Author’s response to reviews

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

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Author’s response to reviews:

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Elisa Giovannetti
Associate Editor
BMC Cancer

Dear Elisa Giovannetti:

I, along with my co-authors, would like to re-submit the attached manuscript entitled “ALK-rearranged lung squamous cell carcinoma responding to alectinib: A case report and review of the literature” (revised Abstract word count: 238 words; revised text word count: 915words; tables: 1; figures: 3; references: 15) as a “Case Report” for publication in BMC Cancer. The manuscript ID is: BCAN-D-16-02802

We wish to thank the reviewers for their valuable and constructive advice regarding our submission. We believe that their insightful suggestions have enriched our manuscript and produced a better and more balanced account of our research.

We have carefully rechecked our submission and made the necessary revisions (highlighted in yellow in the edited file) in accordance with the reviewer’s suggestions. Please find enclosed our point-by-point responses to the comments and concerns raised.
We believe that the quality of our manuscript has been substantially improved and hope that the revised version is now suitable for publication in your esteemed journal. We look forward to hearing from you at your earliest convenience.

Sincerely,

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RESPONSES TO THE REVIEWER’S COMMENTS

Reviewer #1 (Nicola Stefano Fracchiolla)

The paper of Mamesaya et al describe the rare case of an ALK rearranged lung squamous cell carcinoma (SqCC). The patient was initially treated with cisplatin and vinorelbine, with no response. Upon the demonstration of ALK gene rearrangement upon FISH analysis, a treatment with alectinib was started obtaining significant response documented by CT scan. The paper is written fairly well and deserve some interest for the rarity of the clinical case and the response to alectinib. As the evidence in literature is virtually absent on this topic, the publication of this case report might prompt larger studies in order to determine the frequency of SqCC rearranged for ALK gene responding to specific inhibitors.

Comment 1: The authors must report the updated total follow-up of the patient and the duration of response.

Response: Thank you for your important suggestion. We have updated this information at the end of our Case presentation section as follows:

“At the latest follow-up, 11.0 months after commencing alectinib treatment, there was no evidence of progression or any remarkable toxicity” (page 5, lines 19-20).

Comment 2: The authors must briefly comment the case described by Yamamoto et al Mol Clin Oncol. 2016 Jul;5(1):61-63.

Response: Thank you for your valuable suggestion. We have added the following portions to our Discussion section in which we describe the case reported by Yamamoto et al. [7]:

“Yamamoto et al. [7] reported a similar case, which was diagnosed with ALK-rearranged lung SqCC. The diagnosis was confirmed by IHC staining, which was positive for p40, but negative
for thyroid transcription factor-1. The pathological specimen of their case [7] was also obtained from the primary lesion by bronchoscopic biopsy and no adenocarcinoma component was detected in the biopsy specimen. The Yamamoto et al. [7] case was positive on FISH with a rearrangement-positive cell rate of only 20.0%, but negative on IHC staining” (page 6, lines 5-12)

AND

“However, since the Yamamoto et al. [7] case was treated with radiotherapy without chemotherapy, it remains unclear whether the patient exhibited a marked response to ALK targeted therapies” (page 6, lines 15-17).

Comment 3: The authors must briefly comment on the different significance of ALK protein expression and ALK gene rearrangement.

Response: Thank you for your important comment. We have added the following portion to our Discussion section:

“Ilie et al. [8] reported that cases with discordant ALK detection test results (i.e., FISH positive, but IHC staining negative) had lower rearrangement-positive cell rates of 15.0%–20.0% and exhibited a tendency towards a lower response to crizotinib” (page 6, lines 12-14)

Reviewer #2 (Marcello Tiseo)

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

Comment 1: 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).

Response: Thank you for your insightful comments. We have added the following paragraph to the end of our Discussion section:

“There are some limitations to our case report. Our histological specimen was small and was obtained from a mediastinal lymph node. For this reason, there was the potential for an adenocarcinoma component to be contained in other parts or for there to be discrepancies between the primary lesion and metastatic lesions due to the heterogeneity and distribution of the tumor. In contrast, Hou et al. [16] recently reported a high concordance rate of ALK rearrangement between primary tumors and paired metastatic lymph nodes. This supports the findings of our present case” (page 7, line 2-8).

Comment 2: A discussion paragraph should be provided by authors, potentially moving some information from the introduction.

Response: Thank you for your valuable suggestion. We have created a Discussion section (page 5, line 22 to page 7, line 8) and moved some information from our Introduction section, as per your recommendation.

Comment 3: 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.

Response: Thank you for your suggestion. We have summarized all clinical cases reported in the literature by using a table (Table 1), which we have referred to in our Discussion section (page 6, line 17).

Minor Comments

Comment 1: Page 4 line 10: abbreviation for "epidermal growth factor receptor" (EGFR) should be provided, due to its commune use and its repetition at page 5 line 10. Response: Thank you for your valuable suggestion. We have provided the abbreviation for “epidermal growth factor receptor (EGFR)” (page 4, line 3-4).

Comment 2: 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. Response: Thank you for your comment. We have revised this portion in our Case presentation section as follows:

“IHC analysis indicated that the tumor cells were positive (2+ staining) for the ALK antibody (Histofine ALK iAEP Detection Kit; Nichirei Bioscience Inc., Tokyo, Japan)” (page 5, line 10-12).
Comment 3: Page 5 line 14-15: percentage of cells presenting ALK rearrangement should be provided

Response: Thank you for your important suggestion. We have revised this portion in our Case presentation section as follows:

“ALK break-apart fluorescence in situ hybridization (FISH) (Vysis ALK Break Apart FISH Probe Kit; Abbott Molecular Inc., Des Plaines, IL, USA) confirmed the presence of an ALK gene rearrangement with a rearrangement-positive cell rate of 46.0%” (page 5, line 12-15)