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ctDNA-based clinicogenomic analysis of advanced head and neck cancer patients treated with immune checkpoint inhibitors

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BACKGROUND:

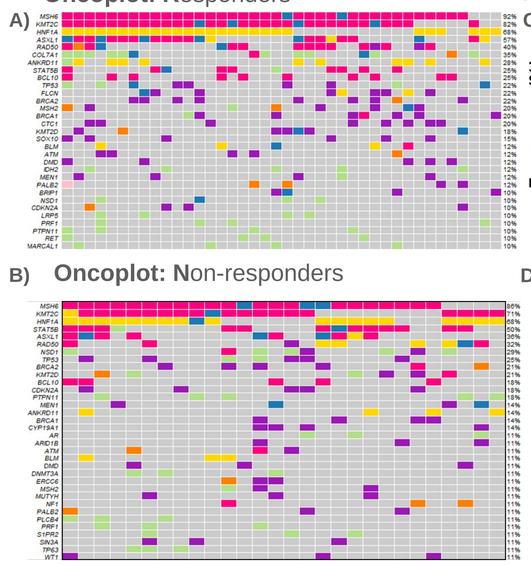
Head and Neck cancer (HNC), a diverse group of malignancies affecting the head and neck region is the most prevalent malignancy in Southeast Asia. Despite the advancement in treatment, 5 years survival rate for HNC remains below 50%, and the majority of patients receiving frontline therapy experience locoregional or incurable metastatic relapse. Immune checkpoint inhibitors (ICI) are recommended for relapsed patients, but only 20% show measurable response. Currently, no predictive biomarker is available to select patient for ICI benefits. Here we report comprehensive genomic profiling (CGP) of advanced HNC patients receiving ICI to understand the clinicogenomic underpinning of the treatment response.

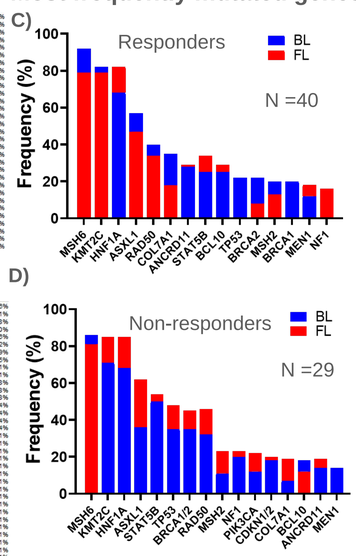
PROBLEM STATEMENT

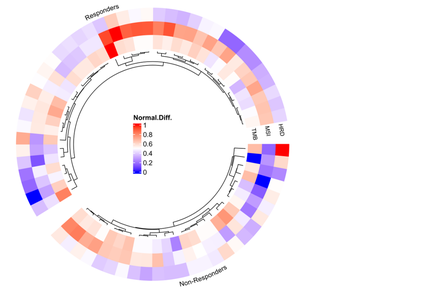
Immunotherapy regiment has improved survival outcomes in metastatic / recurrent HNC. However, response rate is low and significant fraction of population show no clinical benefit. Segregating non-responders (NR) from responders (R) based on genomic signatures may help selection of patients for optimal therapeutic response, but remains underexplored.

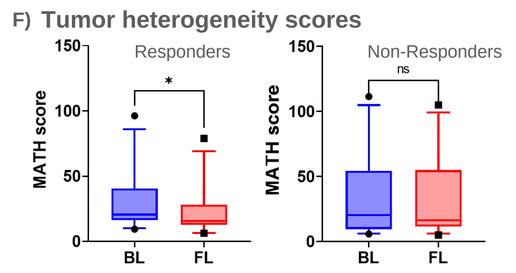
METHODS:

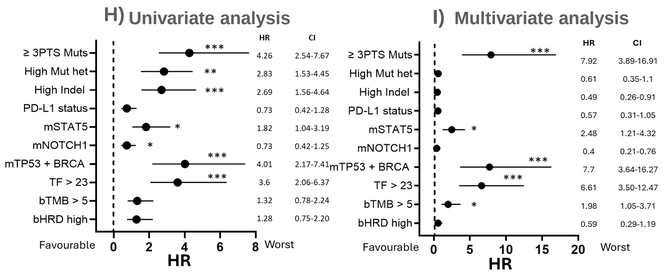
ctDNA was isolated from 69 advanced-stage HNC patients at the baseline and at the end of the therapy (Nivolumab ICI). Sequencing libraries were prepared from ctDNA by hybridization capture using **OncoIndx®** 1080 comprehensive gene panel (GCP). Libraries were sequenced on illumina NextSeq 2000 platform. Resultant raw reads were analysed using iCare™ bioinformatics pipeline for variant calling. Further, variant prioritization and categorization was performed according to the tier classifications of AMP/ACMG guidelines. Progression–free survival (PFS) and overall survival (OS) were determined using Kaplan-Meir method log-rank test. Hazard ratios (HR) were calculated using Cox-regression analysis.

