

P2.135: WES-Derived Neoantigen Quality Biomarker Predicts Immunotherapy Survival Benefit in Patients with NSCLC

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INTRODUCTION

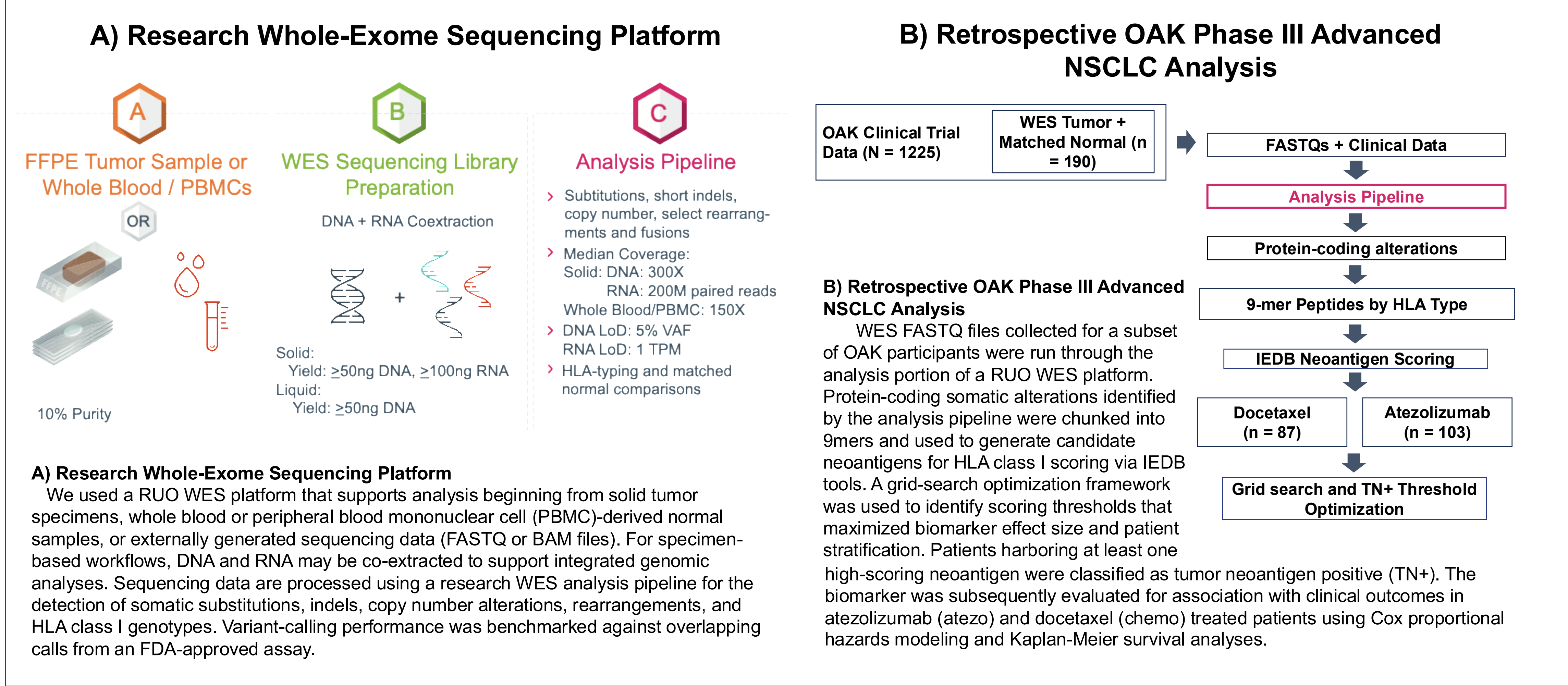
Protein-coding somatic mutations lead to tumor-specific peptides known as neoantigens. Because neoantigens are absent in normal tissue, they are attractive targets for immune-related therapies. Following intracellular processing into peptide fragments, neoantigens may be presented on the tumor cell surface by the major histocompatibility complexes (MHCs) where they can be recognized by T cells and trigger immune-mediated tumor clearance.

Not all protein-coding mutations elicit an anti-tumor immune response. A successful response depends upon many biological factors including peptide processing, patient-specific human leukocyte antigen (HLA) binding affinity, presentation, expression, and clonality. Additionally, tumor immune evasion mechanisms such as loss of HLA heterozygosity, mutations in antigen processing and presentation machinery, and immune checkpoint activation may interfere with anti-tumor responses to neoantigens. As a result, checkpoint inhibitors and individualized neoantigen therapies (INT) rely on not only the quantity of neoantigens, but the quality as well.

