Clinical implications of cardiotoxicity and pharmacokinetics of alectinib in patients with anaplastic lymphoma kinase positive non-small cell lung cancer

Melinda A Pruis et al

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Outline

- Background
- Methods
- Results
- Conclusions

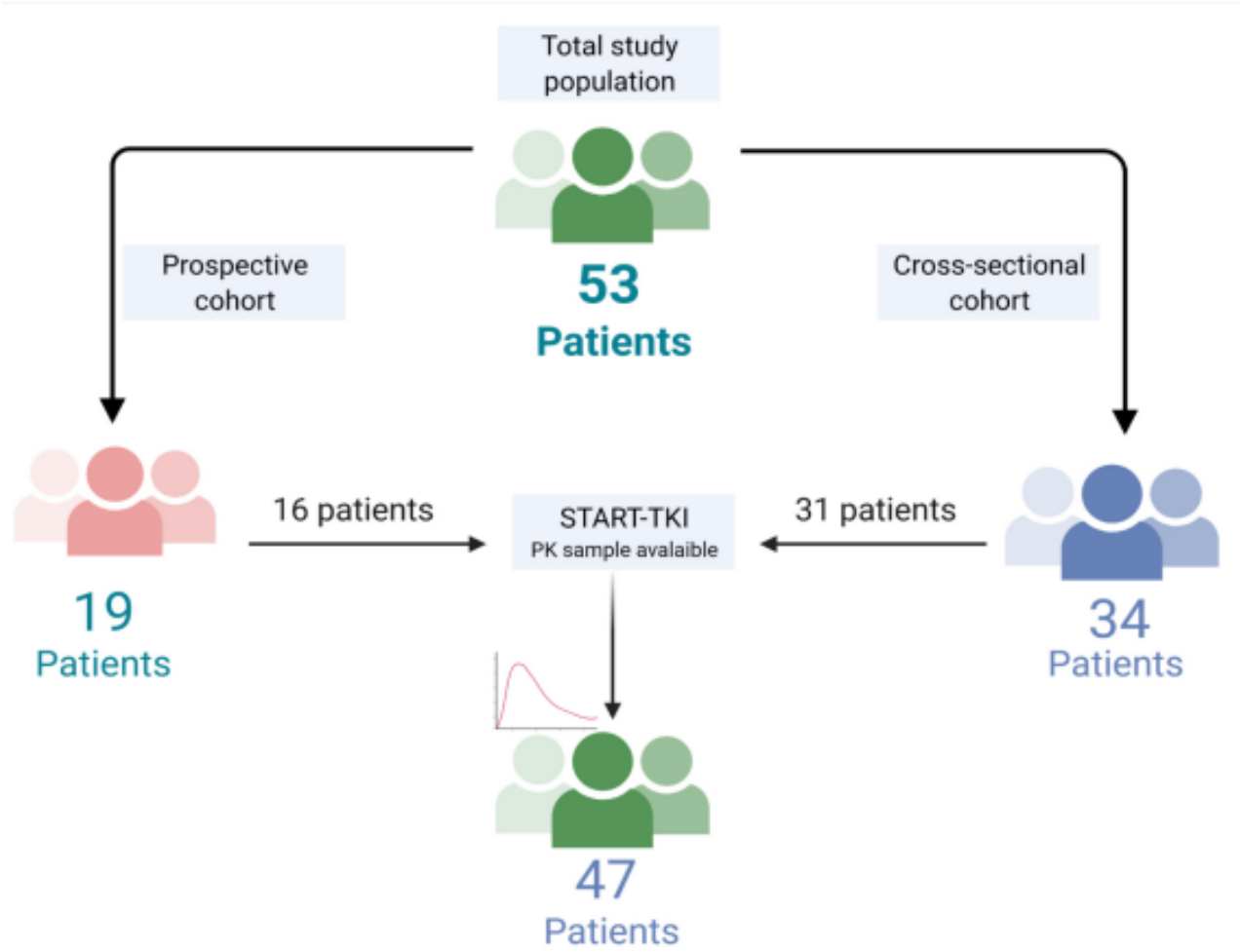
Background

- Patients with advanced ALK positive non-small cell lung cancer (NSCLC) experience long-term survival when treated with alectinib.
- Known adverse events (AE) of alectinib include edema and bradycardia, suggesting potential cardiotoxicity.
- This could threaten safe long-term dosing and lead to dose-reduction which can be detrimental to alectinib's efficacy as there is a relationship between exposure-response.
- We hence prospectively investigated alectinib's cardiotoxicity profile and its exposure-toxicity relationship