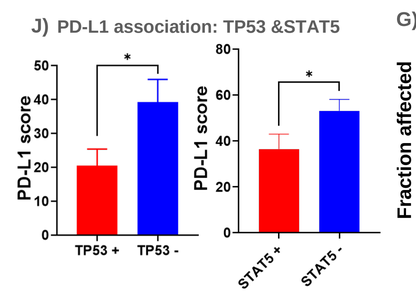


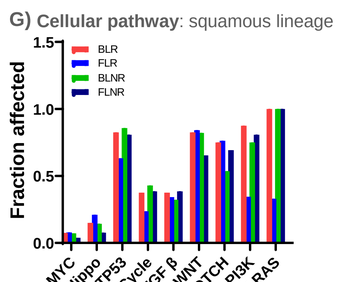


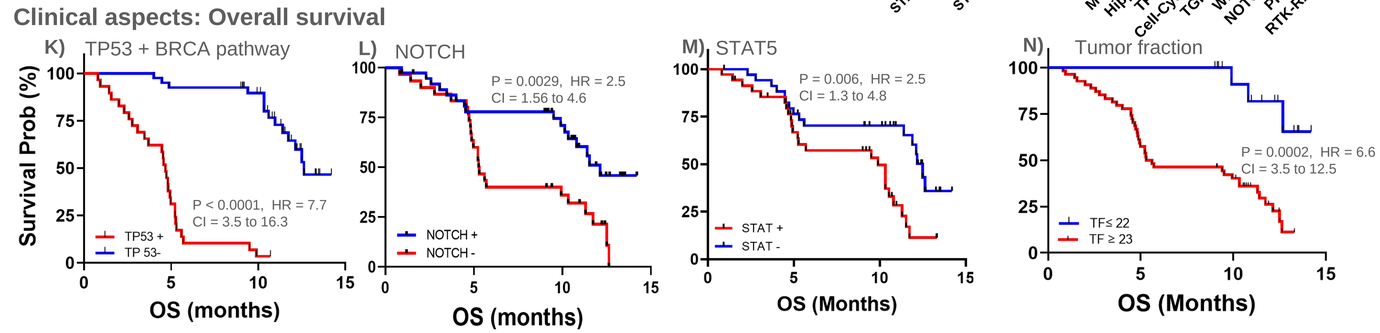












RESULTS:

- At BL, the NR population was enriched with oncogenic gene mutations compared to the R population. TP53 and BRCA pathway mutations (mTP53 + BRCA) showed a strong association with progression-free survival (PFS) and overall survival (OS).
- Patients with co-occurring mTP53 + BRCA had significantly lower PFS (median PFS: 2.77 months for mTP53 + BRCA pathway vs 9.1 months for wt TP53 + BRCA pathway. P = < 0.0001, HR = 3.2-11.6) and OS (median OS: 4.67 months for mTP53 + BRCA pathway vs 12.63 months for wtTP53 + BRCA pathway. P = < 0.0001, HR = 11.18-55.27). NOTCH 1 or 2 variants were enriched in R population, with a beneficial effect on survival outcomes.
- Mutant allele tumor heterogeneity (MATH, a measure of tumor heterogeneity) matrix was high in NR and remained unaffected at the end of therapy. On the contrary, MATH score significantly reduced after the treatment in R population.
- Univariate and multivariate analysis suggested that ctDNA mutations, TF, and high mutational heterogeneity emerged as risk factors for shorter PFS and OS. In contrast total indel burden and NOTCH mutations had beneficial effect.
- Squamous lineage cellular pathway enrichment was also observed to be significantly distinct in R & NR population.
- TP53 and STAT5B mutated population were significantly associated with low PD-L1 scores.

CONCLUSIONS:

- Comprehensive ctDNA profile revealed distinct variants associated with R & NR populations. TP53, STAT5B and BRCA pathway mutations were enriched in NR, while NOTCH 1/2 loss of function mutations were enriched in R.
- Loss of function mutations in TP53, HRR pathway, NOTCH1 and STAT5 were significantly associated with survival benefits.
- ctDNA CGP identified immunotherapy resistance conferring genomic markers for stratifying potential responders for immunotherapy guidance. Larger clinical trials are needed to clinically evaluate the findings.

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