Author’s response to reviews

Title: Safe and effective use of nivolumab for treating lung adenocarcinoma associated with sporadic lymphangioleiomyomatosis: a rare case report

Authors:

Johan Pluvy (johan.pluvy@aphp.fr)

Solenn Brosseau (solenn.brosseau@aphp.fr)

Sandrine Stelianides (sandrine.stelianides@aphp.fr)

Claire Danel (claire.danel@aphp.fr)

Marina Nguenang (marina.nguenang@aphp.fr)

Antoine Khalil (antoine.khalil@aphp.fr)

Bruno Crestani (bruno.crestani@aphp.fr)

Gérard Zalcman (gerard.zalcman@aphp.fr)

Valérie Gounant (valerie.gounant@aphp.fr)

Version: 1 Date: 26 Oct 2018

Author’s response to reviews:

Dear Editor,

We would like to thank both reviewers for the time they have taken to examine our manuscript. In accordance with the reviewers' comments, please find enclosed the revised text of the manuscript. Our point by point answers to the questions raised by the reviewers are provided below, written in italics.

Reviewer #1: The author reported a case of NSCLC in a patient previously diagnosed of lymphangioleiomyomatosis (LAM). The case report is relevant due to the lack of literature of immune checkpoint inhibitor in patients with interstitial and whether it is safety in this subgroup of patients. However, there are a few things I would like to consider.
We thank Reviewer #1 for acknowledging the originality of our case report and for addressing certain suggestions in an effort to improve our report. Please find below our responses.

1. I would strongly recommend the text to be properly reviewed by an English speaking person.

   We are surprised by this statement, given that the entire document (both initial draft and revised one), along with our responses to the Reviewers, were thoroughly reviewed by an English-native professional, working at Cremer Consulting SARL, a medical communication agency specializing in Medical Editing, with its contribution acknowledged at the end of the manuscript. However, we have taken great care of Reviewer #1’s comment and thus carefully double-checked the new draft with an English-native professional. We sincerely hope the revised manuscript will be satisfying on this point.

2. Bibliography should follow the Vancouver style. E.g. when more than 6 authors should be state as 3 authors by et al. and some reference are incomplete.

   The bibliography has been amended according these Vancouver style recommendations.

3. In my opinion, the conclusion should focus more on the safety profile of nivolumab in this patient with previous history of LAM and which other evidence is published regarding checkpoint inhibitors and patients with interstitial lung disease. The authors suggest quite strongly that checkpoint inhibitors might have a role in LAM treatment. As far as I am concerned, there is no clinical based evidence that supports this. It should be clear which type of evidence it has.

   The conclusion has been modified accordingly, on line 198.

   “The use of immune checkpoint inhibitors for treating NSCLC in this patient has proven safe without any serious adverse event or LAM flare-up, along with a good tumor response. Combining nivolumab with sirolimus was well tolerated, without impacting nivolumab efficacy in this case. However, if such a therapeutic choice is made in LAM patients, close patient follow-up is clearly required in order to ensure the absence of LAM flare-up or toxicity upon combination therapy.”

   I would further write below some specific comments that need to be clarified:

   Page 5 Line 99: Add the dose and schedule for sirolimus treatment. Is the dose equivalent to the ones we used with other mTOR inhibitors for renal cancer?
The daily dose for sirolimus was 2mg, which has been further specified on line 99 of the revised manuscript:

"(2mg once daily, whereas the daily dose for treating renal cancer patients is 10mg daily)."

Page 5 Line 100: Figure 1A instead of 1 ???????

Many thanks indeed for this accurate remark; the numbering has now been corrected on Line 109.

Page 5 Line 110: You reported a mutation on BRAF. Did you perform EGFR or ALK testing? PDL1? If not, why you have tested BRAF instead?

Many thanks, once more, for the remark; we have now included the following paragraph into the manuscript’s revised form, on line 114:

"EGFR and ALK testing proved negative. Additional molecular analyses revealed only a potentially oncogenic B-RAF mutation (c1406G>T; p.Gly469Val; COSM459) in exon 11. No c-met skip exon 14, PIK3CA, KRAS, or HER2 mutations were observed. PD-L1 immunohistochemistry testing was negative."

Page 5 Line 113: Did you perform a re-biopsy at relapse?

In answer to this question, we have now specified in the revised manuscript form, on line 119:

“Due to high evidence of relapse on imaging, another tumor biopsy was not performed at that time.”

Page 5 Line 113: Again, did you test PDL1 before or after the start of nivolumab treatment?