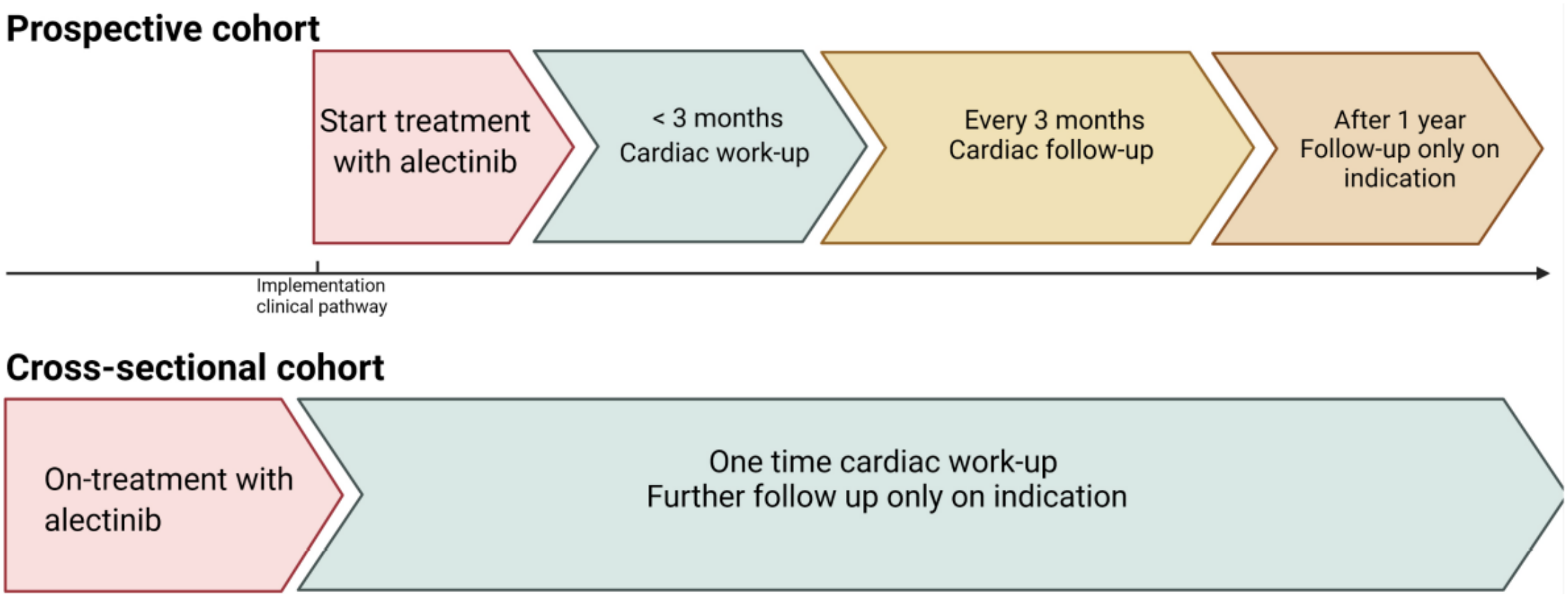
Methods

- In total, 53 patients with ALK positive NSCLC treated with alectinib were included between 6-2020 – 9-2021.
- Patients starting with alectinib after 6-2020 underwent a cardiac work-up at our dedicated cardio-oncology clinic < 3 months after start, at 6 months and at 1 year.
- Patients already receiving alectinib > 6 months underwent a cardiac evaluation once.
- Bradycardia and edema data as well as severe alectinib toxicity (≥3 grade AEs and grade ≥2 AEs leading to dose modifications) were collected.
- Alectinib steady-state trough concentrations (C trough) in blood plasma were used for exposure-toxicity analyses

