Clinicogenomic landscape and outcomes of metastatic colorectal cancer patients with pathogenic *GNAS* variants

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Abstract #3572

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related mortality, with 20-25% of cases presenting with metastatic disease (mCRC). Pathogenic variants in the *GNAS* gene, which encodes the stimulatory alpha subunit of the G protein complex, are found in 1.5% to 4.8% of CRC cases and are more prevalent in mucinous adenocarcinomas. Presence of these mutations has been associated with a lower likelihood of regression following first-line (1L) systemic therapy. However, the specific impact of *GNAS* mutations on treatment outcomes and overall survival in mCRC patients remains under investigation.

METHODS

Lens Workspace (Tempus AI, Inc., Chicago, IL) was used to retrospectively analyze 5,967 de-identified records of stage IV mCRC patients treated with 1L oxaliplatin-based chemotherapy.

Samples were sequenced with the Tempus xT (648-gene panel) or xF DNA assay (105 or 523 genes depending on version) and were divided into *GNAS* wild-type (*GNAS*wt) and *GNAS*-mutated (*GNAS*mut) groups. Tumor mutational burden (TMB) and microsatellite instability (MSI) were calculated. Short variant pathogenic/likely pathogenic mutations and copy number alterations were analyzed for patients that underwent xT testing.

Real-world objective response rate (rwORR) and overall survival (rwOS) were assessed in a subset of patients with available survival data (n=5,070). rwORR was defined as the proportion of patients with a documented complete or partial response within 90 days of treatment start. rwOS was defined as the time from 1L start to death from any cause. Hazard ratio (HR) was calculated using a Cox proportional hazards model and p-values were calculated using the Wald test.

Overview of the Cohort

Characteristic	*GNAS*wt, n=5,854	*GNAS*mut, n=113	p-value[1]
Age at metastatic diagnosis, median (IQR)	59 (50, 68)	60 (50, 70)	0.2
Sex, n (%)			0.2
Male	3,359 (57%)	58 (51%)	
Female	2,495 (43%)	55 (49%)	
Race, n (%)			0.9
White	2,907 (50%)	62 (55%)	
Unknown	1,904 (33%)	36 (32%)	
Black or African American	522 (8.9%)	8 (7.1%)	
Other	352 (6.0%)	5 (4.4%)	
Asian	169 (2.9%)	2 (1.8%)	
Metastatic site, n (% of known)			
Liver	4,455 (77%)	58 (51%)	<0.001
Lung	2,141 (37%)	35 (31%)	0.2
Peritoneum	1,303 (22%)	58 (51%)	<0.001
Lymph node	1,108 (19%)	17 (15%)	0.3
Bone	291 (5.0%)	4 (3.5%)	0.5
Connective, subcutaneous, and other soft tissues	279 (4.8%)	8 (7.1%)	0.3
Ovary	251 (4.3%)	10 (8.8%)	0.032
Other	1,106 (19%)	27 (24%)	0.2
Days from oxaliplatin start to sample collection, median (IQR)	-15 (-35, 21)	-17 (-32, 5)	

[1]Fisher's exact test; Pearson's Chi-squared test.

SUMMARY

- mCRC patients with pathogenic *GNAS* variants exhibit distinct clinicogenomic features and poorer outcomes with first-line oxaliplatin-based chemotherapy compared to *GNAS*wt patients.
- These findings highlight the need for alternative treatment and further research on *GNAS* as a prognostic biomarker in mCRC.

RESULTS

Molecular characteristics by *GNAS* status

Characteristic	*GNAS*wt, n=5,854	*GNAS*mut, n=113	p-value
TMB ≥ 10, n (%)	327 (6.7%)	19 (20%)	<0.001
MSI, n (%)			<0.001
Stable	4,805 (98%)	81 (84%)	
High	95 (1.9%)	14 (15%)	
Equivocal	2 (<0.1%)	1 (1.0%)	
MMR, n (%)			<0.001
Not Deficient	1,753 (98%)	28 (82%)	
Deficient	39 (2.2%)	6 (18%)	

Table 2. Immunophenotype markers such as high TMB and high MSI were more often observed in the *GNAS*wt patients compared to *GNAS*mut patients (p<0.001). Percentages were calculated from total patients with known statuses.

