Background Why some patients fail or have short lived response to immune checkpoint blockade (ICB) immunotherapy largely remains unknown. While baseline molecular assessments have provided clues to prognostic factors, insights into resistance drivers remains elusive. This is partially due to the difficulty in getting access to post progression samples from patients that were either primary resistant or developed acquired resistance after an initial response to ICB. Thus, the tumour-intrinsic and -extrinsic features that are selected for during progression and potentially drive primary and acquired resistance to immunotherapy remain underexplored.

Methods To compare clinical features and immunogenomic drivers of acquired and primary resistance to ICB across major cancers, we analysed and annotated de-identified patient records in the Tempus real-world database1 2 (figure 1). We built an immuno-oncology cohort consisting of >2500 multimodal (DNA, RNA and clinical outcome data) pre-treatment baseline with >1500 post-treatment tumour biopsy samples from mainly NSCLC, TNBC, HNC and Bladder cancer patients. We used bulk RNA-seq data to estimate activation of the hallmark oncogenic pathways1 2 and immune cell composition4 and used panel DNA-seq data (>500 genes) to quantify mutation selection at the gene and pathway levels using dndsce5.

Results Compared to acquired, primary resistant patients tended to have a higher observation of liver lesions at progression. Post-ICB, acquired resistant NSCLC and HNC patients showed a significantly inflamed tumour microenvironment (TME) characterised by higher estimation of infiltration of T cells and myeloid cells and higher activation of interferon gamma (IFNg) signalling as compared to primary resistant patients. In addition, in post-ICB acquired resistance in NSCLC we observed selection for mutations in genes involved in known immunomodulatory pathways, including loss-of-function mutations in B2M in the antigen processing and presentation machinery (APM) pathway and APC in the Wnt pathway. Consistently, acquired resistance patients showed stronger selection for mutations in APM, IBN, WNT, MYC, and Notch pathways as compared to primary resistance patients across NSCLC, HNC and bladder cancer post-ICB.

Conclusions Acquired and primary ICB resistant patients have distinct clinical and molecular features at progression. Their tumours’ TME is fundamentally different with acquired resistance TMEs being infiltrated with immune cells albeit escaped post progression. In addition, ICB selects mutations that potentially activate immunosuppressive pathways such as Wnt and Myc. This multi-modal Real-World Data with post therapy biopsies has given insights for patient selection strategies and provides rational into combination treatment options for acquired resistant patients.

REFERENCES

Ethics Approval All ethics and consent have been obtained in accordance with Tempus Labs IRB approval supporting the use of de-identified data.

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http://dx.doi.org/10.1136/jitc-2023-SITC2023.0620