Flowchart of patient inclusion

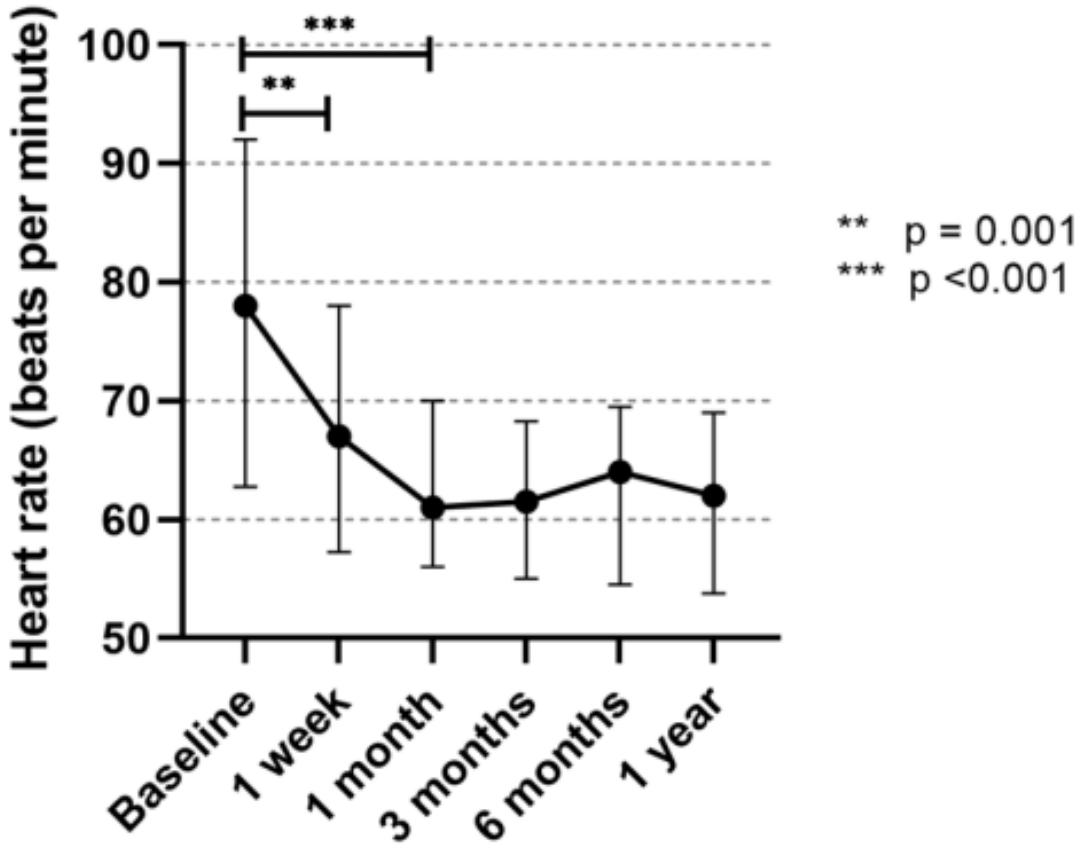


Overview of clinical pathways and patients



Results

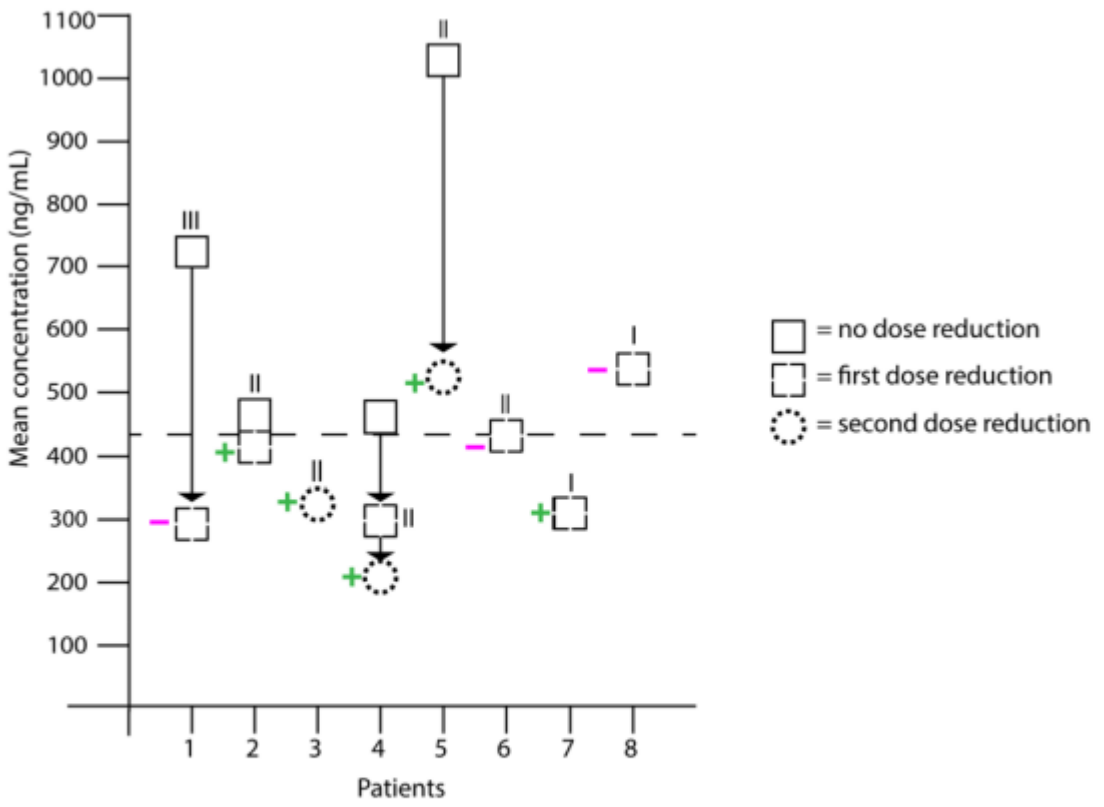
- Left ventricular ejection fraction (LVEF) remained normal in all patients who underwent an on-treatment cardiac work-up (n=34; median 62%; inter-quartile range 58%-64%).
- Median heart rate significantly decreased during treatment with alectinib



