MET and *NF2* alterations confer early resistance to first-line alectinib treatment in *ALK*-positive non-small-cell lung cancer

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Background

- The second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI), alectinib, has shown prolonged survival in naïve *ALK*-rearranged advanced non-small-cell lung cancer (NSCLC), with median progression-free survival (PFS) reaching 34.8 months.
- By the data cut-off date of this study, October 2020, alectinib has been approved in China for only two years (since August 2018).
- Here, we explored the mechanisms of early resistance to alectinib in *ALK*-rearranged NSCLCs.

Methods

- Total 108 *ALK*-rearranged NSCLC patients had confirmed clinical relapse on alectinib within two years, including 52 who received first-line alectinib treatment (1L) and 56 who received alectinib after crizotinib resistance (2L).
- Targeted sequencing of cancer-related genes were performed using tissue or liquid biopsy samples before and after treatment.

Results

Figure 1. Resistance mechanisms were different after 1L and 2L alectinib treatment. Frequent *MET* and *NF2* alterations were identified after 1L alectinib, whereas majority of 2L resistance resulted from *ALK* on-target mutations.

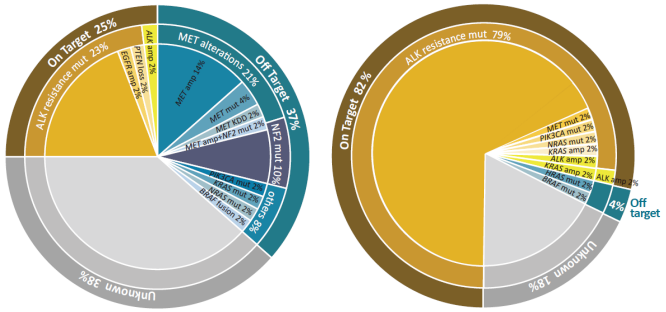


Figure 2. After 1L alectinib, eleven *MET* alterations were found in mutual exclusivity with *ALK* on-target mutations, with PFS ranging from 1 to 19.7 months.

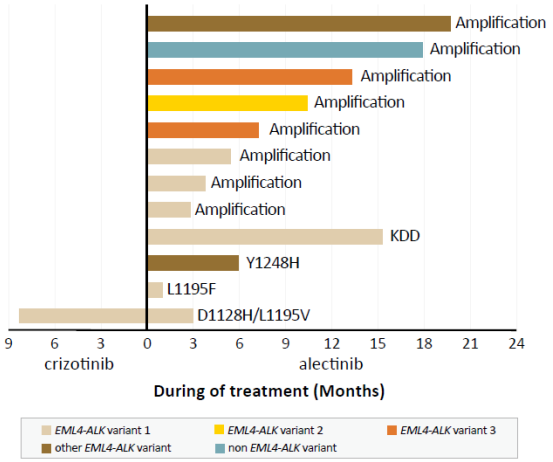


Figure 3. *NF2* variants associated with 1L alectinib resistance might cause loss of function of the merlin protein.

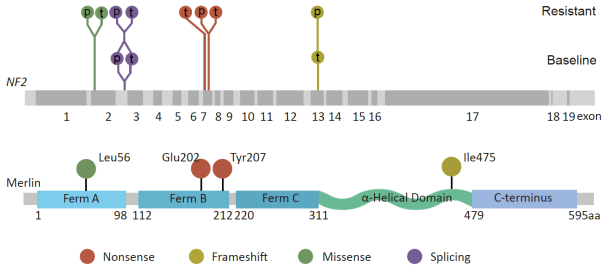
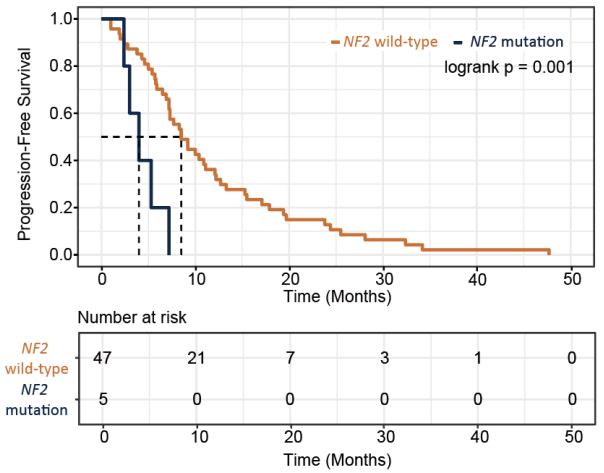


Figure 4. Patients with *NF2* mutations after 1L alectinib treatment were associated with significantly poor outcomes comparing to NF2 wildtype patients



Results

Figure 5. After 1L alectinib, off-target mutations were frequently found with *EML4-ALK* variant 1, whereas *ALK* alterations were often identified with variant 3.

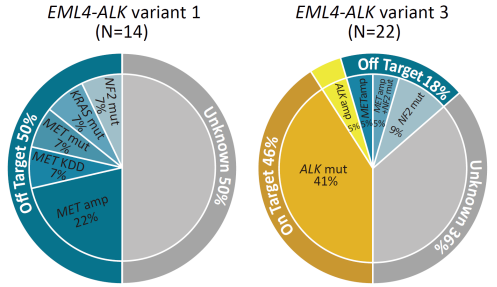
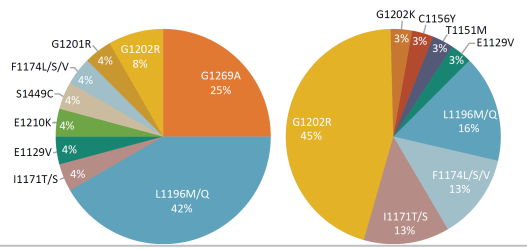


Figure 6. Different ALK mutants were detected after 2L alectinib.



Conclusions

Off-target alterations in *MET* and *NF2* might confer early resistance to 1L alectinib, whereas resistance to 2L alectinib was mainly induced by ALK point mutations. These different mechanism might be informative in guiding future tailored treatment for ALK-positive NSCLCs.

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