

## Peer Review File

Article Information: <https://dx.doi.org/10.21037/tcr-23-2098>

### Reviewer A

Insightful review of a pivotal publication likely to influence future attempts to define patients in relation to optimal use of immunotherapy

**Reply 1: Thank you reviewer A for taking the time to review this commentary. We appreciate the positive feedback.**

**No portion of the manuscript text was modified in response to reviewer A comments.**

### Reviewer B

In this commentary by Sosa, Glathar, and Sinha, the authors have commented on the study by Weed et al., which has been published in Cancer Research. The commentary introduces the study by Weed et al., comprehending the prospective clinical exploration of the structures and cellular composition of the TME in HNSCC tumors. The authors also provided the significance of the study and the techniques used, for example - use of co-detection by indexing (CODEX) multiparametric imaging to identify 20 different cell types organized into 11 "Cellular Neighborhoods" (CN). Notable findings include identifying tertiary lymphoid structures (TLSs) with opposing functions, the prevalence of specific CNs, and the association of the TLS1 CN with improved disease-specific survival.

The commentary is well written, focusing on the pros and cons of the findings of Weed et al. The authors have emphasized the importance of studying the stromal fibroblast component along with immune cells, citing the potential drawback of the Weed et al. study. The authors identified that Weed et al. failed to establish a correlation between clinical parameters and the presence of the tertiary lymphoid structure neighborhoods. The authors also emphasized the need to study/understand the cellular components of the capsule cells, which might be of fibroblast in origin. They also emphasize the importance of sample preparation and acknowledge the study's limitations, such as the small sample size. The need for larger and more diverse patient cohorts, consideration of clinical factors, and the heterogeneity of HNSCC subtypes are highlighted. Overall, the commentary provides new insights and provided solutions while executing the experiments and making inferences out of the results for better clinical application.

**Reply 2: We acknowledge reviewer 2's insight and accurate summation of the key points touched upon in our commentary. Thank you for the feedback.**

**No portion of the manuscript text was modified in response to reviewer B comments.**

**However, the manuscript was carefully edited for grammar, spelling and language flow.**