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Reviewer A

This is an overall interesting, important study currently accruing patients with stage III non-small cell lung cancer who have been treated with standard concurrent chemoradiation and evaluating a hypofractionated boost at one of two dose levels (6.5 Gy-10 Gy x 2) between cycles 2 and 3 of durvalumab. The authors hypothesize that this hypofractionated boost regimen may improve immune-stimulation and disease control compared to the PACIFIC regimen. It is powered this study to show a 20% improvement in 12-month PFS to 75.9%.

Comments:

1) While we do not have a great understanding of in-field and out-of-field progression with the addition of durvalumab after chemoradiation from the PACIFIC trial, 80.6% of the patients whose disease progressed on durvalumab developed intrathoracic-only progression (Rimner et al, ASTRO 2019). Therefore, if the study regimen altered disease progression, the next question becomes whether this a synergistic immunogenic phenomenon or radiobiologic function of delivering a higher biologic dose to the primary tumor. The authors briefly reference some correlative/exploratory endpoints, which may provide in understanding how a hypofractionated boost alters immunity. Are the authors able to describe these correlative/exploratory endpoints in any greater detail?

Reply:
Thank you for this question. We do propose in this study some exploratory endpoints including 1. to evaluate the effects of combined treatment on tumor microenvironment from up to four patients that will be consented for residual primary tumor biopsy two months after hfRT to assess exploratory markers which may include but is not limited to: immune cell gene expression profiles within the tumoral compartments, the presence of IFN-γ tumor necrosis factor-α, IL-2, IL-6, IL-8, IL-10, and IL-12 as well as expression of PD-L1 and the number and phenotype of immune cells such as T-cells, M1 and M2 subtypes of macrophage, and dendritic cells by immunohistochemistry methods; 2. to evaluate the systemic effects of combined therapy by testing circulating tumor RNA/DNA, soluble PD-L1 levels, and cytokine levels in peripheral blood specimen and 3. to correlate these biomarkers with response to durvalumab/hfRT treatment and/or the progression of cancer and/or toxicities. We added the above information to the revised manuscript (see section 1.3 in Introduction, page 4).

2) One criticism of this hypofractionated boost approach is that one may not be able to distinguish between radiographic changes (i.e., inflammation) and residual disease on post-chemoradiation imaging. It would be helpful to understand how the authors are approaching this issue.

Reply:

This is a critically important question. Thank you for the reviewer to bring it up. We do recognize the challenges distinguishing treatment-induced inflammation vs. residual disease on post-dCRT imaging. Thus a PET/CT rather than a CT chest is preferably performed within 5-10 days after completion of dCRT to help guide tumor delineation by including only the solid tumor volume of SUV >4 to avoid contouring atelectasis or treatment-related inflammation which usually has no/low glucose avidity. If PET/CT is not available, for example, due to insurance denial, CT chest imaging will be used for GTV contouring which will only include solid component of the tumor. In either situation, normal tissue constraints will be met at higher priority than tumor coverage during hfRT planning. We edited the text in Methods (page 6).

3) The authors are planning to define the maximum tolerated dose as that at which 2 or more subjects experience dose-limiting toxicity (DLT). However, DLT is not defined in the current manuscript.

Reply:

The definition of DLT is added to page 6-7.

4) The authors acknowledge a primary concern about this regimen being its safety, especially since the cumulative biologic equivalent dose exceeds that of the dose-escalated arm of RTOG 0617. It would be helpful to understand whether there any other stopping rules in place with specifically with respect to pneumonitis. Several real-world studies have shown higher rates of grade 2-3 pneumonitis (>10%) as compared to those seen in the PACIFIC trial.

Reply:

Due to the concern of the safety of the hfRT boost, we planned the trial with a phase I step of 3+3 design with DLT defined (added on page 6-7). In addition, we have proposed to stop the trial if, at any time, a total of two cases developed grade 5 toxicity, with particularly attention paid to pneumonitis, after consolidative RT from side effects caused by immunotherapy and/or consolidative RT if other causes including tumor progression can be ruled out. We have added this information to "stopping rule" section (page 9).

Reviewer B

I congratulate the Authors on conducting an interesting article and choosing such a clinically meaningful topic. I have minor comments:

Line 69 – this paragraph starts suddenly and the connection between previous narration is hardly seen. Maybe some additional sentence would be better there or maybe you could rewrite it somehow?

