Author’s response to reviews

Title: Endoscopic Central Airway Recanalization To Enable First Line Pembrolizumab Treatment In A PD-L1 Strongly Positive Non-Small Cell Lung Cancer: A Case Report

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Author’s response to reviews:

Reviewer #1:

The authors presented the case of lung cancer patient who underwent successful endoscopic airway recanalization followed by pembrolizumab treatment. After recanalization by rigid bronchoscopy and laser, SEMS was placed in the right main bronchus. The patient was able to receive pembrolizumab treatment.

The manuscript is well written and concise. However, this manuscript is unlikely to be of interest to readers journal of cardiothoracic surgery. In my view, this manuscript should be submitted to journals focusing on lung cancer.

Reply:

The treatment of the present case was particularly challenging due to the advanced stage of disease, and the poor clinical conditions of the patient characterized by recurrent pulmonary infections, and severe respiratory distress due to central airway obstruction. Thus, we planned a new multimodal approach, not previously reported, which involved endoscopic central airway recanalization followed by ICI treatment with pembrolizumab. Despite ICI treatment is a medical treatment, however we believe that endoscopic recanalization of central airway may be
a procedure of the interest for thoracic surgeons. For example, in our department endoscopic recanali-
zation is performed by thoracic surgeons and remained the treatment of choice in patients with malig-
nant central airway obstruction when surgical resection is unfeasible. In addition, from a technical point of view in patients with malignant external compression that caused distortion and obstruction of central airway, as the present, we recommended to use a Self-Expanded Metallic Stent (SEMS) rather than silicone stent in order to maintain airway patency.

Changes: lines 113-115 page 5

Reviewer #2

The manuscript by Fiorelli A. et al. reports on a case of NSCLC in which bronchial stenting allowed the use of anti-PD-1 immunotherapy. The study highlights the wave of enthusiasm brought about the success of immune checkpoint inhibitors (ICI) and the multimodal approach necessary to treat lung cancer.

Below are my criticisms/suggestions:

-No CT or clinical documentation of Pembrolizumab efficacy is reported partly limiting the overall significance of the study.

Reply

We included a new figure (named as Figure 4 in the main text) where Chest CT scan performed before (Part A), and 16 weeks after immunotherapy (Part B) showed a reduction in tumor size (white arrow) without sign of lung infection.

Changes: lines 92-94 page 4; and lines 224-226 page 10

-Please provide information on the time interval from resolution of pneumonia or at least stent placement to initiation of Pembrolizumab, as well as drug doses and schedules.

Reply

In the following two weeks, patient did not show clinical signs of pneumonia and presented an improvement of performance status (ECOG 1); chest CT scan (Figure 2/C) confirmed the complete resolution of atelectasis and pneumonia. Therefore, he was eligible to receive Pembrolizumab 200 mg e.v. every 21 day.

Changes: lines 89-92 page 4;

-Although it is well known that the incidence of ICI-related pneumonitis is less frequent with Pembrolizumab than with Nivolumab, Authors should acknowledge this risk when making their
therapeutic decision in a patient with recurrent infective episodes. This issue should be more deeply discussed or described.

Reply

As pembrolizumab therapy is associated with a risk of immune-mediated pneumonitis, the endoscopic recanalization of central airway was planned before starting ICI treatment in order to (i) favor the resolution of atelectasis, (ii) improve dyspnoea and general clinical status of the patient, and (iii) minimize the risk for immune-mediated pneumonitis. Following, the rationale of ICI treatment with Pembrolizumab was to prevent systemic and local disease progression.

The ICI treatment was started two weeks after the endoscopic recanalization, when a complete resolution of atelectasis and pneumonia was achieved as confirmed by improvement of patient’s clinical condition, and by CT scan findings.

Changes: lines 106-110 and lines 115-117 page 4-5

Are the Authors aware of any similar studies on patients with recurrent pneumonia in which endoscopic recanalization was aimed at combining chemotherapy?

Reply

We planned a new multimodal approach, not previously reported, which involved endoscopic central airway recanalization followed by ICI treatment with pembrolizumab. Our strategy was in line with Jeon et al. [3] and of Stratakos et al. [4] who showed that patients undergoing adjuvant chemotherapy and/or radiotherapy after endoscopic airway recanalization exhibited a longer survival than those who received recanalization alone.

Changes: lines 100-105 page 4

In my opinion the order of figures should be changed according to the clinical presentation, indicating that recurrent pneumonia occurred before stent application. Thus, figure 2 should be figure 1 and viceversa.

