Clinical genomic profiling of colorectal cancer by real world data mining

Abstract No 2120

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INTRODUCTION

Activation of the MAPK-signaling by *RAS* - (*KRAS* or *NRAS*) alterations is an important driver event in colorectal cancer (CRC) tumorigenesis that determines treatment selection (1). Real-world data (RWD) mining is an important tool to inform patient selection and stratification (2,3). Here, RWD genomics data mining was conducted using the Foundation Medicine database to explore *RAS* and *BRAF*-alterations in CRC patients and to investigate the general alteration landscape - including rare alterations. The prevalence of microsatellite instability (MSI) and tumor mutational burden (TMB) were also explored.

METHODS

The prevalence of gene alterations and their co-occurrence with *RAS*/*BRAF*-alterations in tumor tissue of CRC patients (N=42800) were investigated using the FoundationInsights™ web platform, which includes harmonized results from the FoundationOneCDx, FoundationOneHeme, and PD-L1 assays from 2012 to March 2022. Data was collected from FMI solid and heme tests from 2012 to March 2022. Alterations that render a particular gene 'altered' included single nucleotide variants (SNVs) or insertion-deletion mutations (Indels), collectively referred to as short variants (SVs), rearrangements (RE) and copy number events (CN). TMB (cut-off 10 mut/MB) and MSI status were also characterized.

RESULTS

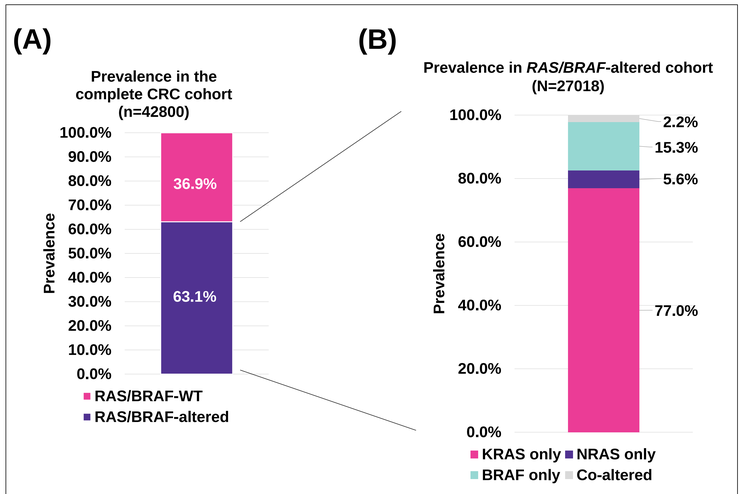

Figure 1. Prevalence and pattern of occurrence of *RAS/BRAF*-alterations in colorectal cancer (CRC)

(A) Percentage of *RAS/BRAF*-altered (SV, CN or RE) samples in the colorectal cancer (CRC) cohort. Of all CRC samples (N=42800), 36.9% were *RAS*/*BRAF*-WT and 63.1% had a known or likely functional *RAS*/*BRAF*-alteration.

(B) Percentage of *KRAS*, *NRAS* or *BRAF*-alterations and their pattern of occurrence in the *RAS/BRAF*-altered cohort (N=27018). *KRAS*, *NRAS* and *BRAF*-alterations were - as expected - mutually exclusive and co-occurring in only 2.2% of samples.

RESULTS

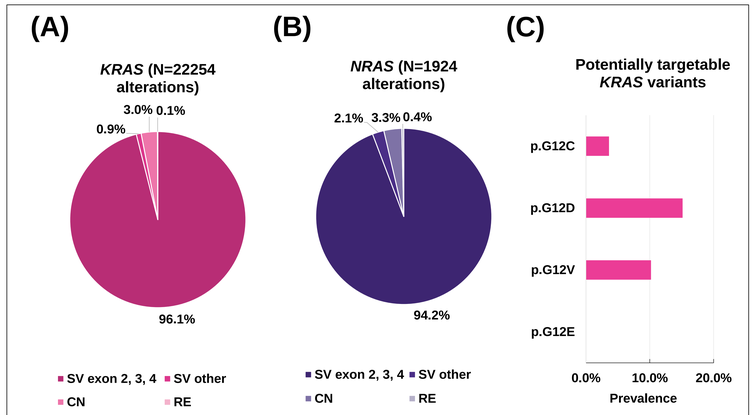

Figure 2. Classification of *KRAS*, *NRAS* and *BRAF*-alterations

(A) Percentage of short variants (SVs) in exon 2, 3 and 4, other SVs, copy number (CN) alterations and rearrangements (RE) of all *KRAS*-alterations, regardless of annotation as functional or presence in a hotspot. 96.1% of all variants are SVs in exon 2, 3 and 4, 0.9% are other SVs, 0.1% are RE events and 3.0% CN events.