Reply:

Thank you for pointing this out. We edited this part in Introduction (page 4).

Line 94 – there is no information in eligibility criteria about necessity of PET-CT and brain

MRI for staging before definite radiochemotherapy. Is this obligatory before patients could be assessed as 'receiving dCRT'? It's not written in the protocol.

Reply:

Thank you for pointing it out. We edited the Eligibility criteria section with clarification of the necessity of PET/CT and brain MRI (page 5).

Line 114-116 – Giving consolidative hfRT after 2nd cycle (start of durvalumab max. 42days + 14days between cycles = 56 days after completing RT) could raise a question about repopulation. From one point of view, giving hrRT in short time should destroy clones of cells that survived after conventional radiochemotherapy – faster delivery of hfRT may be then resonable. On the other hand, in publication from University of Kentucky (1) patients were scanned with PET/CT approximately 1 month after completion of dRT and median time between completion of dRT and SBRT was 2 months – is this the reason of making such a pause between dRT and hfRT or it is due to Pacific (durva after 42 days)? Why hfRT after 2nd cycle of durvalumab, not after 1st? A similar trial is being conducted now and there SBRT is given after 1st cycle of durvalumab (2).

Reply:

We appreciate the very thoughtful questions the reviewer raised. Yes, starting durvalumab within 42 days after completing dCRT is based on PACIFIC trial design so that our results can be compared to the historical results of PACIFIC trials for efficacy since this is a single armed phase I/II study. Safety was a main consideration when we were designing the trial. Delivering hfRT boost between the second and third cycle of durvalumab was a decision made from our multidisciplinary team without the knowledge of the other trial from the other institution at the time of applying for grant support from AstraZeneca, Inc.. It is our preference to start hfRT after at least two cycles of durvalumab to make sure no severe toxicities occur prior to adding hfRT boost, again mainly for safety concerns. We made modifications on page 6.

Line 122 – Only 4D IMRT is possible? What about DIBH – is it used in your Institution? Further, if the trial is positive, for 3rd phase including DIBH in protocol would be also important for institutions where SBRT in provided with DIBH.

Reply:

This is a good suggestion. We have both techniques available in our institution. However, we observed in the practice that some of the lung cancer patients may have hard time to complete the high fractional dose of hfRT treatment with one course/arc of DIBH. hfRT planning is almost always done by using non-coplanar VMAT which renders the liability of OSMS not very high. Thus we only allowed 4D technique in this trial. However, if the trial can lead to a phase III study in the future, we may consider allowing all SBRT planning techniques including DIBH.

O.R. Alcibar (3) published interesting review about SBRT boost in dRT. Also review by S. Demaria et al.(4) or Z. Zhang et al.(5) is important when we talk about possible combinations

of IO with RT. I think it might be beneficial to put them in the discussion.

1. Kumar S, Feddock J, Li X, Shearer AJ, Hall L, Shelton BJ, et al. Update of a Prospective Study of Stereotactic Body Radiation Therapy for Post-Chemoradiation Residual Disease in Stage II/III Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys [Internet]. 2017 Nov 1 [cited 2023 Apr 17];99(3):652–9. Available from: https://pubmed.ncbi.nlm.nih.gov/29280459/
2. Durvalumab and Consolidation SBRT Following Chemoradiation for Locally Advanced Stage III Non-Small Cell Lung - Full Text View - ClinicalTrials.gov [Internet]. [cited 2023 Apr 17]. Available from: https://clinicaltrials.gov/ct2/show/NCT03589547
3. Alcibar OL, Nadal E, Palomar IR, Navarro-Martin A. Systematic review of stereotactic body radiotherapy in stage III non-small cell lung cancer. Transl Lung Cancer Res [Internet]. 2021 Jan 1 [cited 2023 Apr 17];10(1):529–38. Available from: https://pubmed.ncbi.nlm.nih.gov/33569334/
4. Demaria S, Guha C, Schoenfeld J, Morris Z, Monjazeb A, Sikora A, et al. Radiation dose and fraction in immunotherapy: one-size regimen does not fit all settings, so how does one choose? J Immunother Cancer [Internet]. 2021 Apr 7 [cited 2023 Apr 17];9(4). Available from: https://pubmed.ncbi.nlm.nih.gov/33827904/
5. Zhang Z, Liu X, Chen D, Yu J. Radiotherapy combined with immunotherapy: the dawn of cancer treatment. Signal Transduction and Targeted Therapy 2022 7:1 [Internet]. 2022 Jul 29 [cited 2023 Apr 17];7(1):1–34. Available from: https://www.nature.com/articles/s41392-022-01102-y

Reply:

Great suggestions. We have incorporated these studies in the edited manuscript in the Discussion (page 11).

