Dear Editors,

Enclosed is the submission package for the manuscript titled “PD1 Ligands Functionality: A Biomarker of Response to Anti-PD1 Treatment in Patients with Head and Neck Squamous Cell Carcinoma,” submitted for consideration as a Research Article in JAMA Otolaryngology – Head & Neck Surgery. This study introduces a groundbreaking biomarker for predicting responses to anti-PD1 treatment in head and neck squamous cell carcinoma (HNSCC) patients, focusing on the functional binding of PD1 ligands—PDL1 and PDL2—assessed by the innovative IcAR technology. Notably, while the methodology and technology was previously published in Science Advances1, this marks the first instance of employing this bio-sensing technology for an HNSCC cohort.

The landscape of HNSCC treatment has been significantly transformed by immune checkpoint inhibitors (ICIs) targeting the PD1/PDL1 pathway. However, predicting responses to anti-PD1 therapy remains a formidable clinical challenge. The current standard biomarker, Combined Positive Score (CPS) of PDL1 staining, presents limitations in sensitivity, variability, and correlation with clinical outcomes. Our study addresses this challenge by establishing the functionality of PD1 ligands as a robust biomarker for predicting responses to anti-PD1 treatment in HNSCC patients. Conducted at Rambam Medical Center and Ben Gurion University of the Negev, our single-center retrospective analysis involving 29 HNSCC patients who received anti-PD1 therapy between 2017 and 2022 yields significant insights:

1. **Superior Predictive Power:** Our study demonstrates the superiority of IcAR-PD1 over CPS in predicting treatment responses, highlighting enhanced accuracy in assessing anti-PD1 therapy outcomes.
2. **Line of Treatment Independence:** Importantly, our findings indicate that the predictive superiority of IcAR-PD1 is not influenced by the treatment line, emphasizing its reliability across various stages of therapeutic interventions.
3. **Relevance of PDL2:** IcAR-PD1 underscores the critical role of PDL2 in anti-PD1 therapy outcomes, providing a comprehensive understanding of functional interactions and emphasizing the significance of PDL2 in predicting treatment responses.

Our study aligns with the mission and scope of JAMA Otolaryngology – Head & Neck Surgery, offering significant insights into the predictive value of PD1 ligands functionality in anti-PD1 treatment for HNSCC patients. We believe our findings hold clinical relevance and can impact the current landscape of treatment strategies for this patient population.

We kindly request that you consider our manuscript for peer review with the aim of its eventual publication in JAMA Otolaryngology – Head & Neck Surgery.

Sincerely,

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References:

1. Kaufman B, Abramov O, Ievko A, et al. Functional binding of PD1 ligands predicts response to anti-PD1 treatment in patients with cancer. *Sci Adv*. 2023;9(21). doi:10.1126/SCIADV.ADG2809