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

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I. Background

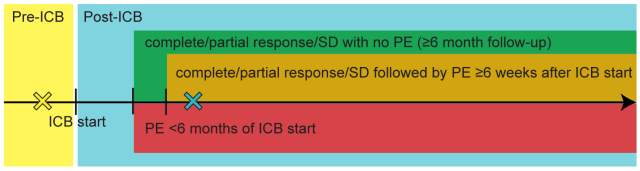
Resistance to immune checkpoint blockade (ICB) is a major clinical issue across cancer types, yet, remarkably little is known which immunogenomic features emerge as patients progress on therapy. This is partially due to the focus so far on baseline sample analysis, reflecting the difficulty in getting 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

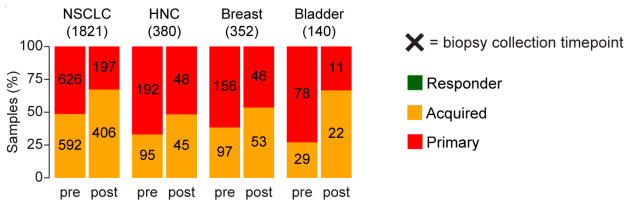
To map the clinical features and immunogenomic drivers of acquired and primary resistance to ICB across major cancers, we mined and annotated the TEMPUS real-world data resource. We built an immuno-oncology cohort consisting of >2,500 multimodal (DNA, RNA and clinical outcome data) pre-treatment and >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 *ConsensusTME*[1] and used panel DNA-seq data to quantify mutation selection at the gene and pathway levels with *dndscv*[2]. The latter ensures robustness against potential biases in cancer genomics data, including differences in tumour mutational burden, tumour purity, and mutational signatures.

SD = stable disease, PE = progression event



A. Representative timeline of an ICB treatment journey as mapped in TEMPUS.



B. Availability of RNA/DNA-seq samples for PR and AR in the four main indications.

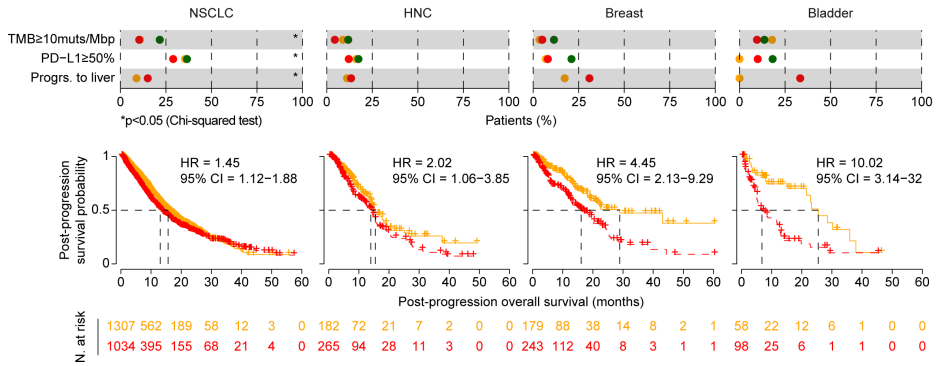
III. Results

AR and PR show distinct clinical features

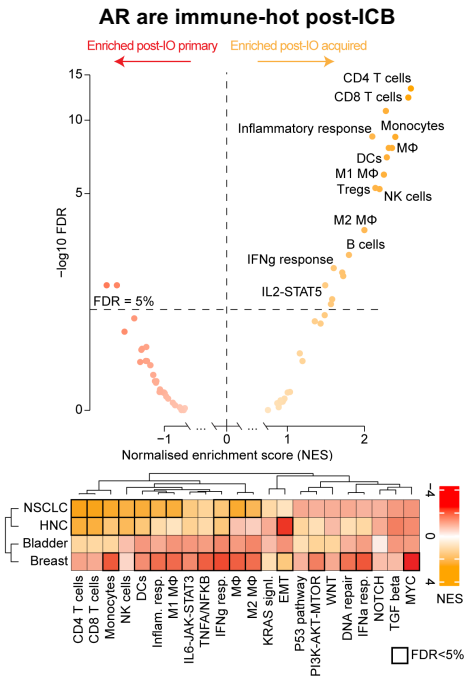
Compared to AR, PR tended to preferentially display liver lesions at progression, which was mirrored by worse post-progression survival, highlighting distinct metastatic organotropism and clinical outcome between the two resistance phenotypes (Figure C).

AR tumours are inflamed but escaped post-progression

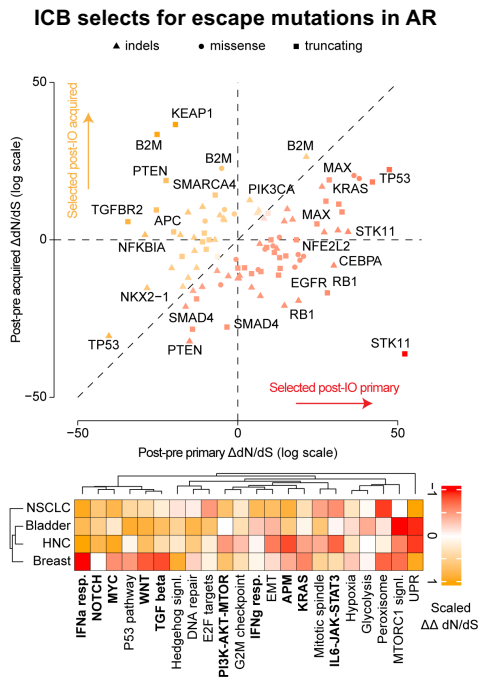
Post-ICB, NSCLC and HNC AR showed an inflamed TME with higher estimation of T and myeloid cells and higher activation of interferon gamma (IFNg) signalling as compared to PR (Figure D). This inflamed TME was counterbalanced by selection for mutations in genes involved in immunomodulatory pathways, including 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).



C. proportion of TMB/PD-L1-high responders/AR/PR, and proportion of AR/PR who showed liver mets post-treatment in the four main indications. Kaplan-Meier survival curves comparing AR and PR are shown for each corresponding indication.



D. Gene set enrichment analysis of post-IO AR vs PR in NSCLC (volcano plot) and all indications (heatmap).



E. Pre/post differential *dnds* estimates in AR vs PR in NSCLC (scatter plot) and all indications (heatmap). **Escape pathway**.

IV. Conclusions & impact

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

References

1. Jiménez-Sánchez *et al.*, Cancer Res., 2019
2. Martincorena *et al.*, Cell, 2018

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