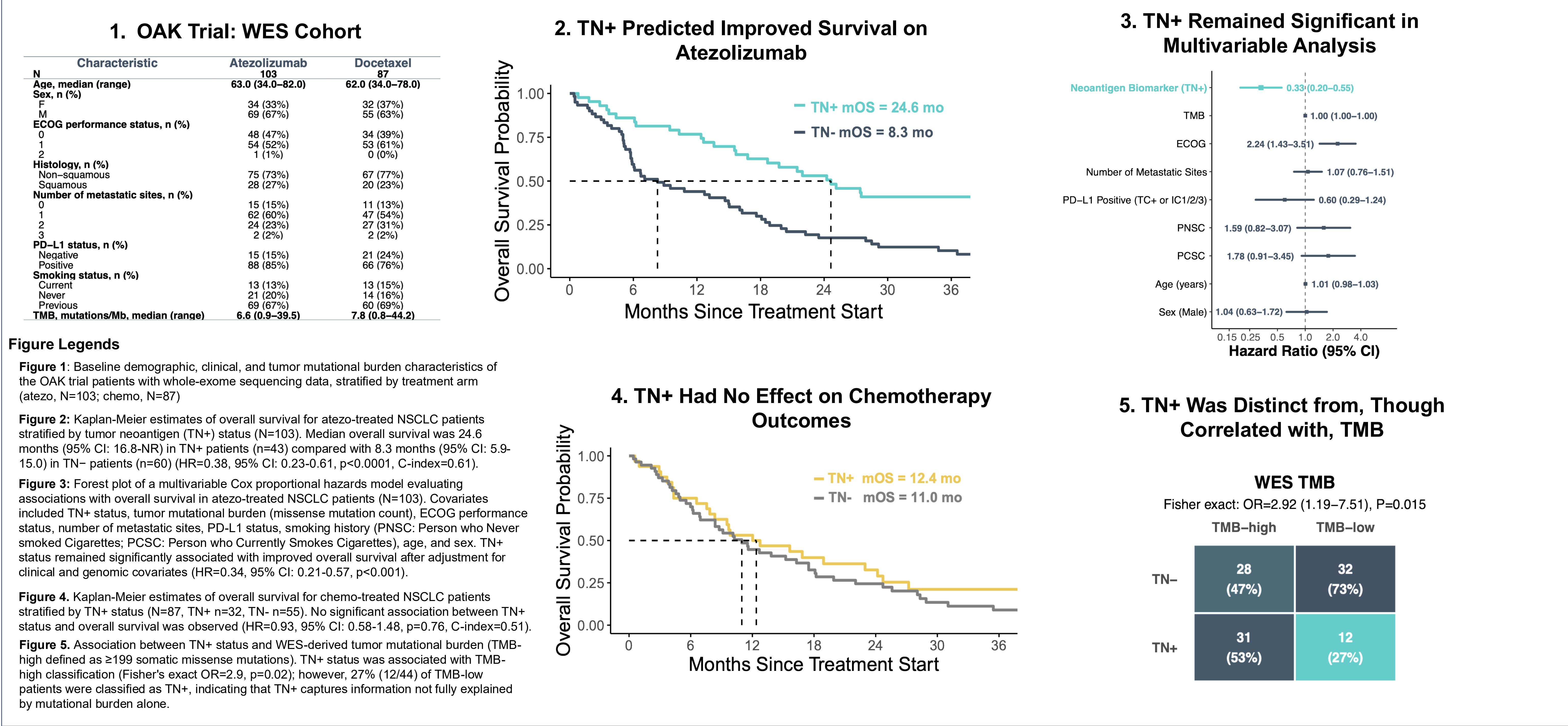
Whole-exome sequencing (WES) enables comprehensive neoantigen detection in tumor specimens, which combined with HLA-typing and neoantigen scoring, allows for systematic characterization of patient-specific neoantigen landscapes. Together, these approaches enable the creation of neoantigen-based biomarkers that may complement existing predictors of immunotherapy response including tumor mutational burden, PD-L1 status, ECOG performance status, and other clinical characteristics.

Here, we present a retrospective analysis of the OAK phase III advanced NSCLC clinical trial (Clinical Trial # NCT02008227), in which matched tumor-normal specimens from a subset of patients underwent WES. Somatic variants were identified using a research use only (RUO) WES pipeline, which was benchmarked against overlapping variant calls from an FDA-approved, panel-based comprehensive genomic profiling assay. The resulting protein-coding alterations were used to identify and score patient-specific neoantigens and develop a neoantigen-based biomarker for immunotherapy response prediction.

METHODS



RESULTS



DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Using an end-to-end whole-exome sequencing (WES) platform, we identified an exploratory tumor neoantigen-based biomarker associated with improved overall survival in atezolizumab-treated NSCLC patients.
- The biomarker showed no association with survival in docetaxel-treated patients and remained significant in the atezolizumab-treated cohort after adjustment for established clinical and genomic covariates, supporting its potential utility as a predictive immunotherapy biomarker.
- Next Step:** Validate the TN+ biomarker in an independent immunotherapy-treated cohort.

REFERENCES & ACKNOWLEDGEMENTS

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- IEDB: Vita R, Blazeska N, Marrama D; IEDB Curation Team Members; Duesing S, Bennett J, Greenbaum J, De Almeida Mendes M, Mahita J, Wheeler DK, Cantrell JR, Overton JA, Natale DA, Sette A, Peters B. The Immune Epitope Database (IEDB): 2024 update. Nucleic Acids Res. 2025 Jan 6;53(D1):D436-D443. doi: 10.1093/nar/gkae1092. PMID: 39558162; PMCID: PMC11701597. www.iedb.org
- Artificial intelligence (AI) Disclosure: AI-assisted tools (Claude Code, Anthropic) was used to support data visualization, data analysis, and to assist with language refinement, grammar, and organizational clarity of the text. All analyses were designed, directed, and verified by the authors, and statistical interpretations and scientific conclusions are the authors' own.