Characterizing the landscape of RING-type E3 ubiquitin transferase-altered (RNF43mut) colorectal cancer (CRC) and defining unique subsets with potential therapeutic vulnerabilities in microsatellite instability-high (MSI-H) CRC

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INTRODUCTION

RNF43 is a tumor suppressor gene that regulates the WNT/β-catenin pathway. RNF43mut commonly present and associated with MSI-H CRC. The identification of unique subsets with potential therapeutic vulnerabilities in MSI-H CRC patients may provide therapeutic strategies for RNF43mut CRC. We evaluated whether genomic and transcriptomic analysis of MSI-H RNF43mut CRC defines distinct subsets with potential therapeutic vulnerabilities.

METHODS

We used Adenocarcinoma CRC Patients (N=11,224) for this study. Inclusion Criteria: Adenocarcinoma CRC tumors of any stage and subtype. The Geneset Variation Analysis (GSVA) was used for overall survival estimation using the Kaplan-Meier method. We compared MSI-H/MMR-D and MSI-H/MMR-D (N=633). Even amongst MSI-H/MMR-D RNF43 WT tumors, MSI-H/MMR-D RNF43 WT was identified in patients with lower median TMB compared to RNF43mut (31 vs 40, respectively).

SUMMARY

- RNF43mut are common in MSI-H CRC and associated with potentially actionable genomic and transcriptomic signatures.
- Functional characterization using proteomics and transcriptomics to better understand the interplay between the WNT signaling and therapeutically relevant pathways (PI3K/AKT, BRAF/MAPK, IGF1R, cetuximab benefit) across MSI-H RNF43mut CRC is ongoing.

RESULTS

Important Notes:
- RNF43mut were significantly older than RNF43 WT at diagnosis (median 70 vs. 59, p<0.001), more likely to be female (56% vs. 44%, p<0.001).
- Prevalence of RNF43mut in the two cohorts analyzed: Overall: 538/11,224 (4.8%), 95% CI: 4.4%-5.2%. MSI-H/MMR-D: 333/653 (51%), 95% CI: 47%-50%
- RNF43mut (N=333) with known seldness.
- Differential Somatic Analysis
- Overall Survival
- Difference in Biomarker
- Retrospective Review
- Molecular Profiling
- Adenocarcinoma CRC Patients (N=11,224)

Figure 1 – Distribution of patients (N=11,224) with known seldness harboring RNF43 WT or RNF43 mutations. More patients with RNF43 mutations were diagnosed with transverse colon and right sided CRC. Note - Construction of this figure only considers those who have one of these seldness (left, right, transverse).

Figure 2 – Comparisons of TMB, % patients TMB-H, % patients PDL-1 positive and % patients MMR-D/MSI-H between RNF43 WT and RNF43mut groups (N=11,224). RNF43 WT exhibited significantly lower median TMB compared to RNF43mut (3 vs 30). Analogously, RNF43 WT exhibited significantly decreased TMB-H (4% vs. 63.6%), PDL-1 positive (4.2% vs. 13.3%), and MMR-D/MSI-H (3.1% vs. 61.9%).

Figure 3 – Amongst MSI-H/MMR-D RNF43mut, RNF43mut hotspots (N=653).

Figure 4 – Amongst MSI-H/MMR-D (N=653), comparisons of co-occurring gene alterations between RNF43 WT and RNF43mut genes were made. The top 5 most frequently altered genes in RNF43 mut are shown (all significant after false adjustment).

Figure 5 – MSI CRC KM curve comparing RNF43mut and WT

Figure 6 – Comparison of TMB between RNF43 WT and RNF43mut groups, amongst patients with MSI-H and/or MMR-D (MSI-H/MMR-D; N=653). Even amongst MSI-H/MMR-D, RNF43 WT exhibited significantly lower median TMB compared to RNF43mut (31 vs 40, respectively).

Figure 7 – Gene Set Variation Analysis (GSVA) was applied to gene expression data to derive single-sample pathway enrichment scores. Differential expression of enrichment scores was performed.