Peer Review File
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Reviewer A

Fantastic research, adding to the real-world data in a large patient population on the use of durvalumab in locally advanced, unresectable NSCLC. Great use of statistics, Kaplan Meier curves for PFS and OS. Minor revisions and would appreciate elaboration on details of some findings if additional information is available.
Reply: Several changes and elaborations have been made as noted in the below responses to the other reviewers

Reviewer B

The authors showed that pneumonitis was not associated with OS and PFS in patients treated with durvalumab. In addition, the authors showed that obesity is risk factor for the pneumonitis. However, there are several concerns in this study. I judged this study is not appropriate for publication in this article.

Major point

1. Performance status, an important factor, is not included in the patient background.

   Reply 1: Performance status was not abstracted as it was not readily available in provider notes, however Charlson comorbidity score was included in order to account for co-morbid conditions.
   Changes in the text: none, however see table 4 in which Charlson comorbidity score is included

2. No information on parameters such as V20, an important risk factor for radiation pneumonitis, is presented.

Reply 2: V20 along with several other radiation parameters including, single fraction dose, radiation technique, GTV, PTV, dose to OARs, MLD, V40, V60; Heart: MHD, V5, V30 where not routinely available in the chart for abstraction. We did collect the information that was available being total radiation dose which is reported in table 1. While we agree this information is important it was not available for abstraction.
Changes to text: none

3. The authors show that obestisy is a risk factor for pneumonia. However, a multivariate logistic analysis including already reported risk factors for pneumonia, such as V20, is needed.

Reply 3: As stated above, while we acknowledge that lack of V20 information is a limitation of this study, the intention was to focus more on clinical risk factors,

additionally V20 was not routinely available in the chart for abstraction.
4. The authors need to indicate why Obestisy was divided into more than 30 and less than 30.

Reply 4: BMI of 30 or higher is classically considered obese, to address this further we have added to table 1 a breakdown of the number of patients who were BMI <30 and greater than or equal to 30. We additionally added the median BMI to table 1. These patient numbers were appropriate for this subgroup analysis.
Changes to text: additions as noted above to table 1

5. Whether pneumonia affects OS has already been examined as cited by the authors and is not novel.

Reply 5: While the relationship between pneumonitis and OS has been explored by other authors, there is no consensus as some have found there to be an effect and some have not as noted in paragraph 4 of the introduction. Therefore, adding real world data with a large sample size is useful to help come to a consensus in the literature
Changes in text: none

Desilets A, Blanc-Durand F, Lau S et al. Durvalumab therapy following chemoradiation compared with a historical cohort treated with chemoradiation alone in patients with stage III non-small cell lung cancer: A real-world multicentre study. Eur J Cancer. 2021 Jan;142:83-91. doi: 10.1016/j.ejca.2020.10.008

Reviewer C

The paper showed the incidence of clinically significant pneumonitis is higher than noted in the PACIFIC trial. Still, this high rate of pneumonitis does not impact OS or PFS. This is an exciting finding in a real-world setting. In addition, the authors found obesity was found to be a significant predictor of pneumonitis. I have several comments below.

[Major]

1. What's the definition of pneumonitis? I think the most pneumonitis might be radiation pneumonitis, and durvalumab-induced interstitial pneumonitis could occur during 1 year of durvalumab treatment. The pathophysiology of the two types of pneumonitis are different, so it would be better to describe the two types of pneumonitis respectively.

   Reply 1: We used the CTCAE 4.0 criteria to define and grade pneumonitis (as published by NCI/CTEP on ctep.cancer.gov). It is true that it is not possible to differentiate for certain if symptoms and radiographic findings are due to radiation pneumonitis vs immune related pneumonitis, however in the clinical setting these would be approached the same as they cause similar radiographic findings and symptoms, and either one could cause interruption of therapy. The PACIFIC trial

that led to the approval of durvalumab in this setting was also not able to differentiate between the two. We therefore did not find it clinically relevant to differentiate between the two, and there is no agreed upon way to do so.
Changes in the text: none

