Abstract 3134

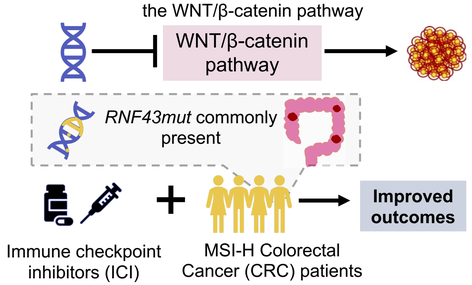
Characterizing the landscape of RING-type E3 ubiquitin transferase-altered (*RNF43mut*) colorectal cancer (CRC) and defining unique subsets with potential therapeutic vulnerabilities in microsatellite instability-high (MSI-H) CRC

Abdul Rafeh Naqash[1], Amin Nassar[2], Lisa Macera[3], Elizabeth Mauer[3], Justin Guinney[3], Calvin Chao[3], Elio Adlib[4], Emanuel Petricoin[5], Arjun Mittra[6], Naoko Takebe[7], Timothy Cannon[8]

[1]Oklahoma University Stephenson Cancer Center, Oklahoma City, OK, [2]Yale School of Medicine, New haven, CT, [3]Tempus Labs, Inc., Chicago, IL, [4]Brigham and Women's Hospital, Boston, MA, [5]George Mason University, Fairfax, VA, [6]The James Ohio State University Comprehensive Cancer Center, Columbus, OH, [7]NCI-Developmental Therapeutics, Bethesda, MD, [8]Inova/ UVA, Falls Church, VA.

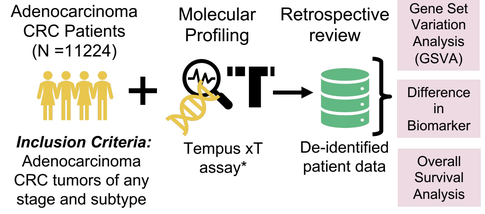
INTRODUCTION

RNF43 is a tumor suppressor gene that represses the WNT/β-catenin pathway



We evaluated whether genomic and transcriptomic analysis of MSI-H *RNF43mut* CRC defines distinct subsets with potential therapeutic vulnerabilities

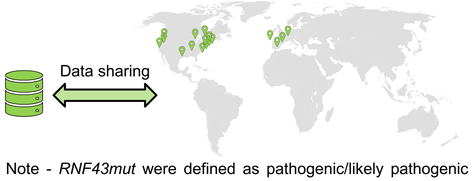
METHODS



Inclusion Criteria: Adenocarcinoma CRC tumors of any stage and subtype

ICI-treated MSI-H CRC from the MSKCC cohort (n=74), publicly available in AACR GENIE v13 was used for overall survival estimation using the Kaplan-Meier method.

AACR GENIE v13 – Cancer registry of real-world clinico-genomic data from 19 international centers



Note - *RNF43mut* were defined as pathogenic/likely pathogenic somatic mutations

*Tempus xT assay - DNA-seq of 648 genes at 500x coverage, full transcriptome RNA-seq

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Correspondence: AbdulRafeh-Naqash@ouhsc.edu

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<0001), more likely be to female (56% vs. 43%, 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%-55%

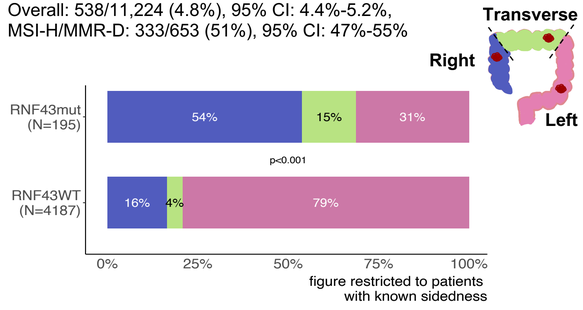

Figure 1 – Distribution of patients (N=11,224) with known sidedness harboring *RNF43* WT or *RNF43* mutations. More patients with *RNF43* mutations were diagnosed with transverse colon and right sided CRC. Note - Construction of this figure **only** considers those who have one of these sidedness (left,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

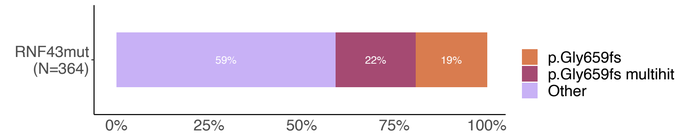

Figure 3 – Amongst MSI-H/MMR-D *RNF43mut*, *RNF43mut* hotspots (N=653)

