

## GLOBAL AND LOCAL COPY NUMBER ABERRATION SIGNATURES AS PROGNOSTIC AND IMMUNOTHERAPEUTIC PREDICTORS

<sup>1</sup>Xuefeng Wang\*, <sup>2</sup>Tingyi Li, <sup>1</sup>Timothy I Shaw, <sup>1</sup>Sijie Yao, <sup>1</sup>Islam Eljilany, <sup>3</sup>Martin D McCarter, <sup>4</sup>Abdul Rafah Naqash, <sup>5</sup>Margaret E Gatti-Mays, <sup>6</sup>Aakrosh Ratan, <sup>7</sup>John Carpten, <sup>8</sup>Howard Colman, <sup>9</sup>Igor Puzanov, <sup>10</sup>Susanne M Arnold, <sup>11</sup>Michelle Churchman, <sup>1</sup>Patrick Hwu, <sup>11</sup>William S Dalton, <sup>12</sup>George J Weiner, <sup>2</sup>Ahmad A Tarhini. <sup>1</sup>Moffitt Cancer Center, Tampa, FL, USA; <sup>2</sup>H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; <sup>3</sup>University of Colorado Cancer Center, Aurora, CO, USA; <sup>4</sup>Stephenson Cancer Center Oklahoma University, Greenville, NC, USA; <sup>5</sup>The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; <sup>6</sup>University of Virginia, Charlottesville, VA, USA; <sup>7</sup>USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; <sup>8</sup>Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; <sup>9</sup>Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; <sup>10</sup>Markey Cancer Center, Lexington, KY, USA; <sup>11</sup>Aster Insights, Hudson, FL, USA; <sup>12</sup>Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA

**Background** Copy number aberrations (CNAs), involving the amplification or deletion of DNA segments, are prevalent in cancer and hold great promise as an alternative approach for predicting responses to immune checkpoint inhibitors (ICIs), complementing established biomarkers such as tumor mutation burden (TMB).

**Methods** We investigated global and local CNAs in predicting patient survival outcomes, while examining the relationship between CNA status and tumor immune scores determined using gene expression data. Real-world lung cancer genomic data from the Oncology Research Information Exchange Network (ORIEN) Avatar project, a network of 18 cancer centers utilizing a common protocol (Total Cancer Care protocol; NCT03977402) to which patients provided written informed consent were utilized. We analyzed copy number profiles from a cohort of 1250 lung cancer patients, including 112 patients who underwent ICI treatments. Global CNA signatures included total copy number burden (TCB) and homologous recombination deficiency (HRD) score. Matched gene expression data were analyzed for immune states using ESTIMATE, CIBERSORTx and EcoTyper. Predictive signatures associated with survival outcomes were identified using Kaplan-Meier analysis, Cox regression, and the R package Xsurv.

**Results** Within the entire cohort, a higher TCB showed a significant association with smoking history ( $P < 0.001$ ) and metastatic status ( $P < 0.001$ ). Additionally, it was also significantly associated with poorer overall survival ( $P < 0.001$ ). The top prognostic CNA genes were identified in 1q21.1 (gain) and 22q11.23 (loss). In the ICI-treated cohort, higher HRD score, rather than TCB, were significantly associated with unfavorable survival ( $P = 0.03$ ). According to the univariable Cox model, the two most significant prognostic CNA signatures were *FAM231C* (1p36.13 gain) and *OR4F5* (1p36.33 loss). Utilizing survival boosting (XSurv), the top prognostic aberrant genes were *OR11H12* (14q11.2), *SLC2A14* (12p13.31), *POM121* (7q11.23) and *NBPF1* (1p36.13). The final XSurv-based predictive model achieved a C-index of approximately 0.8, indicating a strong predictive capability using local CNV information. Immune phenotyping analysis on matched gene expression data revealed that higher TCB or HRD score is significantly associated with the lower overall immune infiltration score as determined by ESTIMATE and suppressed immune states defined by EcoTyper.

**Conclusions** Collectively, our analysis underscores the potential of utilizing CNA signatures to optimize cancer prognosis and immunotherapeutic outcomes, as demonstrated in the context of lung cancer. Our data indicate that, while both TCB and

HRD are closely linked with tumor immune status, only HRD demonstrated predictive value in determining ICI survival outcomes. Further analysis is needed to evaluate the clinical utility of these CNA signatures in other cancer types.

**Acknowledgements** We are grateful to the participating patients and their family members as well as all research staff supporting the conduct of the Total Cancer Care protocol. Trial Registration: NCT03977402. This project is partly supported by ORIEN NOVA Team Science Award (PI: Ahmad Tarhini, MD, PhD), Moffitt Biostatistics and Bioinformatics Shared Resource, and National Institute of Health grant R01DE030493 (PI: Xuefeng Wang, PhD).

**Trial Registration** Trial Registration NCT03977402

**Ethics Approval** For this study, ORIEN members utilized a standard protocol, Total Cancer Care (TCC<sup>®</sup>; NCT03977402), to which patients provided an IRB-approved written informed consent at their participating institutions.

<http://dx.doi.org/10.1136/jitc-2023-SITC2023.0185>