DNA Damage Response and Repair (DDR) Gene Mutations and Correlation with Tumor Mutation Burden (TMB) in Non-Small Cell Lung Cancer (NSCLC)

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BACKGROUND
• Loss of DNA repair fidelity is a common feature of human cancers and can drive genomic instability and tumor evolution.
• DNA repair deficiency has emerged as a predictive biomarker of response to platinum based chemotherapy and PARP inhibition.
• More recently, DNA repair defects have been shown to predict response to immune checkpoint inhibitors.
• Data on the relationship between DNA repair defects and TMB in NSCLC is limited.

STUDY OBJECTIVES
• Characterize the landscape of DNA damage response and repair (DDR) genes mutations in NSCLC
• Correlate DDR gene mutations with immune biomarkers (TMB and PD-L1)
• Identify mutations with the strongest association with high TMB

RESULTS
• DDR genes mutations are common in NSCLC, with RAD50, WRN, CHEK2, ATM, ATR, and MRE11 being the most commonly mutated genes.
• Over half of the DDR mutated tumors have high TMB and one-third have high PD-L1.
• DDR genes mutations are not mutually exclusive.
• BRCA1, PALB2, and POLE mutations are most likely to be associated with high TMB.

METHODS
• We retrospectively analyzed biomarker profiles of 5,667 NSCLC tumors that had undergone molecular profiling between 01/16 - 06/18 (Caris Life Sciences, Phoenix, AZ).
• Profiling included next-generation sequencing of 592 genes, TMB, and PD-L1 expression by immunohistochemistry (22c3).
• Genes of interest: ATM, ATR, BARD1, BLM, BRCA1, BRCA2, BRR1, CHEK1, CHEK2, ERCC2, ERCC3, FANCA, FANCE, FANC2, FANC1, FANCD2, FANC, FANCG, FANCL, MRE11, NBN, PALB2, POLE, PTEN, RAD50, RAD51, WRN
• Samples harboring mutation in at least one of the 29 genes representing several DDR pathways were included in the analysis.
• Available clinical information: Age, gender, histology

ASSOCIATION OF MUTATION WITH HIGH TMB
• Tumors with ≥3 DDR genes mutations are more likely to have a high TMB

CONCLUSION
• DDR genes mutations are common in NSCLC, with RAD50, WRN, CHEK2, ATM, ATR, and MRE11 being the most commonly mutated genes.
• Over half of the DDR mutated NSCLC tumors have high TMB and one-third have high PD-L1.
• DDR genes mutations are not mutually exclusive.
• BRCA1, PALB2, and POLE mutations are most likely to be associated with high TMB.

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