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Shicheng Guo <shg047@eng.ucsd.edu>

Thank you for the review of JTO-D-15-01083R1

1 message

Journal of Thoracic Oncology <em@editorialmanager.com> Mon, Jan 25, 2016 at 1:18 PM
Reply-To: Journal of Thoracic Oncology <mary.todd@iaslc.org>
To: Shicheng Guo <shg047@eng.ucsd.edu>

Journal of Thoracic Oncology

RE: JTO-D-15-01083R1, entitled Exhaled Breath Analysis for Monitoring Response to Treatment in Advanced Lung Cancer, by Dr Nir Peled

Dear Dr Guo,

The editors have made a decision on the above-referenced manuscript that you previously reviewed for JTO. The decision letter is included below. If you have any questions or comments please feel free to contact the journal office via email to Mary.Todd@iaslc.org.

Thank you for your time and efforts,

Mary Sharkey Todd, MFA
Managing Editor
Journal of Thoracic Oncology

To: ********
cc: ********
From: "Journal of Thoracic Oncology" mary.todd@iaslc.org
Subject: Editorial Decision for JTO-D-15-01083R1
CC: ********

Journal of Thoracic Oncology

Jan 25, 2016

RE: JTO-D-15-01083R1, entitled "Exhaled Breath Analysis for Monitoring Response to Treatment in Advanced Lung Cancer"

Dear ******** ********,

I am pleased to inform you that your paper has been found acceptable for publication pending minor revision. I anticipate that you will easily be able to answer the criticisms of the reviewers in a satisfactory manner. I will verify that this has been done upon receipt of the revised manuscript. Please find the comments of the reviewers listed below.

Please include the following materials when you submit your revision:

Completed ICMJE forms for each co-author.

An itemized, point-by-point response to the comments of the reviewers. (Label file "Response to Reviewers")

One version of the revised manuscript that includes continuous line and page numbers; these numbers should be used in the "Response to Reviewers" to indicate where specific changes have been made in response to the editorial feedback and reviews. This version should also include "highlighting" in the manuscript to highlight new material. This feature can be found on the formatting toolbar in Microsoft under highlight. (Label file "Highlighted Version")

Finally, please include a version of the manuscript without highlighting and line numbers. (Label file "Revised Version")

Color figures will be published online at no charge. Color figures will be published in print at the discretion of the Editor. The publisher will convert color figures to grayscale figures for print publication. Therefore, you should submit the color version of your figures as you would like it to appear online.

The revisions should be completed within four weeks to avoid being considered as a new submission.

To submit a revision, go to http://jto.edmgr.com/ and log in as an Author. You will see a menu item called "Submission Needing Revision." Please click on this item to obtain your submission record and begin the revision process.

Your username is: ********
Your password is: ********

With Kind Regards,

Dr. Giorgio Scagliotti
Associate Editor
Journal of Thoracic Oncology

Reviewer Comments:

Reviewer #3: I have reviewed this manuscript which provides the results of a study of exhaled breath analysis for monitoring response to treatment in advanced lung cancer, and have some concerns pertaining the analyses of these data. In total, 39 patients were studied, but the analyses of these data treat the repeated observations among these patients as independent, which is not appropriate. Furthermore, the authors state that RECIST criteria were used, but the version 1.0 or 1.1 should be made clear in the paper, and any models that would be run should also be adjusted for the effects of other known prognostic factors to see if the breath analysis remains an independent predictor of outcome.

I also note that the summary of RECIST provided on pages 5-6 is rather simplistic, as the RECIST criteria are much more detailed than this - were the responses of these patients confirmed by radiologist review? The paper notes that response was categorized from each CT relative to the previous scan - this would actually be incorrect if RECIST were followed because response is measured relative to measurements taken at baseline; progression is measured relative to nadir. It is unclear why it would have any clinical meaning to compare response relative to the prior scan. As such, for each person one would expect at most 2 measures: their best response overall, and the date of progression. If the authors were interested in more granular analysis over time, perhaps the actual tumor measurements should be modeled.

It is unclear how disease control is noted to mean "no worsening of disease." If in fact a tumor grew by 10%, then this would indicate disease worsening, but would not have met the threshold for disease progression.