We would like to thank Reviewer #1 for this question. Accordingly, we have now specified twice in the revised manuscript form, on lines 114 and 127:

“PD-L1 immunohistochemistry testing was negative” (Line 114) in 2015 and was not repeated. “PDL1 staining was negative at diagnosis and not tested again at relapse.” (Line 127)
Page 6 Line 124: Figure 2 should be 1B

This is something we have now corrected in the revised manuscript form, on Line 133.

Page 6 Line 124: "Given that the pneumothorax occurred speedily after nivolumab infusion, nivolumab was not deemed responsible and this drug was thus resumed it in January 2016".

Comment: This is a quite strong statement. I do not the early onset of pneumothorax after nivolumab is a justification to not relate this complication as toxicity of nivolumab. I agree it is more likely to be due to the LAM. It is described that patients with LAM have higher incidence of pneumothorac and indeed the patient has a previous history of pneumothorax

Our thanks go to Reviewer #1 for this accurate comment. Perfectly in line with your concern, we have now amended the sentence in the revised manuscript form as follows, on Line 133:

“Given that the pneumothorax occurred very shortly after nivolumab infusion, we hypothesized that such complication would have been more likely caused by LAM, rather than being directly related to nivolumab. Consequently, we resumed nivolumab therapy in January 2016, with no further recurrence of this adverse event.”

Page 6 line 126: while gradually resuming work - I think the expression is "gradually returning to work" (Check with English speaking person, please).

Again, such wording was reviewed by a native English-speaking professional from Cremer Consulting SARL.

Both phrases are correct. In line with Reviewer #1’s remark, we have now changed the phrasing into "gradually returning to work".

Page 6 Line 128: "Treatment safety has so far been good, except for grade II hypothyroidism."

English correction: Treatment was well tolerated with no major safety issues. Patient developed grade II hypothyroidism (I guess treated with hormone replacement). Again, check the text with English speaking person.
Hypothyroidism has been reported to be a biomarker for efficacy. You might want to address or comment this in your discussion.

“Treatment was well tolerated with no major safety issues. The patient developed Grade II hypothyroidism treated with hormone replacement therapy,” as specified on Line 139.

Page 6 Line 128: "Lung function tests and symptoms worsened".

Clarify: When? Was it slowly progressive? Which clinical symptoms? Please describe a bit more and give data and parameters that are objective.

Owing to Reviewer #1’s remark, we have now clarified this sentence in the revised manuscript form as follows, on Line 140:

"Lung function tests and symptoms worsened progressively from June 2013 to May 2017 (Decline in CVF from 3700mL in June 2013 to 2250mL in May 2017, the decline being progressive)."

Page 6 Line 120-130: "Based on CT follow-up, this worsening was neither related to infection nor visible nivolumab-associated pneumonitis."

We have now specified on Line 143:

“This worsening was not accounted for by infection, tumor progression, or visible nivolumab-associated pneumonitis upon CT-scan follow-up. The patient's deterioration was, therefore, attributed to LAM. While we observed a decline in lung function tests, there was no accelerated decline of lung function tests during nivolumab treatment, nor was there any argument for a LAM exacerbation..”

Clarify: Could it be a worsening of the interstitial disease (LAM) due to the nivolumab? Was any fibrobronchoscopy done? Could you provide images of the worsening ILD? Would be useful to have a picture that shows lung parenchima with LAM lesions evolution before, during nivolumab treatment and after sirolimus was reintroduced. It is relevant to see the different evolution of the cancer (Fig 1) and LAM (potentially new fig 2).
The bronchoalveolar lavage performed at that time revealed low cellularity with predominant macrophage cells.

We have meanwhile added a picture as Fig. 2 showing CT with LAM lesions before nivolumab treatment, during nivolumab treatment, and after combining nivolumab and sirolimus.

Page 6 Line 135: "LAM is a rare cause of diffuse parenchymal lung disease according to the interstitial lung disease classification [11], which has been a key exclusion criterion in original immune checkpoint inhibitor studies in NSCLC"

Clarify: Confusing sentence- It is redundant.

Thanks for this comment. We have amended this sentence as follows, on Line 156:

“LAM is a rare cause of diffuse parenchymal lung disease [11]. Interstitial lung diseases have been a key exclusion criterion in original immune checkpoint inhibitor studies in NSCLC. »

Page 6 Line 139: "This common pathogenesis also constituted the rationale for using immune checkpoint inhibition in this indication, despite the lack of published data on this indication in the literature".

Comment: Too strong! Is there any preclinical data that supports this statement at least?

