Reviewer’s report

Title: ALK-rearranged lung squamous cell carcinoma responding to alectinib: A case report and review of the literature

Version: 0 Date: 02 Mar 2017

Reviewer: Marcello Tiseo

Reviewer’s report:

In this paper, Mamesaya and colleagues report an interesting case of a squamous cell carcinoma of the lung harboring an ALK rearrangement, manifesting thus far disease response under alectinib treatment.

Major comments

- Pulmonary squamous cell carcinoma (SqCC) is a very rare entity in never-smoker patients, and the presence of an adenocarcinoma counterpart, configuring the histologic scenario of an adenosquamous carcinoma, should be excluded with a further biopsy (from the adrenal metastasis potentially), given the limits of a "transbronchial needle aspiration biopsy". Similar cases, firstly diagnosed as SqCC, revealed as adenosquamous tumors harboring EGFR mutations (EGFR Mutations in Squamous Cell Lung Cancer in Never-Smokers. Baik et al. J Thorac Oncol 2013) or ALK rearrangement (ALK-Rearranged Lung Cancer: Adenosquamous Lung Cancer Masquerading as Pure Squamous Carcinoma. Chaft et al. J Thorac Oncol 2012; ALK-rearranged adenosquamous lung cancer presenting as squamous cell carcinoma: a potential challenge to histologic type triaging of NSCLC biopsies for molecular studies. Dragnev KH et al, Clin Lung Cancer 2014) in both histologic counterparts. On the contrary, only one case of pure squamous cell carcinoma of the lung with ALK gene rearrangement by transbronchial biopsy was proven after radical surgery (ALK-rearranged squamous cell carcinoma of the lung. Takanashi Y et al, Resp Case Rep 2015).

Therefore, the authors should point out the potential limit of the small biopsy or cytological smears in the diagnosis of a specific histologic subtype, even in presence of adequate immunohistochemical panels, due to different reasons (tumor heterogeneity and distribution, management and suitability of the tumor sample).

- A discussion paragraph should be provided by authors, potentially moving some information from the introduction. The authors could summarize all clinical cases reported in the literature by using a table that describe: 1) type of tissue sample, 2) method(s) of ALK detection used, 3) previous treatments and response, 4) type of ALK inhibitor, if used, and its treatment outcome.

Minor comments:
- Page 4 line 10: abbreviation for "epidermal growth factor receptor" (EGFR) should be provided, due to its common use and its repetition at page 5 line 10.

- Page 5 line 12-13: the antibody used to detect ALK expression by IHC should be declared, as well as an IHC-intensity score for ALK staining.

- Page 5 line 14-15: percentage of cells presenting ALK rearrangement should be provided

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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