Cost/LY gained)		**Dominant**	
ICER (Cost/QALY)		**Dominant**	

PFS: Progression-Free Survival; PP: Post-Progression; CNS: Central Nervous System; ICER: Incremental Cost-Effectiveness Ratio.

Deterministic Sensitivity Analysis

- DSA demonstrated that the SLP health state utility for alectinib was the most sensitive parameter.
- However, event with minimum and maximum values alectinib remained dominant over crizotinib – Figure 3.

Figure 3. Deterministic Sensitivity Analysis

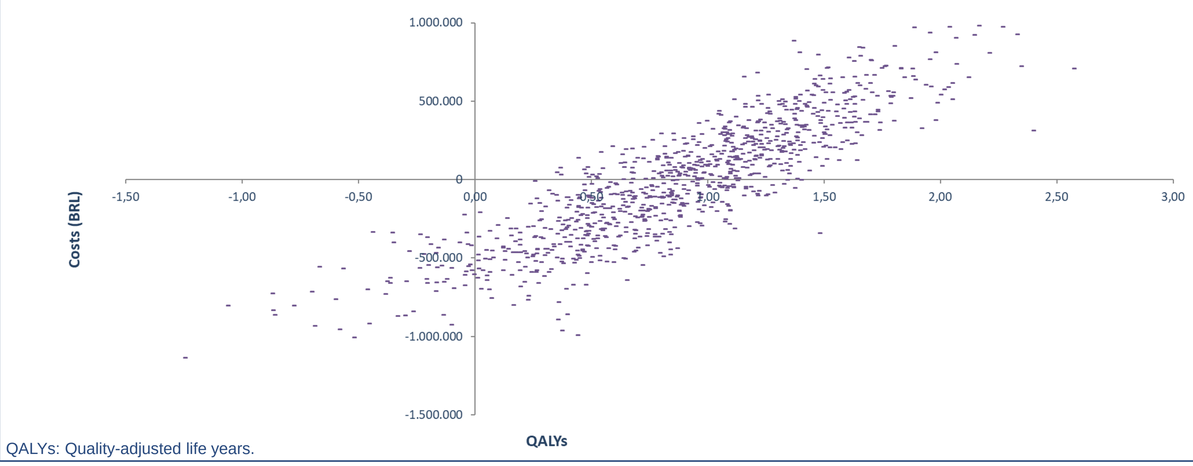


PFS: Progression-Free Survival; PP: post-progression.

Probabilistic Sensitivity Analysis

- Total of 54%, 7% and 39% of PSA simulations were localized on quadrants I, III and IV, respectively – Figure 4.
- Alectinib proved superior effectiveness on 93% and lower costs on 46% of the estimated scenarios.

Figure 4. Probabilistic Sensitivity Analysis



QALYs: Quality-adjusted life years.

Limitations

- Since data from ALEX trial was not complete to model the disease through the lifetime horizon, extrapolation was required, which configures uncertainty for long term outcomes.
- At the time of the analysis, overall survival data from ALEX trial was not mature yet, due to the long survival profile of ALK-positive patients treated with TKi. However, alectinib also demonstrated to be dominant over crizotinib considering PFLY as a measure of effectiveness.
- Reference list prices were used as a base case, which does not account for any particular negotiations and arrangement between health maintenance organizations and suppliers or manufacturers.
- Despite these limitations, the results of DSA and PSA demonstrated robustness in the results, which account for variations that can occur in the real world.

CONCLUSIONS

- Alectinib increased PFLYs, LYs and QALYs for ALK-positive advanced NSCLC patients, compared with crizotinib, and improved CNS protection, with lower CNS progression incidence rates and progression.
- Alectinib decreased costs of progressive disease, compared with crizotinib, due to CNS progression prevention.
- Alectinib presented lower global costs *versus* crizotinib and higher effectiveness. Hence, it was considered dominant on the Brazilian private healthcare system perspective.

DISCLOSURES

- This study was sponsored by F. Hoffmann-La Roche.

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