2. The authors defined significant pneumonitis as grade 2 or higher. But we usually define significant level as grade 3 or higher. What's the rationale for the definition of significance?
   Reply 2: As noted in Reply 1, grade 2 in CTCAE criteria is when pneumonitis becomes clinically relevant as it is defined as symptomatic, requiring medical intervention, and limiting instrumental ADLs, given our focus on clinically relevant data, we chose grade 2 as significant
   Changes in the text: none
3. Several recently published studies suggested radiation-related parameters (ex, V10, mean lung dose) and peripheral blood cell counts are important risk factors for radiation pneumonitis requiring steroid treatment [J Thorac Oncol 2023 Apr 19;S1556-0864(23)00495-1. doi: 10.1016/j.jtho.2023.04.008]. This study also seems to need an analysis including at least several parameters related to radiation therapy.
   Reply 3: As stated in Reviewer B; Reply 2, we did not have access to radiation-related parameters to include in our study. As our study pre-dated peripheral blood cell counts being investigated as a risk factor, we did not abstract that data
   Changes in text: none

[Minor]

1. Total number of enrolled patients should be added to the results of the abstract.
   Reply 1: this change were made
   Changes in text: See page 2, results section
2. The introduction part was relatively too long and less informative. It would be better to summarize only the rationale of this study.

Reply 2: The following changes have been made
Changes in text: Introduction has been shortened, paragraph 1 and 2 have been combined and shortened, see page 3 and 4

3. What's the median value of BMI in this study? I want to know if BMI of 30 is a reasonable cut-off value.
Reply 3: Median BMI is 26
Changes in text: This has been added to Table 1

4. How could CCRT follow by durvalumab in stages I and II (the total number was 22 cases)?
Reply 4: This study was carried out in the VA system. While technically off label from a strict FDA indication standpoint, some providers elected to deliver durvalumab in this setting. We were not able to judge the rationale at the time this decision was

made, however given they received CRT followed by durvalumab we felt it reasonable to include these patients
Changes in text: none

5. It would be better if the median survival time and p-value were shown in the figures.
Reply 5: These changes have been made

6. There was no information of age and sex in Table 1.
Reply 6: These have been added to Table 1

Reviewer D

In this article the authors present RWD on the incidence of pneumonitis in a retrospective cohort of 284 patients. The main message seems to be that the percentage of pneumonitis outside prospective randomized control trials is higher, i.e. in comparison with the PACIFIC trial. The topic is of interest to the clinical and scientific community working in the field of thoracic oncology. However, the paper has a few severe flaws.

Major:

1. Radiation data are entirely missing. Please add them to the methods and results sections (also in the tables) and discuss these data. Specifically add the following data: single fraction dose, total dose, radiation technique, GTV, PTV, dose to OARs (Lung: V20, MLD; Esophagus: MED, V40, V60; Heart: MHD, V5, V30). This is extremely important since radiation can also cause pneumonitis and may have a supra-additive impact together with immunotherapy such as durvalumab.

   Reply 1: please see reply 1 in Reviewer B section
   Changes in text: none
2. Discussion: In this section, the authors should discuss their results in correlation with published chemo-radiation literature (e.g. Furuse 1999, Fournel 2005, Curran RTOG 9410 JNCI 2011, Bradley RTOG 0617 Lancet 2015) and immunotherapy literature (e.g. Suresh K. JTO 2018, Nishino JAMA Oncol 2016, Wass Cancers 2022). The current version of the discussion is largely a repetitive summary of the results.

   Changes to text: additions have been made to paragraph 1 and 2 of the discussion section.

Minor:
Figures
• please add the log-rank p-values to the figures
Reply: p-values have been added to the figures
• it should be Kaplan-Meier instead of Meir
Changes in text: This was corrected in Figure 1 and Figure 2 legends

Reviewer E

The authors, Dr. Akkad et al., have made study evaluating the incidence of pneumonitis concerning Dulvalumab administration following concurrent CRT and the influence for post-treatment survival. The real-world data of the incidence of pneumonitis concerning Dulvalumab administration are important and this study may have some value, however, I consider their study is insufficient to be published from academic journal and I recommend the author to make major revision of this manuscript.
First, their study included patients whose c-stage were stage I or unknown, that consisted of approximately 13% of patients' cohort. This study concluded that the incidence of pneumonitis concerning Dulvalumab was not affect post-treatment survival, however, the staging factor is well known as the strong factor affecting the post-treatment survival and the lack of this data is not accepted if the study discusses the survival outcome. And more, c-stage I disease may not be candidate for CRT followed by Dulvalumab in clinical practice because this disease can be cured by only local therapy such as SBRT. Thus, I consider the authors should conduct this study only among patients with stage II-III disease and patients whose staging were stage I and/or unknown are excluded.
Reply 1: The intent for inclusion was to include patients receiving CRT followed by durvalumab, therefore if the provider elected to give it we thought it would still be useful information to include. This is reflective of practice in a real world setting. Though stage has an effect on survival, we controlled for it in our Cox model.
Changes in text: none