Mutational landscape by *GNAS* status in patients with solid-tumor sequencing

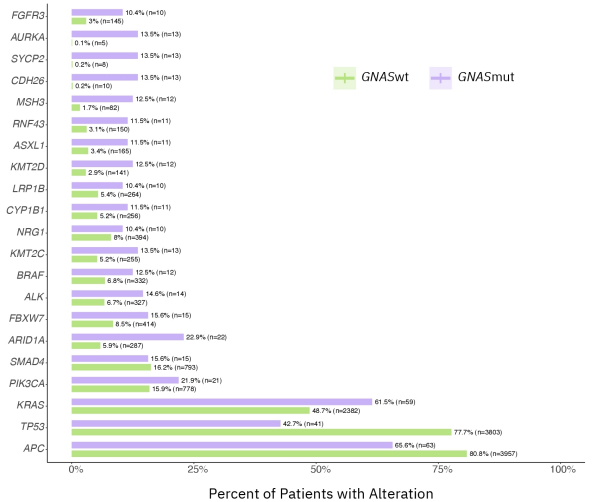
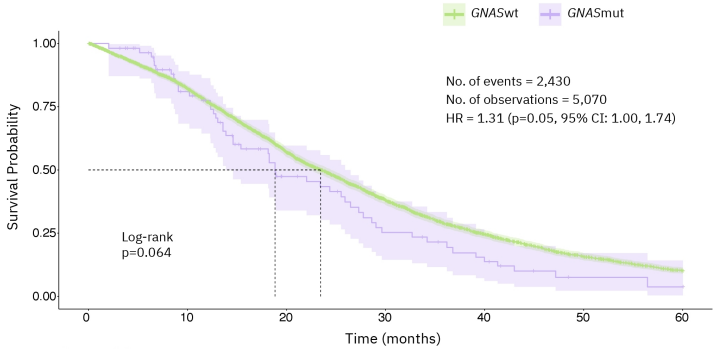


Figure 1. *KRAS*, *ARID1A*, *MSH2/3/6*, and *ATR* were more frequently altered in the *GNAS*mut group, while *TP53* and *APC* mutations were more frequent in the *GNAS*wt group.

rwOS by *GNAS* status



Number at Risk

GNASwt	1249	2403	1566	981	587	354	195
GNASalt	52	47	25	14	8	2	2

Cumulative Number of Events

GNASwt	0	510	1224	1727	2060	2263	2378
GNASalt	0	11	30	41	47	50	51

Figure 2. *GNAS*mut patients had reduced rwOS compared to *GNAS*wt patients (HR=1.31, p=0.05).

rwORR by *GNAS* status

Characteristic	GNASwt, n=4,983	GNASmut, n=87	p-value
Objective Response at 90 Days			0.009
Responder	1,021 (66%)	15 (44%)	
Non-Responder	534 (34%)	19 (56%)	
Objective Response at 180 Days			0.002
Responder	1,672 (66%)	23 (45%)	
Non-Responder	870 (34%)	28 (55%)	
Objective Response at 365 Days			0.009
Responder	1,906 (60%)	25 (43%)	
Non-Responder	1,265 (40%)	33 (57%)	

Table 3. rwORR at 90 days was significantly lower in *GNAS*mut patients compared to *GNAS*wt (44% vs. 66%, p=0.002). Percentages were calculated from total patients with known rwORR. rwORR was consistently different at 180 and 365 days as well (data not shown).

ACKNOWLEDGMENTS
We thank Matthew Kase for poster development.