Many thanks to Reviewer #1 for this comment. We have now stated:

"According to Maisel et al. [15], PD-L1 is up-regulated in human lung tissue with LAM and in a murine model of LAM. This murine model shows hyperexpression of PD-L1 in stromal cells, with PD-1 also highly expressed by activated T-cells. In this model, in vivo treatment with anti-PD1 antibody improved mouse survival."

and provided the reference of a recent article, and that of the accompanying editorial:


AJRCM in press: “Could immunotherapy sink its teeth into LAM?” by Pietrobon A, Delaney SP, and Stanford WL.
According to Klarquist [13] and Carbone [14], LAM cells bear antigenic similarities with melanoma cells, such as sharing several common immune markers. To illustrate, some LAM cells can express gp100 and other melanoma antigens (MART-1) that tend to be recognized by T-cells. Thus, the authors hypothesized that immunotherapy successfully developed against melanoma could constitute a reasonable treatment approach for LAM, despite interstitial lung disease commonly being the disease presentation mode.

Comment: Check with English speaking person, please. I guess authors thought that "theoretically" LAM could response to nivolumab but I do not think there is enough evidence for this statement. Authors should soften this association. Indeed, the patient did not respond to it. Last sentence is written a bit confusing.

English wording was thoroughly reviewed by a native-English-speaking professional and deemed to be correct.

LAM is a rare cause of diffuse parenchymal lung disease according to the interstitial lung disease classification [11], which has been a key exclusion criterion in original immune checkpoint inhibitor studies in NSCLC.

Again check text with English speaking person.

English wording was thoroughly reviewed by a native English-speaking professional and deemed to be correct.

This common pathogenesis also constituted the rationale for using immune checkpoint inhibition in this indication, despite the lack of published data on this indication in the literature. We weighed up the risks and benefits before using immunotherapy, and then proposed this treatment strategy to the patient; in the end, our decision proved to be congruent with the recent expert review by Postow et al. [12].

Comment: It feels like the authors considered nivolumab a possible treatment option for LAM. Again I do not think there is enough evidence. When referring to Postow et al. paper it looks like you are justifying the use of nivolumab for LAM efficacy instead of justifying safety issues.
Many thanks indeed for this comment. In our case, nivolumab was clearly indicated for lung cancer treatment, but not for LAM management. We have now clarified this issue in the revised manuscript form as follows, on Line 161:

“We had weighed up the risks and benefits before using immunotherapy for lung cancer treatment, prior to proposing this treatment strategy to the patient”.

Page 7 Line 161 "To date, the tumor response is still responding"

Redundant… Please, correct the text with English speaking person.

English wording was reviewed by a native English-speaking professional, and the term “response” was omitted.

Page 7 Line 167 "Although sporadic LAM is a rare condition, it can be associated with NSCLC"

Comment: Quite strong association! Are any association between LAM an NSCLC? Have patients with LAM a higher risk of developing NSCLC?

We entirely agree with this comment. We have now amended the sentence as follows, on Line 193:

“Since LAM is a very rare condition, its association with lung cancer has only been reported in very few cases.”

Accordingly, there are no accurate data to support that LAM patients would exhibit a higher risk of developing NSCLC.

Figure 1: Use the common names of the drugs and not the commercial ones to be consistent with the text.

In reply to this remark, we have now corrected this issue in the revised manuscript form.

Finally, the most striking point for me is the safety of nivolumab in a patient with LAM and concomitant immunosuppressive agent and the fact that concomitant sirolimus does not seem to have deemed the efficacy of nivolumab in this patient. There is still controversy of immunosuppressive agents concomitant with immunotherapy. Authors might want to address it.

Many thanks for this comment with which we fully agree.
 Accordingly, we have amended the conclusion as follows, on Line 200:

“The use of immune checkpoint inhibitors for treating NSCLC in this patient proved safe without any serious adverse event or LAM flare up, along with a good tumor response. Combining nivolumab and sirolimus was well tolerated, without impacting efficacy nivolumab efficacy for this patient. However, if such a therapeutic choice is made in LAM patients, a close follow-up is clearly required in order to ensure the absence of LAM flare up or any toxicity.”

Reviewer #2: This case report describes the case of a young female smoker with a history of LAM resistant to oestrogen therapy and on Sirolimus before developing a synchronous lung cancer. There is a 2 year period of a stable, SUV high, apical lung mass where the patient was off Sirolimus treatment, before obtaining a diagnosis of lung adenocarcinoma. This was treated with stereotactic radiotherapy, then two lines of cytotoxic chemotherapy on progression and eventually Nivolumab, to which an excellent response was finally obtained. 18 months after starting Nivolumab, her LAM symptoms progressed and concurrent Sirolimus treatment was given with apparent clinical response.

