Real-world analyses of *BRAF* alterations in patients with non-colorectal gastrointestinal cancers

Amit Mahipal[1], Zhaohui Jin[2], Emily A. Teslow[3], Ellen Jaeger[3], Melissa C. Stoppler[3], Sakti Chakrabarti[1]

[1]Department of Oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [2]Department of Oncology, Mayo Clinic, Rochester, MN; [3]Tempus Labs, Chicago, IL

ASCO Gastrointestinal Cancers Symposium

Abstract No.: 759

INTRODUCTION

- *BRAF* V600E mutations are present in 5 - 10% of patients with advanced colorectal cancer (CRC) and associated with poor prognosis.
- Recently, there was tumor agnostic FDA approval of dabrafenib + trametinib for *BRAF* V600E mutated solid tumors.
- However, the frequency of *BRAF* alterations (*BRAF*alt), especially non-V600E, in other gastrointestinal (GI) cancers are not well described.
- This study characterizes *BRAF*alt in CRC vs other GI cancers (non-CRC).

METHODS

GI Cancer Patients
N = 51,560

Molecular profiling with Tempus assays*

Study Criteria:
- Presence of pathogenic/likely pathogenic *BRAF* alterations
- DNA, RNA or ctDNA NGS sequencing

Retrospective Analysis

The frequency of *BRAF*alt, co-mutations, MSI, TMB and MMR were compared between CRC and (non-CRC) by Chi-squared/Fisher's Exact or Wilcoxon rank-sum tests. False-discovery rate correction was used for multiple testing.

*Briefly, Tempus xT is a targeted, tumor/normal-matched DNA panel that detects single-nucleotide variants (SNVs), insertions and/or deletions (indels), and copy number variants (CNVs) in 648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity. Tempus xF is a targeted liquid biopsy DNA panel that identifies SNVs and indels in 105 genes, CNVs in six genes, and chromosomal rearrangements in seven genes. Tempus xR is a whole-exome capture transcriptome RNA-seq assay for pan-cancer quantification of gene expression, assessment of alternative splicing, and detection of oncogenic fusions.

SIGNIFICANCE

- *BRAF* alterations were identified in **8.9% of CRC and 2.2% of non-CRC cohort**.
- Frequency of *BRAF* alterations varied by tumor type with the highest observed in **colon (11%), jejunum (9.6%), and intrahepatic bile duct (5.3%).**
- Among the *BRAF* alterations, **fusions** (12% vs 2.2%, p <0.001) and **amplifications** (3.1% vs 0.3%, p <0.001) were **higher in non-CRC vs CRC**. *Also, BRAF* V600E was most common in all GI tumors, but higher in CRC vs non-CRC (75% vs 27%, q<0.001).
- MSI-H (30% vs 4.%, p <0.001) and TMB-H ≥10 mut/MB (32% vs 6.7%, p <0.001) were **more frequent in *BRAF* altered CRC** vs non-CRC.

RESULTS

Table 1. Demographics of *BRAF* Mutated GI Tumors

	CRC N = 1,838[1]	Other GI N = 678[1]	p-value[2]
Gender			<0.001
Female	1,043 (57%)	308 (45%)	
Male	795 (43%)	370 (55%)	
Race			<0.001
White	924 (85%)	305 (77%)	
Black or African American	69 (6.4%)	44 (11%)	
Other	67 (6.2%)	23 (5.8%)	
Asian or Pacific Islander	24 (2.2%)	25 (6.3%)	
Unknown	754	281	
Ethnicity			0.7
Not Hispanic or Latino	571 (89%)	188 (89%)	
Hispanic or Latino	67 (11%)	24 (11%)	
Unknown	1,200	466	
Age at Diagnosis, years	67 (57, 76)	66 (58, 73)	0.029
Unknown	23	8	
Stage within 60 days of sample collection			<0.001
Stage 4	970 (76%)	347 (83%)	
Stage 3	208 (16%)	36 (8.6%)	
Stage 2	84 (6.6%)	23 (5.5%)	
Stage 1	7 (0.6%)	12 (2.9%)	
Unknown	569	260	
Initiation of *BRAF* inhibitor prior to sample collection	52 (2.8%)	11 (1.6%)	0.086
Assay			>0.9
xT	1,339 (73%)	494 (73%)	
xF	499 (27%)	184 (27%)	

[1] n (%); Median (IQR)