*Median heartrate and inter-quartile range on different timepoints. ** = p = .001, *** = p < .0001.*

Results

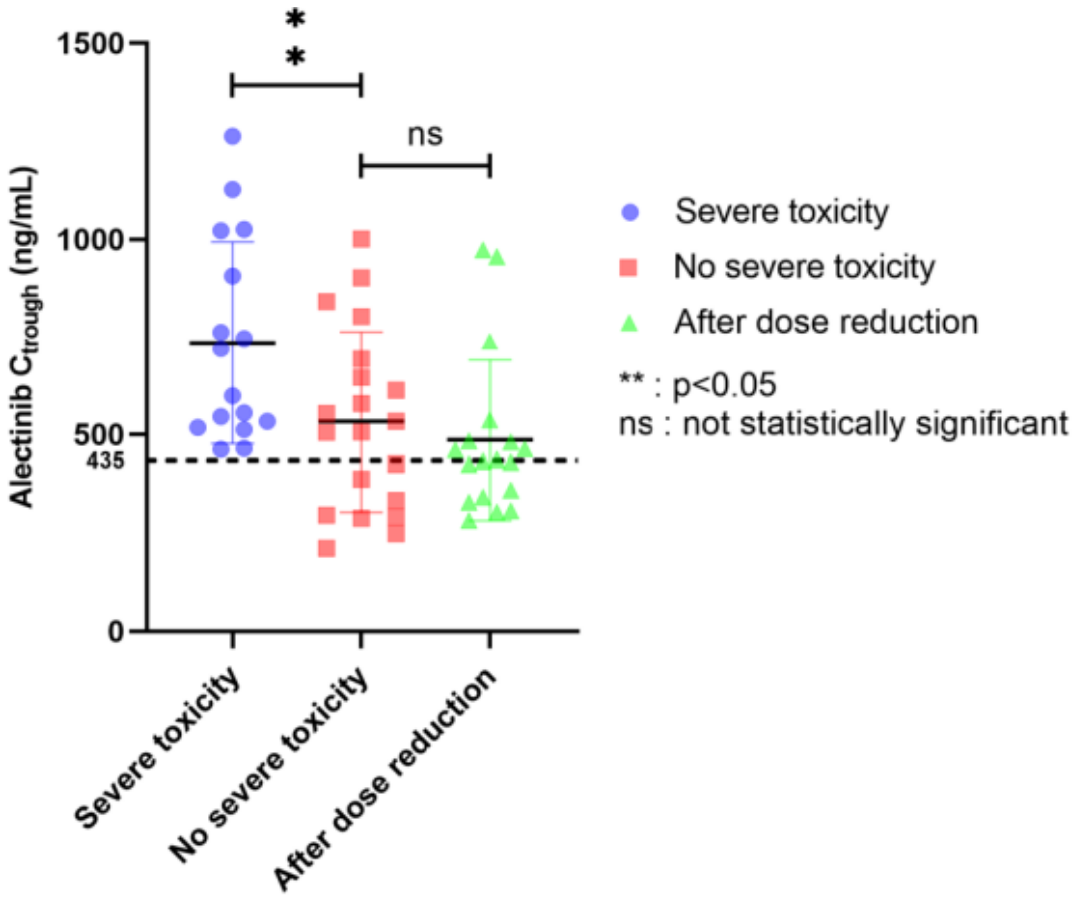
- Seven patients (13%) developed alectinib-related edema. 22 patients (22/53) developed alectinib-related bradycardia (16 grade 1; 5 grade 2; 1 grade 3 resulting in a pacemaker placement).
- Nine patients required at least 1 dose reduction.
- This resulted in a sub-therapeutic
- C_{trough} in 5 patients (therapeutic threshold > 435ng/mL)



Mean plasma concentrations of alectinib before and after dose-reduction for bradycardia.
The roman numbers indicate the CTCAE grade of bradycardia.
+ = bradycardia improved, - = bradycardia unchanged or worsened.

Results

- Patients who experienced severe toxicity had a significantly (38%) higher alectinib Ctrough (735 vs. 533ng/mL; p=0.02)



Difference in alectinib minimal plasma concentration (C_{trough}) between patients with and without severe toxicity when treated with alectinib 600 mg bid and after dose-reduction to 450 mg bid.
*Means and standard deviations are shown. ** = p < .05, ns = not significant.*

Conclusions

- There were no signs of diminished LVEF and alectinib-induced edema does not seem to be cardiac-related.
- Bradycardia occurred more frequently than previously reported (43%) and was an important reason for dose-modifications, resulting in sub-therapeutic exposure in the majority of these patients.
- In general, patients with severe toxicity have a relatively high exposure to alectinib well above the therapeutic threshold.


THANK YOU