Abstract #537280:

Association of *FBXW7* mutation with prolonged survival in microsatellite instability-high colorectal cancer treated with immune checkpoint blockade

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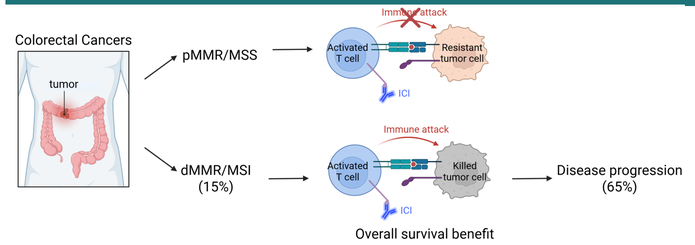
Background



- Biomarkers for ICI efficacy in microsatellite instability-high (MSI-H) colorectal cancer (CRC) are not well defined
- Co-occurring genomic alterations may impact prognosis after immune checkpoint inhibitor (ICI) treatment
- *FBXW7* targets proteins for degradation by ubiquitin ligases
- Mutations (MT) in *FBXW7* are prevalent in CRC and are associated with shorter survival

Research Goal: To identify candidate biomarkers of improved survival in MSI-H CRC treated with ICI

Methods

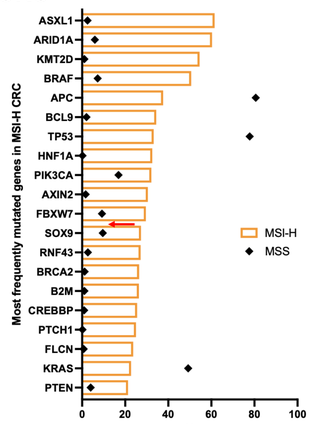
- A total of 29,446 CRC (MSS, n = 27,323; MSI-H, n = 2,123) samples were tested by next generation sequencing (592, NextSeq; WES, NovaSeq) and WTS (NovaSeq; Caris Life Sciences, Phoenix, AZ).
- Microsatellite instability or mismatch repair (MSI/MMR) status was determined by immunohistochemistry (IHC).
- Immune cell proportions were estimated using WTS deconvolution (xCell).
- PD-L1 positivity was determined by IHC of PD-L1 clone SP142 [clone Roche (Ventana)].
- Real-world median overall survival (mOS) data were derived from insurance claims, calculated from ICI (Nivolumab, Pembrolizumab) initiation to last contact, and analyzed using Kaplan-Meier.
- Statistical significance was assessed by chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q < 0.05$).

Conclusions:

- **First report of a positive association with *FBXW7* mutation and overall survival in MSI-H CRC treated with PD1/PD-L1 blockade, irrespective of PD-L1 and KRAS expression**
- **Confirmation of mutant *FBXW7* as a predictive biomarker of response to ICI requires validation in independent cohorts**

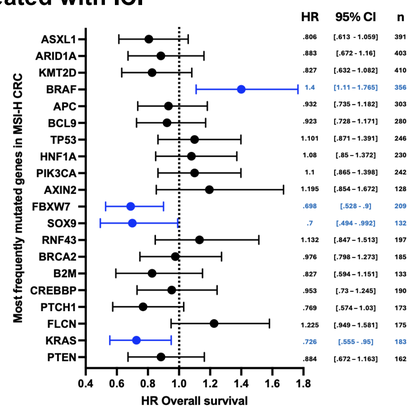
Results

Fig 1. Top 20 mutated genes in MSI-H and MSS CRC



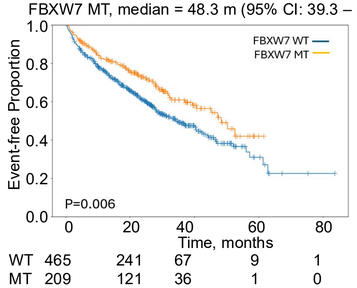
FBXW7 is one of the 11th most frequent mutations in MSI-H CRC (29.6% (n=608) vs 9.24% (n=3,025, p<0.05) compared to MSS CRC.

Fig 2. Association of the frequently mutated genes with OS in MSI-H CRC treated with ICI



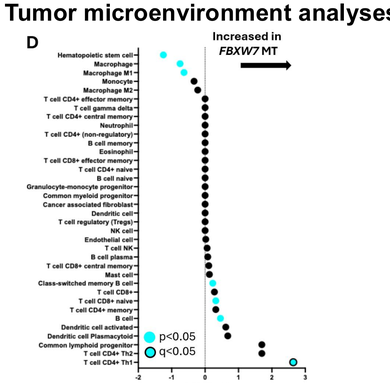
BRAF MT were associated with shorter OS (HR=1.4). Mutations in *FBXW7* (HR=0.7), *SOX9* (HR=0.7) and *KRAS* (HR=0.7) were associated with improved OS, all p<0.05

Fig 3. *FBXW7* MT with ICI had improved survival in MSI-H CRC



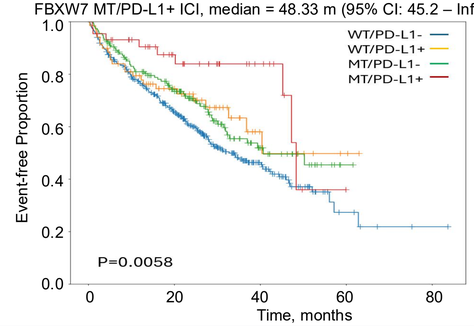
mOS improved in with *FBXW7* MT (48.3 m vs 34.2 m, HR 1.4) compared to wildtype when treated with ICI.

Fig 4. Tumor microenvironment analyses



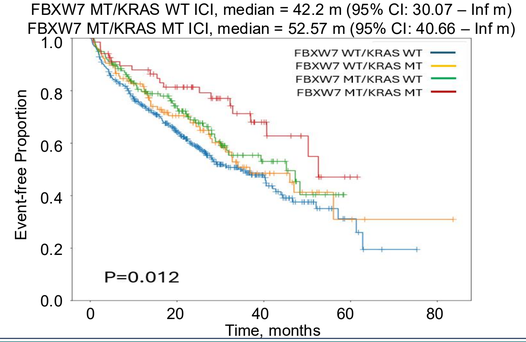
FBXW7 MT had a significantly higher proportion of CD4+ Th1 T-cells, as well as increased B-cells, CD8+ naïve T-cells, and class-switched memory B-cells compared to *WT*

Fig 5. mOS *FBXW7* MT and WT with ICI stratified by PD-L1 status



Median OS was 32.7 months in *FBXW7* WT and PD-L1- cases, 40.4 months in *FBXW7* WT and PD-L1+, 40.7 months in *FBXW7* MT and PD-L1-, and 48.3 months in *FBXW7* WT and PD-L1+. Overall *FBXW7* MT with PD-L1 positivity had higher mOS with ICI.

Fig 6. *FBXW7/KRAS* double MT with ICI had improved mOS



Median OS in *FBXW7* WT and *KRAS* WT MSI-H CRC treated with ICI was 35.0 months and 36.8 months in *FBXW7* WT and *KRAS* mutant. In contrast median OS was 45.2 months in *FBXW7* mutant and *KRAS* WT and 52.6 months in double mutants.

Acknowledgements

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