Second, their definition of 'overall survival' and 'progression free survival' in this study were vague, especially when the periods started. Were the start point of these periods the first administration of concurrent CRT, or the first administration of Dulvalumab, or the last administration of Dulvalumab, or the time when concurrent CRT followed Dulvalumab just finished? Please clarify this issue.
Reply 2: The time period used was date of first durvalumab though 9/14/2021
Changes in text: This was clarified in the results section, see Methods section, paragraph 3

Third, Cox proportional hazards analysis is the method evaluating the difference of hazard between factors in whole period, and not for the evaluation of point estimation such as the 2-year OS. The description concerning the statistical analyses is inadequate, and I recommend the author to ask statisticians to review their study.
Reply 3: Cox proportional hazards models are a form of survival analysis that that are routinely used to assess the association between the survival time and one or more predictor variables. We agree these models produce hazard ratios, and are more informative as to the risk of an event over a time period. They are not used to produce point-estimates. While we feel the paper is appropriately written in this regard, we have adjusted some wording to clarify this concern. It should be noted that Kaplan-

Meier methods were also employed for survival analysis and are more appropriate for point-estimation.
Changes in text: The following changes have been adopted to clarify this issue:

- In the abstract we have added a sentence outlining the role of cox proportional hazards models in the publication.
- On page 7 we have added in "risk of death" when referring to Cox analysis for overall survival at 2 years.
- In the Results section on page 9, we have changed "predictors of OS" to "risk factors for death.

Fourth, according to their manuscript, approximately 18% of patients had history of autoimmune disease, which are well known the risk factor of interstitial pneumonitis concerning the administration of immune-checkpoint inhibitor. However, their study evaluated the influence of this factors not as an independent risk factor but as one consistent of Romano Co-mobidity index. I consider this bundling is not adequate and I recommend the risk evaluation of history of autoimmune disease as independent factor.
Reply 4: Additional statistical evaluation for rheumatological disease as described by Romano did not show an association between rheumatologic disease and pneumonitis incidence, OR 4.04. While we would be happy to include this as a separate component, we are not sure it adds value to the reader.
Changes to text: none

In their manuscript, the term 'PD-L1' and 'PDL-1' were both used. The correct term is 'PD-L1', and please correct it.
Changes to text: This has been corrected throughout the manuscript
In some line in 'Results section', the number of patients was written in brackets. However, this style may confuse the readers because the regulation of this journal for citation is also presented as the number in brackets. Please revise this adequately such as '(132 cases)'.
Changes to text: This has been corrected in the results section

Reviewer F

This is an excellent study, that needs just few more things to be added to increase its value:
-There are few things to be taken into account regarding considering evidenced pneumonitis as solely a durvalumab-related pneumonitis. Late radiation pneumonitis might develop as well, with post-radiation fibrosis typically developing about 6 months later following radiotherapy, so it would be good to make a comment about this when we define post-radiotherapy "durvalumab-related pneumonitis".
Reply 1: There are no agreed upon guidelines to differentiate radiation induced pneumonitis and durvalumab pneumonitis, though in this clinical setting the outcome would be the same, interruption of durvalumab administration. Given this we did not differentiate between the two

Changes in text: A sentence has been added in the Limitations section to acknowledge this issue

-Also, few necessary data (if available) would be of great interest to include in this analysis that relate to evidenced radiation pneumonitis before introduction of durvalumab.

Reply 2: We defined asymptomatic pneumonitis as a new change in radiographic findings after completing CRT + durvalumab, therefore patients included in this study but nature did not have previous pneumonitis before the introduction of durvalumab

Changes in text: none

-Another necessary thing to be added in Discussion part is related to some known mechanism how obesity may influence the development of pneumonitis which has been recognized already in radiation pneumonitis. When a patient has obesity, their adipose tissue becomes dysfunctional, promoting the formation of an inflammatory environment, the excessive production of inflammatory adipocytokines, such as tumor necrosis factor-alpha and IL6, leads to a mild state of chronic inflammation. (Reference: Katsui K, Ogata T, Sugiyama S, et al. Visceral adipose mass and radiation pneumonitis after concurrent chemoradiotherapy in patients with non-small cell lung cancer. Cancer Diagn Progn. 2021;1(2):61-67. doi:10.21873/cdp.10009)

Reply 3: We are in agreement

Changes in text: this has been added to paragraph 2 of the discussion section