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

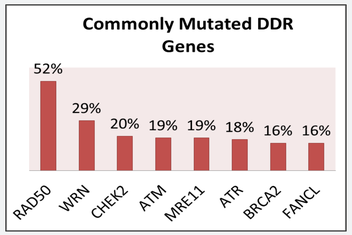
- Characterize the landscape of DNA damage response and repair (DDR) genes mutations in NSCLC
- Correlate DDR gene mutations with immune biomarkers (TMB and PD-L1)
- Identify mutations with the strongest association with high TMB

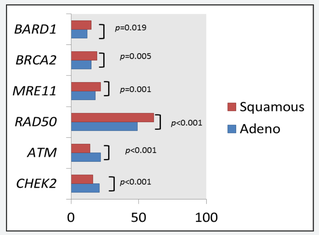
METHODS

- 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, BRIP1, CHEK1, CHEK2, ERCC2, ERCC3, FANCA, FANCC, FANCD2, FANCE, FANCG, FANCL, MLH1, MSH2, MSH6, 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

RESULTS

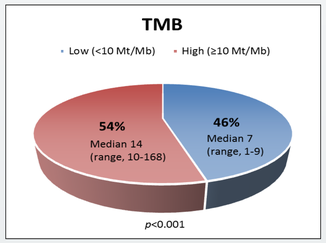
Frequency and Distribution of DDR Genes Mutations

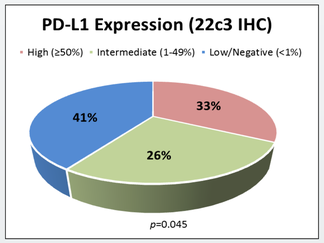




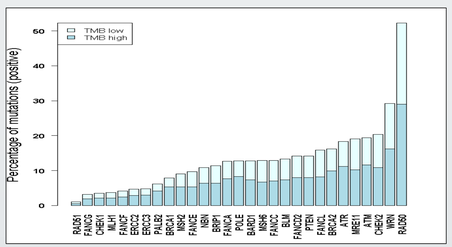
- No difference in the frequency and distribution based on age (<50y vs ≥50y) and gender (M vs F)

TMB and PD-L1 Distribution among DDR Mutated NSCLC

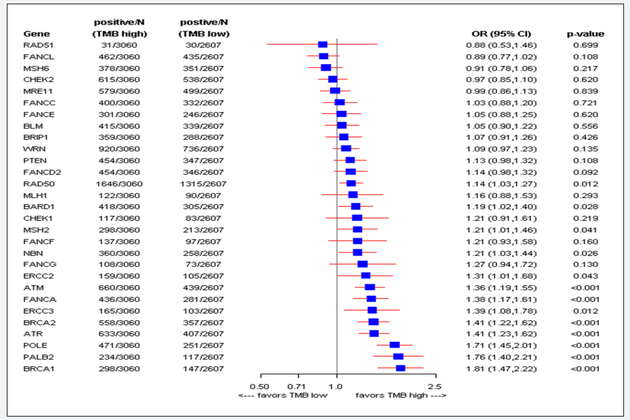




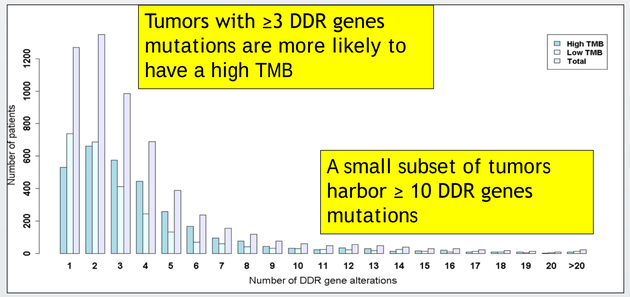
Distribution of TMB based on Gene Mutation



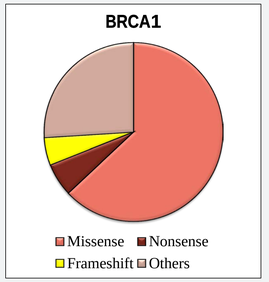
ASSOCIATION OF MUTATION WITH HIGH TMB

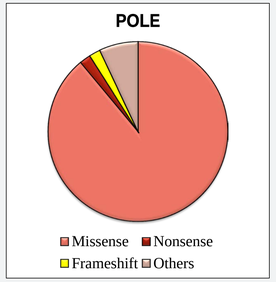


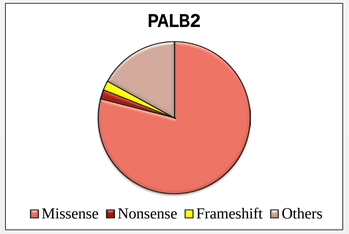
DDR GENES MUTATIONS ARE NOT MUTUALLY EXCLUSIVE



Missense Mutations are the Most Common







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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