**Peer Review File**

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**Reviewer A**

**Comment 1:** Lines 53-55: The difference in results with the pooled cohort was an interesting finding from S1314. The authors could discuss that this discrepancy may have been a result of the inherent limitations of the COXEN in a cohort of multiple regimens. As the original authors note in the study, this may have contributed to significant statistical noise.

***Reply 1:*** *We have made the following changes to address this comment in a new paragraph in lines 62 – 69.*

***Changes in the text:*** *It is interesting to consider why the GC but not the ddMVAC model correlated with OS in the pooled cohort. Although the COXEN model has been validated in multiple clinical cohorts treated with multiagent chemotherapy, the prediction scores for combination regimens are derived from computational compilation of the scores for each agent alone. This may negatively impact the fidelity of the biomarker, especially when four agents (ddMVAC) as opposed to only two agents (GC) are used (1,3). Since cisplatin is the dominant agent in both regimens, it is perhaps not surprising that there is overlap in the predictive capacity of the GC model to patients treated with ddMVAC. The larger sample size of the pooled cohort likely also contributes to the statistical significance of the GC model in the pooled cohort.*

Lines 78-80: The author's discussion of pathological complete response as an important surrogate endpoint for clinical trials is good.

**Comment 2**: Lines 104-107: The exploratory analysis of ctDNA as a predictor of NAC response is indeed very interesting. Are the results mentioned here using the entire pooled cohort of ddMVAC and GC?

***Reply 2:*** *The sub analysis included samples collected from 72 patients treated with either GC or ddMVAC. We have modified the sentence on lines 103-106 to clarify this.*

***Changes in the text:*** *One important example is an exploratory study of plasma cell free DNA (cfDNA) methylation using the Infinium MethylationEPIC BeadChip array (Illumina, San Diego, CA) on blood samples collected from 72 patients before and after one cycle of NAC with either GC or ddMVAC (12).*

**Comment 3**: Lines 110-111: What were the three condensed subtypes?

***Reply 3:*** *The three condensed subtypes were added in lines 121-126.*

***Changes in the text:*** *The authors tested three different classifiers (The Cancer Genome Atlas (TCGA), the MD Anderson, and the Consensus classifiers) and condensed the TCGA and*

*Consensus models into three subtypes. The condensed TCGA classifier consisted of basal-squamous/neuronal, luminal, and luminal infiltrated, and the condensed Consensus classifier included basal-squamous/neuroendocrine, luminal, and stroma-rich (15).*

Lines 116-118: This is a very good point. It would be most clinically relevant if MIBC subtyping could impact NAC treatment decisions.

Lines 121-125: This is also a very interesting point that could be used for future updates of S1314

**Reviewer B**

Well written commentary with relevant conclusions. Notable 5 year OS with downstaging with NAC

***Reply:*** Thank you for your comments!

**Reviewer C**

**Comment 4:** The manuscript provides a clear and detailed overview of the SWOG S1314 trial and the evaluation of the COXEN model. The structure is well-organized, with a logical flow from the trial design to the outcomes.

Here's my suggestions and minor Revisions:

Line (L.) 26-30: Clarify the meaning of "COXEN" in the introduction, as it is introduced before (L. 26) its full name is provided (L. 30)

**Reply 4:** *Modification to lines 26 and 31 was made to introduce earlier the acronym COXEN. However, the authors feel that the current order of the introduction flows best with introducing the SWOG 1314 trial given the commentary nature of the paper, with the description and explanation of the COXEN model done immediately after.*

**Reviewer D**

This is well written and a comprehensive analysis.

I don't have any suggestions to improve.

***Reply:*** Thank you for your comments!

**Reviewer E**

**Comment 5:** In this short paper, the authors provided a summary of the SWOG S1314 as well as a perspective on the biomarker discovery in the context of muscle-invasive bladder cancer. I do not have major comments, I only suggest the authors to include insights from a previous study from the same group that aims to identify novel biomarkers to predict therapy for MIBC patients:

Mi, Haoyang, et al. "Predictive models of response to neoadjuvant chemotherapy in muscle-invasive bladder cancer using nuclear morphology and tissue architecture." Cell Reports Medicine 2.9 (2021).

***Reply 5:*** *This commentary addresses specifically analyses linked to S1314. It is a short commentary that cannot address all potentially predictive markers of response to NAC in a comprehensive fashion. While the paper suggested by Reviewer E is very interesting, it is beyond the scope of this commentary. Furthermore, this analysis lacks external validation.*