Multimodal Real-World Data reveals immunogenomic drivers of acquired and primary resistance to immune checkpoint blockade

Mohamed Reda Keddar1, Sebastian Carrasco Pro2, Roy Rabbie3, Zeynep K. Atak3, Ana Camelo Stewart1, Ross Stewart1, Kathleen Burke2, Ben Sidders3, Sajan Khosla3, Scott A. Hammond3, Douglas C. Palmer3, Jonathan Dry3, Martin L. Miller1

1Oncology Data Science, Oncology R&D, AZ, Cambridge, UK, 2TEMPUS Labs Inc., Boston, MA, USA, 3Early Oncology R&D, AZ, Gaithersburg, MD, USA, *contributed equally

I. Background

Resistance to immune checkpoint blockade (ICB) is a major clinical issue across cancer types, yet, remarkably little is known which immunogenomic features emerge as patients progress on therapy. This is partially due to the focus so far on baseline sample analysis, reflecting the difficulty in getting access to post progression samples from patients that were either primary resistant (PR) or developed acquired resistance (AR) after an initial objective 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.

II. Methods

To map the clinical features and immunogenomic drivers of acquired and primary resistance to ICB across major cancers, we mined and annotated the TEMPUS real-world data resource. We built an immun-o-ncology cohort consisting of >2,500,000 (DNA, RNA and clinical outcome data) pre-treatment and >1,500 post-treatment tumour biopsy samples from mainly non-small cell lung cancer (NSCLC), breast cancer, head and neck cancer (HNC) and bladder cancer patients (Figure A-B).

In addition to comparing various clinical variables including post-progression survival between AR and PR, we used bulk RNA-seq data to estimate activation of oncogenic pathways and composition of the tumour microenvironment (TME) with ConsensusTME3 and used panel DNA-seq data to quantify mutation selection at the gene and pathway levels with dndscv4. The latter ensures robustness against potential biases in cancer genomics data, including differences in tumour mutational burden, tumour purity, and mutational signatures.

AR and PR show distinct clinical features

Compared to AR, PR tended to preferentially display liver lesions at progression, which was mirrored by worse post-progression survival, highlighting distinct metastatic organotropism and clinical outcome between the two resistance phenotypes (Figure C).

AR tumours are inflamed but escaped post-progression

Post-ICB, NSCLC and HNC AR showed an inflamed TME with higher estimation of T and myeloid cells and higher activation of interferon gamma (IFNg) signalling as compared to PR (Figure D). This inflamed TME was counterbalanced by selection for mutations in genes involved in immunomodulatory pathways, including loss-of-function mutations in B2M (antigen processing and presentation machinery – APM) and APC (WNT) in NSCLC (Figure E). Consistently, AR showed stronger selection for mutations in APM, IFN, WNT, MYC, and Notch pathways as compared to PR across NSCLC, HNC and bladder cancer (Figure E).

IV. Conclusions & Impact

1. PR show poorer prognosis than AR
2. Post-progression AR tumours are more inflamed than PR
3. Distinct clinicogenomic profiles of AR vs PR could inform patient selection strategies
4. Immune-hot profile of AR can be harnessed by next-gen IO to reestablish an effective anti-tumour immune response.

References
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