[2] Pearson's Chi-squared test; Wilcoxon rank sum test

Figure 1. Landscape of BRAF Alterations Types Across CRC and Non-CRC GI Tumors

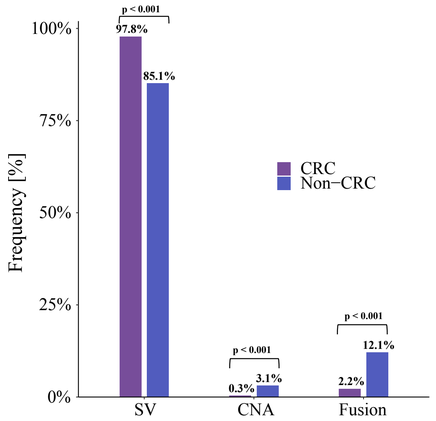


Figure 2. Frequency of Individual BRAF Alterations Across CRC and Non-CRC GI Tumors

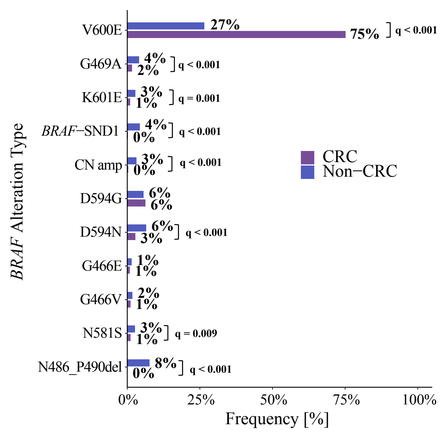


Figure 3. Landscape of BRAF Alterations Types Across Non-CRC GI Tumors

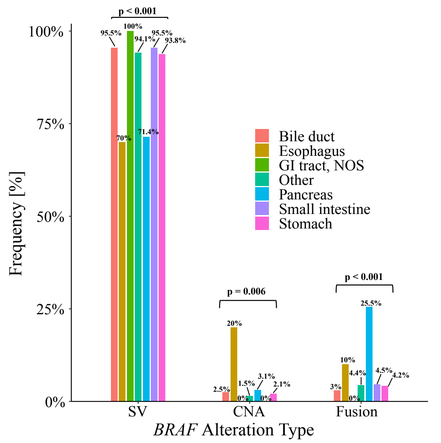


Figure 4. Frequency of MSI-H and TMB-H in BRAF altered GI Tumors (xT only)

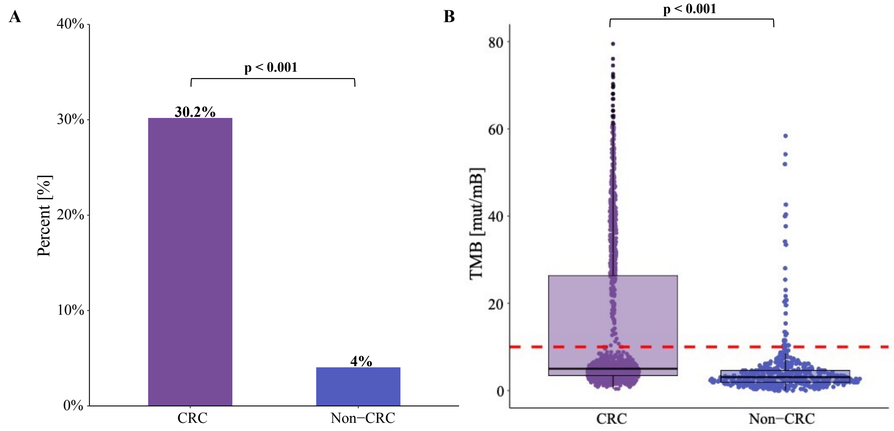
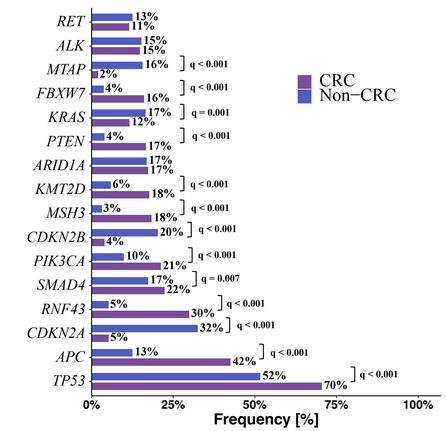


Figure 5. Most frequently co-mutated genes



ACKNOWLEDGMENTS

We thank Vanessa M. Nepomuceno, Ph.D. for poster development and review.

Correspondence: Amit.Mahipal@uhhospitals.org