Genomic Landscape and Immune Phenotype of Malignant Pleural Mesothelioma

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BACKGROUND

- Malignant pleural mesothelioma (MPM) is a relatively uncommon malignancy with poor prognosis and no major therapeutic breakthroughs over the past decade.
- Better understanding of the genomic landscape and distribution of immune biomarkers in this disease has the potential to enable development of novel therapies.

STUDY OBJECTIVES

- Investigate the genomic landscape of MPM.
- Analyze the differences of TMB and PD-L1 expression in MPM.
- Assess the differences in genomic alterations and TMB/PD-L1 in the context of age, gender, and molecular pathway alterations.

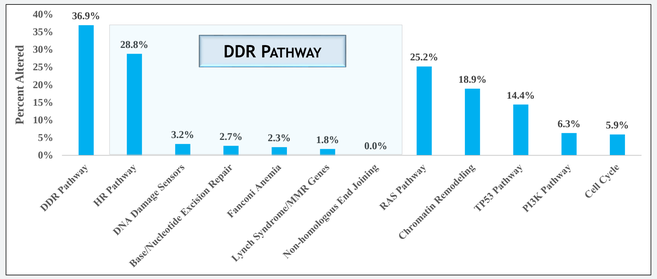
METHODS

- We retrospectively analyzed molecular profiles of MPM tumors (N=222) submitted to Caris Life Sciences.
- Profiling included next-generation sequencing (NGS) of 592 genes, Tumor Mutational Burden (TMB), and PD-L1 expression by immunohistochemistry using SP142 antibody.
- Analyzed pathways:
  - DNA damage response and repair (DDR): *ATM, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CDK12, CHEK1/2, ERCC1/2/3/4/5, FANCA/C/D2/E/F/G/L, MLH1, MRE11, MSH2/6, MUTYH, NBN, PALB2, PMS2, POLE, PRKDC, RAD50/51B, WRN, XPA, XPC*
  - Cell cycle regulation: *CCND1/2/3, CCNE1, CDKN2A, CDK4/6, CDKN1B/2A, MAX, MYC, RB1*
  - Chromatin remodeling (CR): *ARID1A/2, ASXL1, BCL11A/B, BCL7A, BRD3/4, DNMT3A, EP300, EZH2, KDM5A/5C/6A, KMT2A/C/D, NSD1/2/3, PBRM1, SETD2, SMARCB1/A4, SS18, SS18L1*
  - RAS/MAPK: ARAF, BRAF, CRKL, H/K/*NRAS, MAP2K1/2/4, MAP3K1, NF1/2, RAF1*
  - PI3K/AKT: *AKT1/2/3, MTOR, PIK3CA/G, PIK3R1/2, PTEN, RICTOR, TSC1/2, ZNF703*
  - *TP53 Pathway: MDM2, PRDM1, TP53*
- Available clinical information: Age and gender

RESULTS

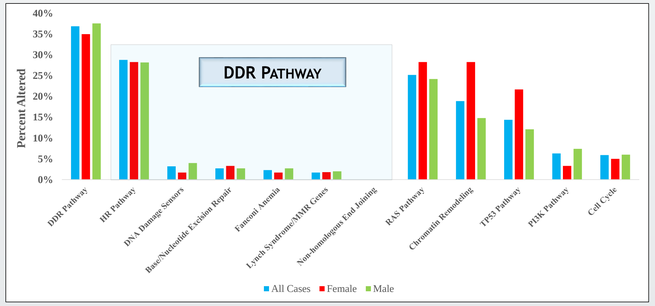
- Median age – 72 years (range, 37-90) • 73% men, 27% women

Gene Alterations by Pathway



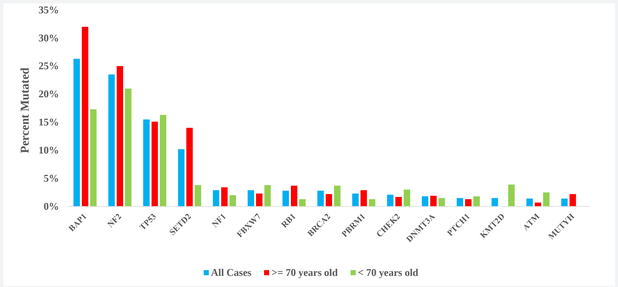
81% of cases had at least one pathway alteration. DDR, especially homologous recombination (HR), was the most commonly mutated pathway.

Pathway Alterations by Gender



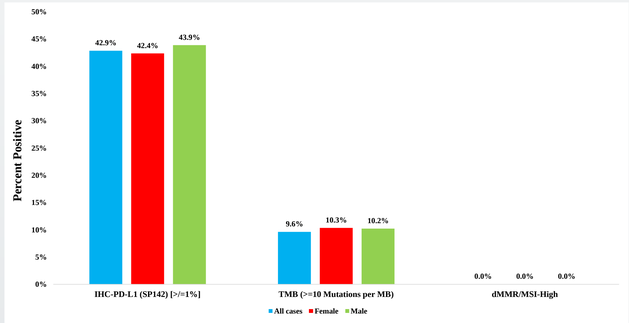
No statistically significant differences were found, except for CR pathway being more commonly mutated in women (p=0.02)

PATHOGENIC AND PRESUMED PATHOGENIC MUTATIONS BY AGE



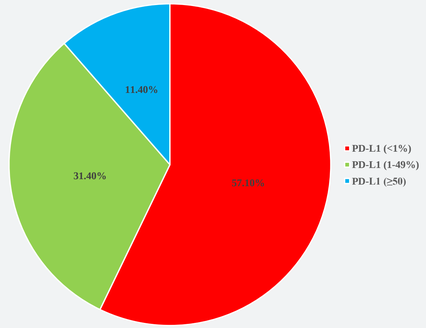
Genes mutated in ≥5% of cases included *BAP1* (26.3%), *NF2* (23.5%), *TP53* (15.5%), *SETD2* (10.2%). HR gene *BAP1* and CR gene *SETD2* mutations trended to be more prevalent in pts ≥70 yo (p=0.02).

PD-L1, TMB, and MSI



TMB was high (>10 mutations/Mb) in 9.6% of tumors (n=20). None of the tumors were Mismatch Repair Deficient/Microsatellite Instability-High (dMMR/MSI-H).

Distribution of PD-L1 Expression (SP142 IHC)



No statistically significant difference in PD-L1 expression among different pathways

CONCLUSION

- The majority of MPM tumors harbor alteration in one of the key cellular pathways.
- HR pathway mutations are the most common.
- The majority of tumors were PD-L1 negative and carry low TMB indicating low immunogenicity. No age and gender specific differences exist except for *BAP1* and *SETD2* mutations.

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