Reply to Mizuno: implication of mutation profile of resected lung adenocarcinoma

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We read with a great interest the Editorial by Mizuno and Sakao (1), and we thank the authors for their interest in our work (2) as well as for their kind comments.

Indeed, the interest to primary lung adenocarcinoma, its mutation profile and the lymph-nodal involvement's prognostic role has never been as strong as in the last few years.

Definitively, we agree with Mizuno about the paucity of knowledge on appearance of mediastinal lymph-nodal involvement without hilar one (skip-N2 metastasis) in non-small cell lung cancer (NSCLC). The role of tumor-containing lobe, tumor location and possible visceral pleura invasion remain a matter of interest.

In this contest, our study takes into light a possible correlation between *EGFR* mutation presence and skip-N2 lymphatic spread. On the other hand, no correlation between skip-N2 and KRAS mutation was observed. As reported, the results of our study were revealed in a population characterized by (I) a lower incidence of skip-N2 metastasis than the majority of rates reported in literature (3-6); (II) a lower rate of EGFR mutations than in similar studies conducted in Asian population (3).

As the authors mentioned, these findings could rise interest in mutation profile investigation in still unexplored contest. Indeed, the possible impact of *EGFR* mutations on the mechanisms underlying the skip N2 pathway of lymph nodal metastasis is also unclear. We believe that this study could represent a first prompt in this field of translational research.

Due to the small population, our study did not analyze impact of different *EGFR* exon mutations and *KRAS* amino-acid substitutions on skip-N2 nodal involvement and prognosis. Moreover, effect of different complementary treatment (e.g., chemotherapy, radiotherapy, biological therapy and immunotherapy) according to skip-N2 metastases and different mutation profiles were unexplored and probably needs a prospective setting.

In conclusion, we hope that our results support future study and translation research on mutation profile of surgically resected adenocarcinoma of the lung.

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Footnote

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Ethical Statement: The authors are 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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