Abstract 5053: Characterization and Impact of Canonical Wnt Signaling Pathway (WSP) Alterations on Outcomes of Metastatic Prostate Cancer

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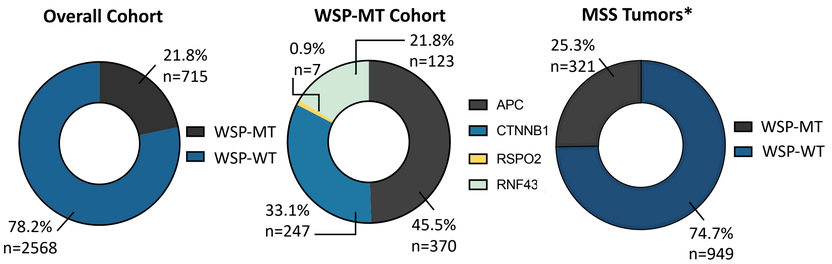
Background

- The Wnt signaling pathway (WSP), which is comprised of the canonical (β-catenin dependent) and non-canonical pathways, is an evolutionarily conserved pathway that plays a key role in regulating multiple cellular events during embryonic development and normal adult tissue homeostasis.
- Wnt signaling is frequently alerted in many cancers, including prostate cancer, and has been associated with tumorigenesis, progression, and metastasis.
- In addition to mediating downstream effector cascades that promote cancer growth and metastatic spread, the WSP has also been shown to cooperate with other cell signaling pathways, including the AR pathway, to mediate prostate cancer progression and transition to castration resistance.
- We utilized a multi-institutional real-world dataset to characterize molecular alterations in the canonical WSP in men with prostate cancer, and correlate alteration status with overall survival (OS).

Study Design

- Prostate cancer patients who underwent tissue-based DNA and RNA sequencing utilizing a commercially available CLIA-certified assay (Caris Life Sciences) were investigated.
- Next generation sequencing (NGS)/whole exome (WES) and transcriptome sequencing (WTS) was performed on prostate cancer tissue derived from prostatic and/or metastatic sites.
- Patients with somatic activating mutations in *CTNNB*, pathogenic fusions in *RSPO2*, or inactivating mutations in *APC* or *RNF43* were characterized as having aberrant canonical Wnt signaling (WSP-MT).
- Patients with microsatellite stable (MSS) tumors with somatic activating mutations in *CTNNB*, pathogenic fusions in *RSPO2*, or inactivating mutations in *APC* or *RNF43* (excluding tumors with a *RNF43* (G659fs*) mutation) were classified as having aberrant canonical Wnt signaling (WSP-MT).
- Subset analyses were conducted in metastatic prostate cancer samples with microsatellite stable (MSS) tumors excluding *RNF43* (G659fs*) mutations as WSP-MT.
- Comparative analyses were done using Fisher-Exact or X2 tests, and significance was determined by adjusted p value using Benjamini-Hochberg correction (q<0.05).
- OS was obtained from insurance claims data and calculated using Kaplan-Meier estimates. Enriched mRNA transcripts were identified as those with an adjusted p value <0.001, logFC >1.5, and (-)log10 FDR >20.



*WSP-MT tumors had a greater frequency of dMMR/MSI-H status (18% versus 2%, q <0.001), therefore analysis conducted in MSS tumors excluding *RNF43* (G659fs*) mutations as WSP-MT.

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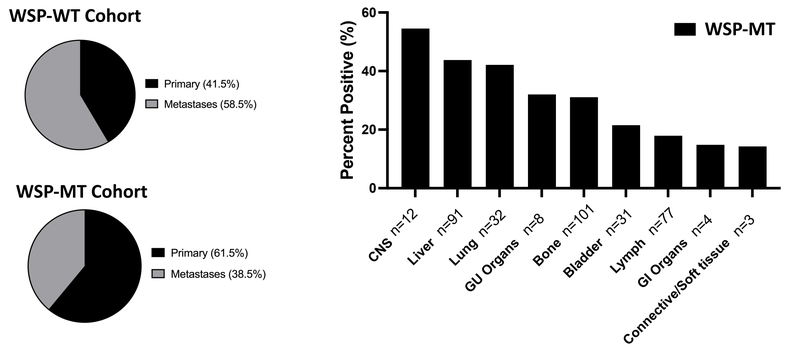
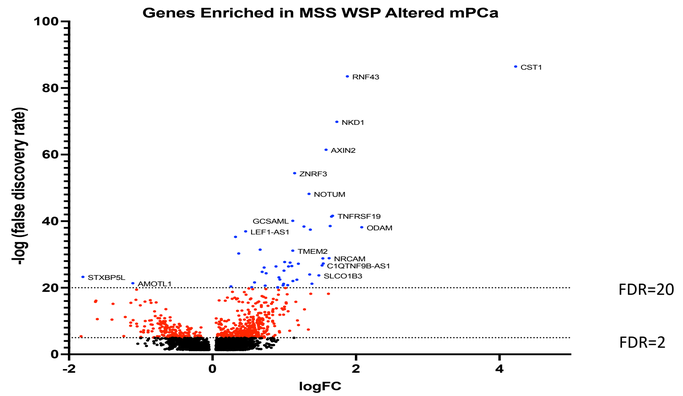
- Canonical WSP alterations are enriched in metastatic vs. primary tumors, with highest prevalence in visceral (CNS, liver, lung) metastases
- WSP alterations co-occur with *SPOP* mutations and are depleted for *RB1* alterations
- Clinical outcomes in WSP-mutant cancers are worse with both hormonal and chemotherapies; thus novel therapeutics are urgently needed for such patients.

