Editorial

Choice of first-line anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) based on the results of a systematic review and network meta-analysis

Edyta Maria Urbanska

Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Correspondence to: Edyta Maria Urbanska, MD, PhD. Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. Email: Edyta.Maria.Urbanska@regionh.dk.

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Several approved first-line anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) options may confound physicians treating patients with metastatic *ALK*-rearranged non-small cell lung cancer (NSCLC). Beyond issues associated with different access to the drug and reimbursement procedures, the choice of the first-line therapy remains challenging. Tan *et al.* have provided a systematic review and network meta-analysis (NMA) to compare the relative efficacy and toxicity of different ALK TKIs in treatment naïve patients with *ALK*-rearranged advanced NSCLC (1). The authors have taken into consideration nine phase III randomized clinical trials: PROFILE 1014, PROFILE 1029, ALEX, ALESIA, J-ALEX, ALTA-1L, ASCEND-4, eXalt3 and CROWN. NMA assessed these trials in terms of transitivity (exchangeability across studies) and consistency (similarity of direct and indirect estimates).

As presented in *Tab. 5* by Tan *et al.*, the quality of these trials was assessed to be at low risk of bias, except for performance and detection bias for subjective outcomes due to the open-label design. The outcomes of interest were progression-free survival (PFS) by independent review criteria (IRC), PFS by investigator assessment (IA), overall survival (OS), IRC-PFS in patients with and without brain metastases, objective response rate (ORR), intracranial response, and toxicities. The determination of the overall ranking of each treatment was proceeded by the surface under the cumulative ranking curve (SUCRA), which visualizes a numeric presentation of the overall ranking and presents a percentage associated with each evaluated therapy. The conclusions showed that Lorlatinib had the greatest SUCRA (the higher the likelihood that the treatment is top rank), namely the highest probability of benefit in terms of IRC-PFS, both in patients with baseline brain metastases, where Lorlatinib was followed by Alectinib, and in patients without baseline brain metastases, where Lorlatinib was followed by Ensartinib and Alectinib. In terms of OS, Alectinib had the highest SUCRA and was superior to all other ALK TKIs and chemotherapy. The certainty of evidence was evaluated by using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methods to address differences in these trials between patients, interventions, and endpoints, as they may distort an indirect comparison (intransitivity) (2). Though, as the authors have discussed, their findings may be biased by some broken links, e.g., only one trial addressed the comparison of Lorlatinib with Crizotinib, while comparison of Alectinib with Crizotinib was studied in three trials. Furthermore, several unreported estimates, e.g., OS and IA PFS in chemotherapy naïve subgroups in ALTA-1L and J-ALEX trials, or outcomes for patients with and without brain metastases stratified by prior chemotherapy in ALTA-1L could

not be included in this NMA. Regarding toxicities and safety, Alectinib had the highest SUCRA, and was superior to all other ALK TKIs and chemotherapy with regards to the lowest odds of experiencing grade 3 or higher adverse events. Toxicities were also strongly associated with specific ALK TKIs: diarrhea, vomiting, nausea, and loss of appetite with Ceritinib, vision disorder with Crizotinib, rash with Ensartinib, and oedema with Lorlatinib. The NMA analysis then, made it possible to include all these available ALK TKI treatments in a specific clinical situation of first-line treatment and in one model; the possibility of comparing different interventions, even when there are no direct comparisons, and the possibility of increasing the strength (certainty) of the data by combining direct and indirect estimates of effects. Furthermore, some potential effect modifiers such as age, gender, and proportion of patients with brain metastases were comparable across all the trials. The current paper, in contrast to the previously published meta-analyses and NMA of ALK TKIs (3-5), included trials of chemotherapy allowing comparisons of Ceritinib, last results of ALTA-1L and J-ALEX with updated outcome for CROWN and eXalts3 trials. Despite lack of head-to-head comparison and the complexity of selection of first-line ALK TKIs, Tan *et al.* in their systematic review and NMA provide good informative value and practical support for physicians treating *ALK*-rearranged NSCLC patients.

Despite these advantages, the article shows a great, but also intricate attempt to manage the inevitable caveat of cross-trial comparisons, where the entire *ALK*-rearranged NSCLC population was handled, and no consideration was taken into individual patients. With other words, the *ALK*-rearranged NSCLC patients were in such analysis interpreted as a same, single disease, diagnosed with the same methods. The difference or inconsistency of molecular diagnoses may be an important confounding factor, as the fusion partner or *EML4-ALK* fusion variant may result in different response to different ALK TKIs. As we know from ALTA-1L study, ORR of Brigatinib was 84% for *EML4-ALK* variant 1, and 91% for *EML4-ALK* variant 3 (6). Correspondingly, ALEX study showed that ORR of Alectinib for *EML4-ALK* variant 1 was 90%, and for *EML4-ALK* variant 3 was 68% (7). Furthermore, *EML4-ALK* variant 3 showed the lowest sensitivity for Crizotinib compared with other variants (8). Moreover, the different diagnostic methods like immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH) and next-generation sequencing (NGS), used in the analyzed studies for identification of *ALK* positive status, may have impact on response and PFS (9-11). Finally, *ALK*-rearranged NSCLC patients represent also a unique population, where most of these patients receive a second or later line of treatment achieving median OS about 7 years (12). This fact also has an impact on OS, independently from the first treatment choice. Therefore, it is questionable whether the choice of the first line is so decisive, and whether NMA approach is legitimized without taking into consideration molecular diagnoses and the fact that many variables in this patient population have non-linear impact. The choice of Lorlatinib as a first line according to this NMA analysis may also pose further challenges both in terms of toxicities, and progression, especially in cases with acquired secondary compound *ALK* mutations. A cautious interpretation of this NMA comparison should also address the fact that first-line ALK TKIs non-responders constitute about 9–40% due to *de novo* resistance, and these patients remain the understudied group (13). On the other hand, these nine phase III trials were not designed to profoundly consider the disease's biology and generate additional molecular data. Therefore, a new model of future clinical trials operating with genomic-defined *ALK*-rearranged NSCLC subgroups is needed to help further NMA analyses in terms of precision medicine (14).

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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