The precise timing of breath sampling could be made clearer. For example, the paper states that samples were taken "close to the start" of treatment - how close? Within how many days? Similarly, repeat samples were taken prior to subsequent cycles - how soon before the next cycle administration, in days?

The authors conclude that this technology may allow "quicker recognition" than RECIST analysis, but I note that this study did not demonstrate that the timeframe to results was shorter.

I think it's unusual that only 11 patients experienced disease progression in this cohort. With adequate followup, I would have guessed that many more patients would have progressed.

I also note that use of the term "surrogate" is note really warranted here, as there are rigorous statistical criteria to demonstrate that one endpoint is a surrogate for another.

Reviewer #4: The present study by Dr. Agmon investigates the utility of exhaled breath analysis markers trying to take the place of RECIST based on Spiral CT. The author has answered comments from reviewer 1 and 2, but I still have following concerns:
1. As the former reviewer mentioned, sample size in present study was too small and therefore the reproducibility of the conclusion would be not solid, especially the sample were divided into NSCLC and SCLC. An independent dataset must be collected and the conclusion should be validated.
2. Research about exhaled breath in lung cancer has been published much in recent years, the innovativeness and the superiority of the study should be provided compared with previous studies in the discussion section.
3. The first sentence in Method section quoted [7, 71, and 87]. [7] is an article on Expert Rev. Mol. Diagn in 2011, but I can't find [71] and [87]

Reviewer #5: This is an interesting report on VOC and its use to monitor clinical outcome/correlation with RECIST.

The authors appear to be using RECIST 1.0 (Therasse et al. 2000), while modern studies, including the time frame that these samples between 2012-13 were collected use RECIST 1.1 criteria (Eisenhauer et al. 2009). It is unclear for the rationale for RECIST 1.0 and not applying RECIST 1.1 considering the time frame that this study was conducted and analysis being reported in 2015/16, particularly since the authors report central reading by an expert radiologist. If the radiologist is an author, should include the radiologist's initials (first, last) at the end of that sentence row 54, pg 5. Furthermore, more details on the type of CT ordered should be presented. This may actually impact the reporting of response, particularly if only CT chest was performed for all patients or if you have a mix of CT chest/abd or even CT chest, abd, pelvis. That could explain some of the discrepancies that authors discuss as interesting patterns in the hot plot in the Discussion section--pg 14 rows 28-57.

While the authors are reporting on a mix of stage 3 and 4 lung cancer patients, this reviewer and I believe readers would be curious to know, if any of the stage 4 lung cancer patients did not have presence of lung cancer in the lungs at the time of enrollment. Or if any patients categorized by response had discordance between lung primary and distant metastatic disease. In other words, does the VOC signature essentially report out response from the primary or could obvious extrathoracic PD or PR (e.g. in the liver, bone, brain, or adrenals) influence the VOC signature to be categorized as PD or PR. It would be critical for future adoption of VOC in lieu or supplement to imaging if VOC is independent of tumor location and more reflective of overall systemic tumor burden. Perhaps if there is not enough to glean from the data they have, in addition to making mention of this in the Discussion, the authors can point to any references for non-thoracic cancers and VOC that might support that VOC signature for tumor responsiveness is independent of tumor location.

Complete Revision Instructions:

PRELIMINARY STEPS:
1. Click on the "Submissions Needing Revision" link.
2. To view the previous decision letter and reviewer comments, please click the blue decision term listed under the View Decision menu.
2. If you would like to download the previous manuscript in order to make revisions, click on "Download Files" under the Action menu.

RESUBMISSION STEPS:
3. To BEGIN the RESUBMISSION: Click "Submit Revision" under the Action menu.

4. Proof each screen to ensure the information is still correct (the Title, Authors, etc), then click Next at the bottom of each page.
5. On the Attach Files screen, be sure to click beside each previous submission item that you would like included in the following submission. BE SURE TO CHOOSE TO CARRY OVER YOUR COPYRIGHT FORM.
6. Now, as you did previously, simply upload the parts of your manuscript. When you are finished, please click Next.
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9. Wait for the PDF to Build. When it has been built, you will see the link "View Submission" in the Action menu. Click "View Submission," and open the manuscript in order to proof your work.
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11. If you find no problems with the manuscript, please click "Approve Submission" from the Action menu. Your re-submission is now complete!