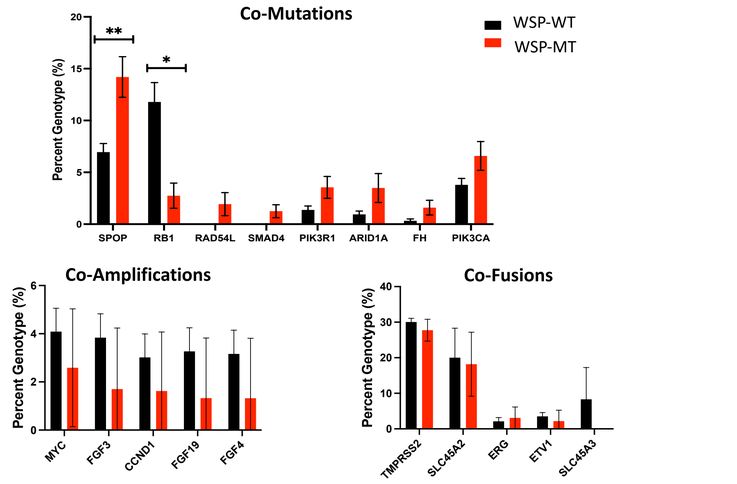
Distribution of WSP-MT by Site of Metastasis



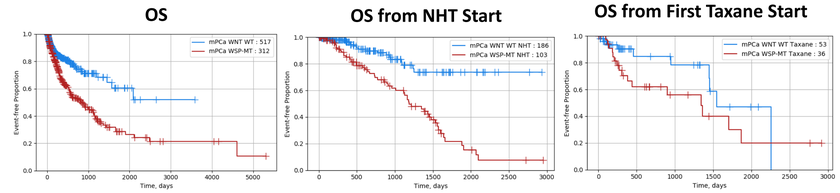
Transcripts Enriched in MSS WSP-MT Tumors



Co-Occurring Alterations in MSS WSP-MT Tumors



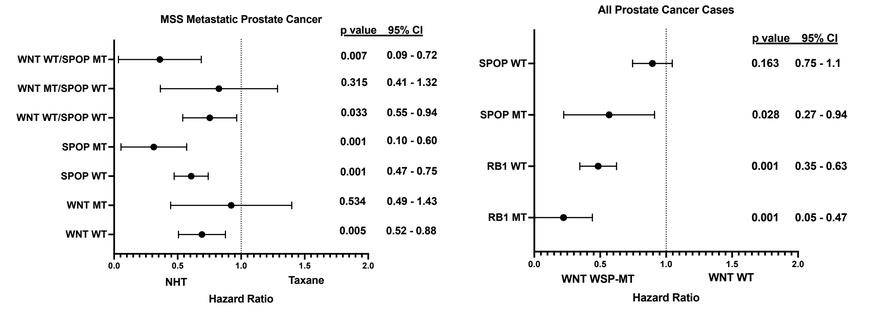
Association with Overall Survival



Median OS WSP-MT 839 days
Median OS WSP-WT not reached
HR 0.49, 95% CI 0.37-0.65, p<0.0001

Median OS WSP-MT 1186 days
Median OS WSP-WT not reached
HR 0.25, 95% CI 0.15-0.44, p<0.0001

Median OS WSP-MT 1343 days
Median OS WSP-WT 1548 days
HR 0.50, 95% CI 0.22-1.16 p=0.085



[96]:
```
df_info.loc[wnt_dict['WNT WT'],'Met Site'].value_counts()
```

[96]:
```
Prostate                1612
Lymph                    361
Bone                     232
Bladder                  120
Liver                    116
Other                     71
Lung                      46
GI organs                 27
GU organs                 19
Connective/Soft Tissue    19
Brain                     10
Name: Met Site, dtype: int64
```

[97]:
```
df_info.loc[wnt_dict['WNT Mut'],'Met Site'].value_counts()
```

[97]:
```
Prostate                264
Bone                    101
Liver                    92
Lymph                    77
Lung                     32
Bladder                  31
Other                    27
Brain                    12
GU organs                 8
GI organs                 4
Connective/Soft Tissue    3
Name: Met Site, dtype: int64
```