

## IDENTIFYING GENETIC FACTORS FOR RESISTANCE AND RESPONSE TO IMMUNE CHECKPOINT INHIBITORS (ICIS) IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS USING REAL-WORLD DATA

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**Background** ICIs are a promising class of drugs that have improved the treatment of a broad spectrum of cancers. Biomarkers such as high Tumor Mutation Burden (TMB), high PD-L1 expression, or high Microsatellite Instability (MSI) are predictive of improved response to ICIs.<sup>1-3</sup> However, not all patients with these biomarkers respond well to ICIs and some develop resistance over time. The underlying molecular mechanisms of resistance are poorly known. We leveraged our deeply curated real world clinico-genomics database (ConcertAI Genome360™) of NSCLC patients treated with ICIs to identify the drivers of resistance and response.

**Methods** This retrospective study used the ConcertAI Genome360™ NSCLC dataset. The eligible patients had advanced NSCLC treated with ICIs (N=2532). A subset of these patients also had high TMB/PD-L1/MSI (TPM) status (N=986). The following analysis was performed for both the TPM unselected and high TPM populations. The patients were subdivided into responder and non-responder cohorts based on their response to ICIs. For each patient in both cohorts, genes with pathogenic mutations, fusions and copy number changes were identified and enrichment analysis was performed between cohorts. Biomarkers with p value less than 0.05 were further considered for pathway analysis along with the immune signaling network to identify pathways and genes responsible for response and resistance to ICIs in spite of TPM high status.

**Results** We identified segments which predicted response or resistance to ICIs (table 1). TERT promoter mutations and loss of function (LOF) mutations in STAG2 promote high TMB and PD-L1 expression respectively.<sup>4,5</sup> We also see them enriched in our overall responder cohort, however, the effect of STAG2 LOF mutations towards response to ICIs is seen even in the TPM high population indicating the effect is due to more than just upregulation of PD-L1. LOF mutations in ATM/ATR genes were also enriched in the overall responder cohort in-line with previous observations in murine cells.<sup>6,7</sup> Gene amplifications in CDK12 and CEBPA genes were predictive of resistance to ICIs and interestingly, amplifications in CDK12 and RET were also highly predictive of resistance to ICIs in the TPM high cohort which was heavily biased towards response to therapy.

Pathway analysis on the combined results identified that genes in the cGAS-STING pathway are playing a vital role in determining response.

**Conclusions** Our analysis highlights some of the underlying mechanisms for response or resistance to ICIs which can provide clues for designing new combination trials for patients whose tumor progresses on ICIs.

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**Abstract 531 Table 1** Genomic segment of response towards ICIs treatment

Overall Cohort treated with ICI (N = 2532)			
Gene Name	Status	Response	p value
STAG2	LOF Mutations	Responder	0.001
NF1/2	LOF Mutations	Responder	0.015
ATM/ATR	LOF Mutations	Responder	0.031
RBM10	LOF Mutations	Responder	0.043
TERT	Promoter Mutation	Responder	0.048
CDK12	Amplification	Non-responder	0.011
CEBPA	Amplification	Non-responder	0.028
PDL1/MSI/TMB high cohort treated with ICI (N = 986)			
Gene Name	Status	Response	p value
STAG2	LOF Mutations	Responder	0.03
KRAS	GOF Mutations	Responder	0.041
CDK12	Amplification	Non-responder	0.003
RET	Amplification	Non-responder	0.017

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