(B) Percentage of SVs in exon 2, 3 and 4, other SVs, copy number (CN) events and rearrangements (RE) of all *NRAS*-alterations, regardless of annotation as functional or presence in a hotspot. 94.2% of all variants are SVs in exon 2, 3 and 4, 2.1% are other SVs, 0.4% are RE events and 3.3% CN events.

(C) Percentage of samples with the potentially targetable KRAS p.G12C, G12D, G12V and G12E variants. Relative to all samples (N=42800) the potentially targetable KRAS p.G12C, p.G12D and p.G12V variants were present in 3.6%, 15.1% and 10.2% of samples, respectively. The p.G12E variant was present in less than ten samples.

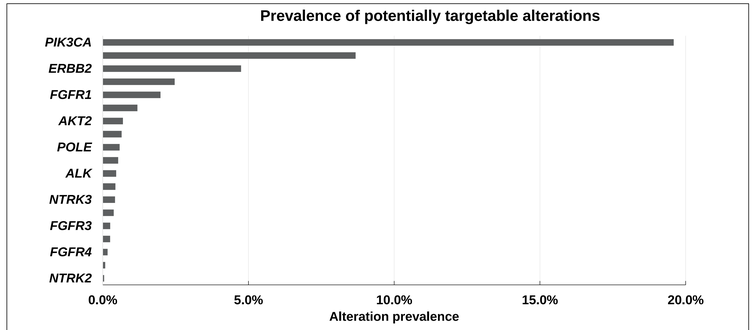

Figure 3. Quantification of potentially targetable alterations

Percentage of samples that show an alteration in a potentially targetable gene or pathway relative to all samples, sorted by prevalence. The five most frequently altered potentially targetable genes were *PIK3CA* (19.6%), *PTEN* (8.7%), *ERBB2* (4.7%), *EGFR* (2.5%) and *FGFR1* (2.0%). *NTRK*-alterations (*NTRK1/2/3*) were present in 0.9%, *ROS1*-alterations in 0.4%, *RET*-alterations in 0.6% and *ALK*-alterations in 0.5% of samples, respectively.

RESULTS

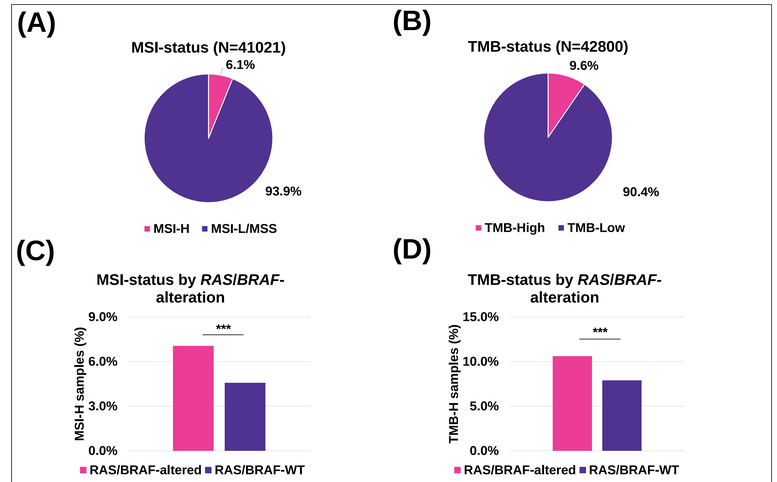

Figure 4. Quantification of immuno-oncology biomarkers

(A) Percentage of samples with high microsatellite instability (MSI-H). 6.1% of samples were MSI-H.

(B) Percentage of samples with high tumor mutational burden (TMB-H). 9.6% of samples were TMB-H (≥10 mut/MB).

(C) MSI-H samples were significantly more abundant in the *RAS/BRAF*-altered subset. In the *RAS/BRAF*-WT subset 4.6% were MSI-H, whereas in the *RAS/BRAF*-altered subset 7.1% were MSI-H. Statistical comparison was performed with Fisher´s exact test, * p<0.05, ** p< 0.01, *** p < 0.001.

(D) TMB-H samples were significantly more abundant in the *RAS*/*BRAF*-altered subset. In the *RAS*/*BRAF*-WT subset 7.9% were TMB-H, whereas in the *RAS*/*BRAF*-altered subset 10.6% were TMB-H. Statistical comparison performed with Fisher´s exact test, * p<0.05, ** p< 0.01, *** p < 0.001.

CONCLUSIONS

- **RWD based clinical genomic profiling confirms that the vast majority of *RAS*-alterations in CRC are SVs in exons 2, 3 and 4.**
- **Both TMB-H and MSI-H samples are significantly more abundant in the *RAS/BRAF*-altered cohort**
- **RWD confirms that PI3K-, ERBB- and FGFR-signaling pathways are frequently altered in CRC**
- **RWD based clinical genomic profiling has the potential to support comprehensive clinical study design as well as patient selection/stratification**

REFERENCES

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