

Peer Review

Review of: "Personalized mRNA Neoantigen Vaccines Reach Phase III: A Critical Commentary on the INTerpath-001 Melanoma Trial"

Marcus Schmidt¹

1. Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany

This is a timely, well-written, and thoughtful commentary on the recent positive phase III readout of INTerpath-001 and, more broadly, on the current state of individualized mRNA neoantigen vaccination in oncology. I found the manuscript informative and appropriately balanced.

A particular strength is that the authors provide sufficient background on the biological rationale and manufacturing concept of personalized neoantigen vaccines for readers who are not deeply familiar with this rapidly evolving field. At the same time, they place the INTerpath-001 findings into the appropriate evidentiary context, including the preceding randomized phase IIb KEYNOTE-942 experience. The comparison of the two trials is useful and clearly illustrates the important methodological progression from a relatively small open-label phase IIb study to a large, double-blind, placebo-controlled phase III trial.

I particularly appreciate the restrained interpretation of the currently available phase III evidence. The authors explicitly distinguish a positive phase III topline result from a demonstrated overall-survival benefit or an immediate change in clinical standard of care. They appropriately emphasize that hazard ratios, confidence intervals, detailed safety data, subgroup analyses, and ultimately mature overall-survival data remain necessary before the magnitude and clinical relevance of the benefit can be fully assessed. This avoids the excessive enthusiasm that sometimes accompanies major developments in personalized cancer vaccination and makes the commentary scientifically credible.

The discussion of potential limitations is similarly well-judged. In particular, the authors appropriately acknowledge that melanoma represents an unusually favorable biological setting for neoantigen

vaccination because of its high mutational and neoantigen burden, and that successful phase III validation in melanoma cannot simply be extrapolated to less immunogenic tumor types. They also discuss important practical challenges, including manufacturing time, individualized production, regulatory complexity, cost, infrastructure, and equitable access.

I have only one substantive suggestion that might broaden the translational perspective of the commentary. The authors briefly and appropriately refer to encouraging early findings with individualized mRNA vaccination in resected pancreatic cancer, an archetypally immunologically “cold” malignancy. However, there is now also clinical evidence from early triple-negative breast cancer (TNBC), a tumor type that is immunologically more active than pancreatic cancer but considerably less mutation-rich than melanoma. An adjuvant phase I study of individualized neoantigen mRNA vaccination in TNBC demonstrated robust, polyepitopic, and durable vaccine-induced T-cell responses, including *de novo* responses persisting for years. Although the small, non-randomized study obviously cannot establish clinical efficacy, these findings provide an informative intermediate biological example between highly immunogenic melanoma and very immunologically cold tumors such as pancreatic cancer. I would therefore encourage the authors to briefly include this experience in Section 5 or Section 8.2 when discussing whether individualized neoantigen vaccination may generalize beyond melanoma. This would further strengthen their central and appropriately cautious argument that the applicability of the platform across different tumor immunological contexts remains an empirical question.

Apart from this relatively minor suggestion, I have no major concerns. The manuscript is clearly structured, scientifically balanced, and highly relevant given the importance of the INTerpath-001 announcement for the field. Importantly, the authors neither understate the significance of the first positive phase III trial of an individualized neoantigen therapy nor overinterpret what is currently still a topline result. Their concluding concept of “calibrated optimism” is, in my view, an appropriate characterization of the present state of the field.

Declarations

Potential competing interests: M. Schmidt reports receiving personal fees from AstraZeneca, BioNTech, Daiichi Sankyo, Eisai, Eurobio, Exact Sciences, Gilead, Greenwhich Life Sciences, Lilly, Menarini-Stemline, Molecular Health, MSD, Novartis, Pantarhei Bioscience, Pfizer, Pierre Fabre, and Roche. His institution has received research funding from AstraZeneca, BioNTech, Celcuity, Eisai, Genentech, the German

Breast Group, MSD, Novartis, Palleos, Pantarhei Bioscience, Pfizer, Pierre Fabre, and Roche. He is also listed as an inventor on patents EP 2390370 B1 and EP 2951317 B1.