Reply

We have done it.

Changes: line 73 page 3; line 75,76,91 page 3; lines 209-215 page 10.

I believe that "combined approach" is more appropriate than "multidisciplinary".

Reply

We have changed it.
Reviewer #3

The authors present an interesting, novel, and multidisciplinary approach to the treatment of a patient with metastatic non-small cell lung cancer involving endoscopic recanalization of a stenotic central airway followed by immunotherapy. While the case report contains an important clinical message and will certainly be of interest to the readers of the Journal of Cardiothoracic Surgery, I'd like the authors to clarify and address few areas of concern to me that warrant inclusion of additional details.

First off, while pembrolizumab therapy is associated with a risk of immune-mediated pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies, there is no absolute or relative contraindication to the initiation of pembrolizumab therapy as cited by the authors. Hence, the statement "the presence of lung infection is a contraindication to treatment" is misleading and warrants revision. It may be better to state that endoscopic recanalization and treatment of central airway obstruction was achieved prior to initiation of immunotherapy so as to minimize the risk for immune-mediated pneumonitis in a patient with a history of recurrent episodes of pneumonia.

Reply

We have done it as following: As pembrolizumab therapy is associated with a risk of immune-mediated pneumonitis, the endoscopic recanalization of central airway was planned before starting ICI treatment in order to (i) favour the resolution of atelectasis, (ii) improve dyspnoea and general clinical status of the patient, and (iii) minimize the risk for immune-mediated pneumonitis. Following, the rationale of ICI treatment with Pembrolizumab was to prevent systemic and local disease progression; FDA and EMA have approved Pembrolizumab as first line treatment in patients with advanced NSCLC and PD-L1 strong expression, as the present, based on the results of KEYNOTE-024 study [5].

Changes: line 106-112 page 4-5

While it is significant to note that endoscopic recanalization helped resolve atelectasis and improve dyspnea and general clinical status of the patient, I'd like the authors to offer additional details on how long they waited since the recanalization procedure before initiation of immunotherapy. Authors report that a post-procedure CT chest after 1 week showed resolution of atelectasis and pneumonia and hence the patient was deemed eligible for immunotherapy and if 1 week is indeed the time the team waited before initiation of therapy, a statement like
"endoscopic recanalization of right main bronchus resolved recurrent lung infections" is again misleading and little far fetched. If the authors in fact waited longer than a week (say if the patient was observed for several weeks without any recurrent episode of pulmonary infection) it is important that they share information on time period between recanalization and initiation of immunotherapy and if patient remained free of pulmonary infections during this time period.

Reply

In the following two weeks, patient did not show clinical signs of pneumonia and presented an improvement of performance status (ECOG 1); chest CT scan (Figure 2/C) confirmed the complete resolution of atelectasis and pneumonia. Therefore, he was eligible to receive Pembrolizumab 200 mg e.v. every 21 day.

Changes: lines 89-92 page 4

The authors claim in the abstract section that 'at nine month follow-up, the patient was alive with stable disease'', but in actual description of the case, they say "after four months, the patient is still alive without disease progression". It is unclear if the actual follow-up period is 4 months or 9 months.

Reply

You are right, we have corrected it in the abstract and in the main text as following:

At 16 weeks follow-up, the patient was still alive and no further lung infections were recorded; chest CT scan (Figure 4) showed a local reduction of tumor size without sign of lung infection.

Changes: lines 92-94 page 4

This will need to be clarified. Also, though not a major concern, the authors may want to consider revising few of the terms to keep up with the more common terminologies used by the larger audience in the field of cardiothoracic surgery, such as revising "non-small cell lung cancer" to "non-small cell lung cancer", "immune therapy" to "immunotherapy", "immune check-points inhibitors" to "immune checkpoint inhibitors". Finally, though not a major deal breaker, I'd like the authors to proofread for spacing and grammar before their final submission - for example, in the main title a space is needed between "pembrolizumab" and "treatment". Despite the above-mentioned areas of concern to me that warrant further revision and clarification, I find the case report to be novel and interesting in its approach to combining endoscopic recanalization with immunotherapy for patients with metastatic non-small cell lung cancer suffering from central airway obstruction and atelectasis-related pulmonary infections. In summary, this is an interesting case report that needs further revision before it can be accepted for publication in the Journal of Cardiothoracic Surgery

Reply
We apologize for the mistakes. We have corrected it. The paper was fully revised in order to improve the quality of language.

Changes: line 2, line 37, line 57 page 1, 2, 3