In spite of the fact that the "highly immunogenic" (line 153) LAM had been stable while untreated for five years until Nivolumab therapy started, the authors conclude that "this case highlights the safe and effective use of nivolumab for managing metastatic lung adenocarcinoma that occurred in a patient with sporadic LAM".

This was a successful case that meets the high need to contextualize lung immune therapy in real-life practice, especially when confronted with rare co-morbidities, but fails to do it in a way that describes the many uncertainties inherent to a case report. Instead, it transmits a sense of causality, for example when hypothesising about the pathophysiological similarities of LAM with melanoma, and chooses to omit the possibility that Nivolumab could have triggered a LAM exacerbation.

We would like to sincerely thank Reviewer #2 for such favorable comments and accurate suggestions for enabling us to clarify our case. Please find below our responses.

Line 102 - the SUVmax of the apical mass is described could only be obtained through a PETCT, and not with a CT as stated
We perfectly agree with this comment and are sorry for the confusion. We have thus amended this sentence, in the revised manuscript version, at Line 104:

"(SUVmax=4.8)"

Line 107 – please state that Sirolimus was not re-started

We have now clarified this point in the revised manuscript version, at Line 149:

"In May 2017, sirolimus, stopped since 2013,..."

Line 106 - Biopsy of the apical mass revealed fibroelastosic scarring in 2013. It is not clear the reason why a second biopsy on a high SUV mass in a young smoker was not performed. There is no indication of how often imaging was repeated before radiological growth in 2015, and it is not clear if it grew slowly or it was a sudden pattern of growth two years later (if it had grown earlier, it would have met the criteria for stereotactic radiotherapy before it was administered).

Many thanks again for this accurate comment. The decision to monitor CT without immediately repeating transthoracic biopsy was made, owing to the very small lesion size in a patient with functional impairment. For this reason, we thought that performing such a biopsy would have been too risky.

We have now explained this decision in the revised manuscript version, at Line 108:

"The decision to monitor CT without immediately repeating transthoracic biopsy was was made, owing to the very small lesion size in a patient with functional impairment. For this reason, we thought that performing such a biopsy would have been too risky (Figure 1)."

Line 121- Persistence of pneumothorax at 48 hours justifies surgical pleurodesis, not a 2-month hospitalization.

Reviewer #2 is entirely correct, and we have now clarified this in the revised manuscript form, at Line 129.

"The persistence of pneumothorax at 48 hours justified surgical pleurodesis, along with a 2-month hospitalization in the thoracic surgery department, because of prolonged air leak. "
Line 130- Please state the patient's deterioration was attributed to LAM

Thanks for this comment. We have now explain in more details, at Line 144:

“This worsening was not accounted for by infection, tumor progression, or visible nivolumab-associated pneumonitis upon CT-scan follow-up. The patient's deterioration was, therefore, attributed to LAM. While we observed a decline in lung function tests, there was no accelerated decline of lung function tests during nivolumab treatment, nor was there any argument for a LAM exacerbation.”

Line 132- How often was the patient followed up and what investigations were done? Did the patient have regular lung function tests? Was there any evidence on toxicity of Nivolumab and Sirolimus combination? How was the ethical challenge of lack of evidence confronted?

Many thanks indeed for such essential questions. We have now further specified, at Line 150:

“It was a collective decision that was shared with the patient, because of the ethical challenge raised due to the lack of scientifically-sound evidence. CT-scans were performed every 2 to 3 months, and lung function tests every 6 months.”

Line 141 - The phrasing suggests risks and benefits were discussed amongst the medical team and not with the patient

Reviewer #2 is entirely right as for the phrasing. It must, therefore, be stressed that we explained all our therapeutic proposals to the patient, who expressed her accordance with the therapeutical strategy proposed, after having taken the time (several days) to think everything over while discussing the issue with her family and general practitioner.

We have now stated in the revised manuscript form, lat Line 150: "It was a collective decision that was shared with the patient”.

Line 166 - The conclusion should state the possibility to administer Nivolumab in patients with LAM, the need for close LAM follow up while on Nivolumab treatment and the possibility of concomitant treatment of both afflictions.
Many thanks, once more, for this suggestion with which we perfectly agree. We have now stated, in the revised manuscript version, at Line 195:

"The use of immune checkpoint inhibitors for treating NSCLC in this patient was proven safe, without any serious adverse event or LAM flare up, along with a good tumor response. Combining nivolumab and sirolimus was well tolerated, without impacting nivolumab efficacy in this patient. If such a therapeutic choice is made in LAM patients, a close follow up is clearly required in order to ensure the absence of LAM flare up or any other toxicity."

Valérie Gounant