

# DSEN ABSTRACT

## Crizotinib and Incidence of Death: A Systematic Review and Network Meta-analysis of *ALK* Inhibitors for Non-small Cell Lung Cancer

### Summary

- We observed that all *ALK* inhibitors improved progression-free survival relative to chemotherapy, and that alectinib and brigatinib were associated with improved progression-free survival compared to crizotinib and ceritinib.
- Alectinib improved overall survival relative to chemotherapy and crizotinib, although the findings may have been influenced by crossover between treatment groups following disease progression.

### Key messages

- There exists limited clinical trial data directly comparing the efficacy of individual *ALK* inhibitors and we found no studies involving patients with *ROS1* rearrangements.
- Additional studies are needed.

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### What is the issue?

- Anaplastic lymphoma kinase (*ALK*) inhibitors are therapies used for individuals with non-small cell lung cancer (NSCLC) to improve overall and progression-free survival.
- Currently, four *ALK* inhibitors are approved for use in Canada and the US: crizotinib, ceritinib, alectinib and brigatinib. There is interest in their comparative clinical efficacy and safety.
- Previous reviews were limited by the use of a pair-wise meta-analysis approach, which permits comparison of only two therapies at one time. A network meta-analysis (NMA) allows the comparison of multiple treatments at one time and provides estimates of their relative effectiveness and safety combining direct and indirect evidence, which is more informative for clinical decision-making.

### What was the aim of the study?

- The aim of this study was to conduct a comprehensive systematic review of *ALK* inhibitors for *ROS1* or *ALK*-positive NSCLC.
- We used NMA methodology to provide an estimate of progression-free survival, overall survival and serious adverse events for each drug.

### How was the study conducted?

- This review was registered *a priori* (CRD42017077046) and followed guidance from the Cochrane Handbook for Systematic Reviews for Interventions.
- The systematic search is current to July 2019.

### What did the study find?

- We included 48 reports of 15 unique randomized controlled trials.
- Progression-free survival may be improved by alectinib and brigatinib relative to other *ALK* inhibitors; however, the assessment of overall survival is likely influenced by treatment crossover and should be interpreted with caution.
- Crizotinib and alectinib, but not ceritinib, increased the risk of serious adverse events when compared with chemotherapy.
- Treatment-related deaths were infrequent among *ALK*-positive NSCLC.
- Results in full are available in the publication.

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