Reviewer C

This is a protocol paper on consolidation hSRT for LANSCLC. It is a topic of great interest. Thank you for the opportunity to review this important paper.
My comments about this study protocol are as follows

1. please indicate how the OAR dose for the standard treatment portion prior to enrollment and the dose with fSRT will be calculated when combining the dose with fSRT, since the fraction size are different. In addition, whether the dose constraint for normal tissue is appropriate may vary depending on the pre-registration radiotherapy. Please specify how this problem will be overcome.

Reply:

The dose constraints for the standard treatment portion are defined per standard care but in general with stricter constraints. For example, the V20Gy of total lung is recommended to be <30% instead of <37%; spinal cord Dmax < 45Gy instead of 50.4Gy which are usually allowed per other trials such as RTOG0617. The dose constraints of normal tissues for the hfRT boost are estimated based on the dose constraints per definitive SBRT studies. In our trial design, even with potential dose escalation of hfRT based on the phase I portion of the study, the dose constraints will not change to ensure

the normal tissue constraints to be met as the priority for safety. We edited the manuscript on Page 6.

2. please clarify the definition of DLT. Usually, dose-limiting toxicity in high-dose RT is late toxicity, and the absence of DLT for several months or so is not synonymous with being safe. How to ensure the safety of the patients is questionable. If the expected frequency of SAEs is in the range of a few percent level, is it reasonable to increase the dose in only three cases?

Reply:

Thank you for pointing this out. Definition of DLT is added to page 7. We agree that late toxicity is a main concern of the high-dose RT study. That is why we planned to enroll only one to two patients per month for the phase 1 study and have a mandated one-month break after the last patients enrolled and treated with hfRT before we can move on to phase 2. We also have designed an interim analysis to be conducted at six months after enrolling the 12th patients, and a stopping rule for the study that the trial will be stopped if, at any time a total of two cases developed grade 5 toxicities after hfRT from side effects caused by the treatment. The stopping rule and interim analysis were added to the Statistical Analysis section on page 9-10.

Reviewer D

The paper by Chi Zhang et al. presents an ongoing study with an interesting question and design, investigating the addition of consolidative hypofractionated radiotherapy boost concomitantly with durvalumab consolidation after CRT in patients with unresectable NSCLC, thus presenting a design "PACIFIC plus RT boost".

The manuscript is well written.

The introduction including background, rationale and objectives is coherent. In the methods section, the study procedures and each intervention are well described, including statistics. It is surprising that the topic of safety has not been given a larger place in this section. The main concern of the study is certainly toxicity of the additional RT boost, specifically the risk of pulmonary toxicity in conjunction with immunotherapy. Safety has been defined as one of the primary endpoints in this study. It remains unclear how this endpoint is measured, particularly what the inclusion criteria are from the pulmonary side, and how pulmonary toxicity is/was assessed as the study progresses. The discussion is a good summary of the scientific efforts in this area and summarizes ongoing studies and results.

Reply:

Thank you for the positive comments on our Discussion. For the safety endpoint, we do have the phase 1 part of the study to determine the DLT which is added to Page 6. We also have interim analysis (for efficacy) and stopping rule limiting high grade toxicities with the information added to page 9-10. However, since patients receiving dCRT are those not being surgical candidates with quite poor long-term prognosis, we did not include the pulmonary function as one of the inclusion/exclusion criteria.

The main criticism of the presented work is that no results are presented. As far as can be seen from the manuscript, the study is ongoing since June 2021. One would expect first data (e.g.,

safety and efficacy) at the current time. However, no data are presented. Therefore, it remains unclear what new insights the current work provides (other than a study presentation).

Reply:

Due to COVID19 pandemic, we only started to enroll patients until late year 2022 with significant delay after receiving the funding. We are finishing the phase 1 part of the study. We do plan to submit results of the study once we have more efficacy data available but do so in a separate publication.