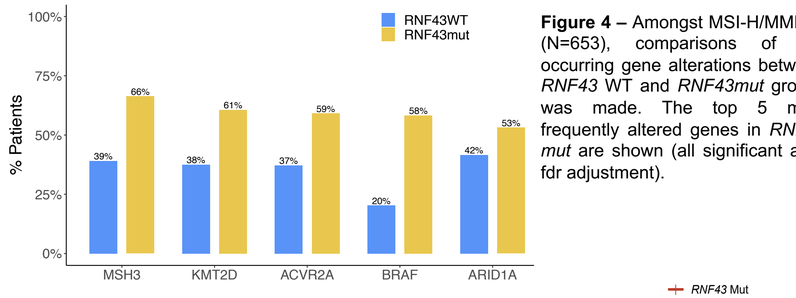

Figure 4 – Amongst MSI-H/MMR-D (N=653), comparisons of co-occurring gene alterations between *RNF43* WT and *RNF43mut* groups was made. The top 5 most frequently altered genes in *RNF43 mut* are shown (all significant after fdr adjustment).

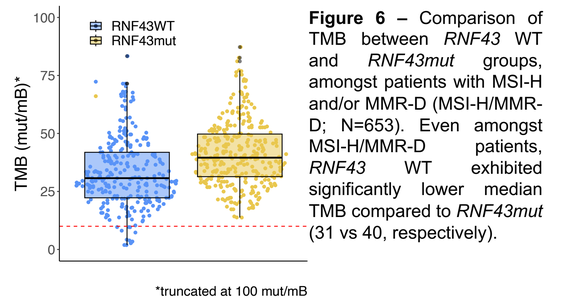

Figure 6 – Comparison of TMB between *RNF43* WT and *RNF43mut* groups, amongst patients with MSI-H and/or MMR-D (MSI-H/MMR-D; N=653). Even amongst MSI-H/MMR-D patients, *RNF43* WT exhibited significantly lower median TMB compared to *RNF43mut* (31 vs 40, respectively).

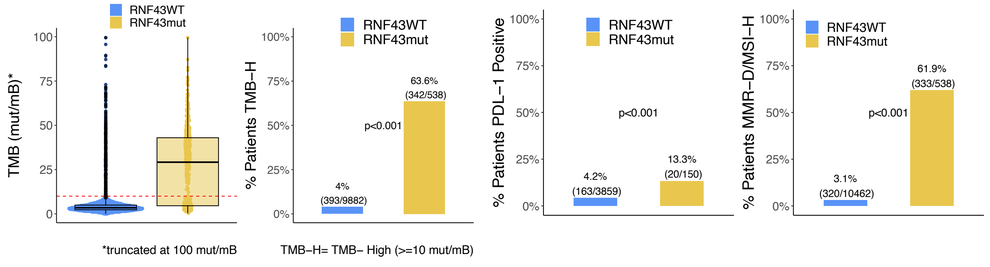

Figure 2 – Comparisons of TMB, % patients TMB-H, % patients PDL-1 positive and % patients MMR-D/MSI-H between *RNF43* WT and *RNF43mut* groups (N=11,224). *RNF43* WT exhibited significantly lower median TMB compared to *RNF43 mut* (3 vs 30, respectively). Analogously, *RNF43* WT exhibited significantly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

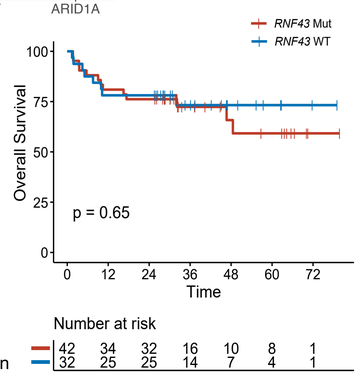

Figure 5 – MSI CRC KM curve comparing *RNF43mut* and WT

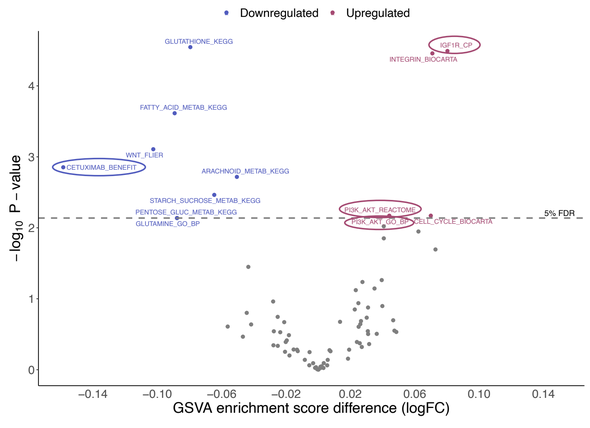

Figure 7 – Gene Set Variation Analysis (GSVA) was applied to gene expression data to derive single-sample pathway enrichment scores. Differential expression of enrichment scores was performed.