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Characterization of Sub-Clonal RAS/BRAF Alterations in an Anti-EGFR Treated Advanced CRC Cohort using a Liquid Biopsy-Based Real World Clinical Genomics Database

Khalid Abubaker[1¶], Danyi Wang [2¶], Zheng Feng [2¶], Christopher Stroh[1], Jiemin Liao[3], Gordon Otto[1], Juergen Scheuenpflug[1#]

[1]Global Clinical Biomarkers and Companion Diagnostics, Translational Medicine, Global Development, Merck Healthcare KGaA, Darmstadt, Germany;

[2]Clinical Genomics, Global Clinical Biomarkers & Companion Diagnostics , Translational Medicine | Biometrics & Precision Medicine , EMD Serono , A business of Merck KGaA, Darmstadt, Germany; [3]Guardant Health, Redwood City, CA, US

¶ Co-First Author # Corresponding author

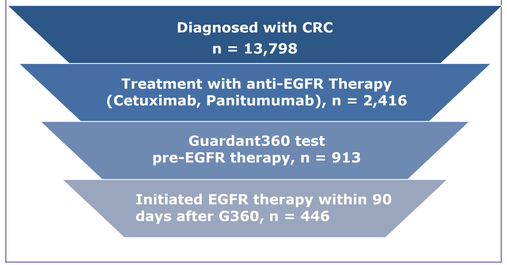
INTRODUCTION

- Anti-EGFR monoclonal antibodies are treatment options for RAS and BRAF V600 mutation-negative CRC patients.
- However, the literature suggests that CRC patients with sub-clonal RAS and BRAF mutations may still benefit from anti-EGFR therapies.
- Distinguishing between acquired/sub-clonal and clonal RAS/BRAF is critical for predicting the efficacy of anti-EGFR rechallenge therapy.[1]
- The Guardant INFORM™ real-world clinical-genomic database was utilized to assess the impact of sub-clonal RAS and BRAF alterations detected in circulating tumor DNA (ctDNA) by the Guardant360® test on the clinical outcome of CRC patients treated with anti-EGFR therapy.

METHODS

- Patients were selected from the Guardant INFORM™ database using the following inclusion criteria:
  - Diagnosed with advanced CRC in the US;
  - Treated with anti-EGFR therapies starting within 90 days after a Guardant360 test result;
  - And the presence of BRAF V600E and/or canonical KRAS/NRAS mutations (codons 12, 13, 59, 61, 117, 146).
- Time to next treatment (TTNT) was assessed as proxy for progression free survival. TTNT and overall survival (OS) were compared for various RAS/BRAF mutation clonality cutoffs using log-rank tests and Cox proportional hazards models.

Figure 1. Cohort Identification of CRC patients Pre-anti-EGFR Therapy



RESULTS

- Of the 13,798 CRC patients in the Guardant INFORM database, 91% had detectable ctDNA, 913 received a Guardant360® test before anti-EGFR therapy, and 446 (48.8%) initiated anti-EGFR therapy within 90 days after the test.
- Among this cohort, 11% (n = 50) had a BRAF V600E mutation and 9% (n = 40) had a RAS mutation.
- The median RAS/BRAF clonality was 0.84 (IQR = 0.57, 1.00).
- The associated clinical outcomes for patients with sub-clonal and clonal RAS/BRAF mutations using clonality cutoffs from 0.3 to 0.8 are reported (Table).

Table 1. Hazard Ratios by Clonality Cut-Offs

RAS/BRAF Mutation Clonality* Cutoff	Sub-clonal**		Clonal**	
	HR (95% CI)	P value	HR (95% CI)	P value
TTNT				
0.3	0.96 (0.42, 2.18)	0.913	1.72 (1.15, 2.59)	0.009
0.4	1.03 (0.48, 2.21)	0.946	1.72 (1.14, 2.60)	0.010
0.5	0.97 (0.45, 2.08)	0.931	1.77 (1.17, 2.66)	0.007
0.6	1.04 (0.51, 2.13)	0.922	1.76 (1.16, 2.66)	0.008
0.7	1.03 (0.55, 1.94)	0.919	1.90 (1.23, 2.93)	0.004
0.8	1.30 (0.75, 2.24)	0.350	1.72 (1.08, 2.74)	0.022
OS				
0.3	1.72 (0.84, 3.54)	0.142	2.47 (1.61, 3.79)	<0.001
0.4	1.85 (0.93, 3.66)	0.079	2.42 (1.57, 3.74)	<0.001
0.5	1.79 (0.90, 3.54)	0.097	2.46 (1.59, 3.80)	<0.001
0.6	1.92 (1.00, 3.69)	0.050	2.40 (1.55, 3.73)	<0.001
0.7	1.83 (1.03, 3.26)	0.041	2.60 (1.63, 4.14)	<0.001
0.8	2.16 (1.29, 3.61)	0.003	2.33 (1.40, 3.86)	0.001

*Clonality = (*RAS* or *BRAF* MAF)/(maximum MAF).

**Reference group is patients without *RAS*/*BRAF* mutations.

Figure 1. Kaplan Meier Curves for TTNT Outcome by Clonality Cut-Offs

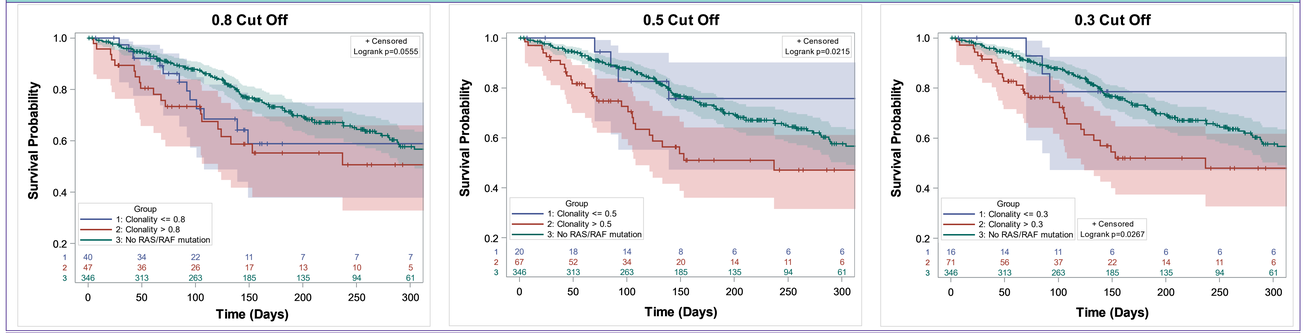
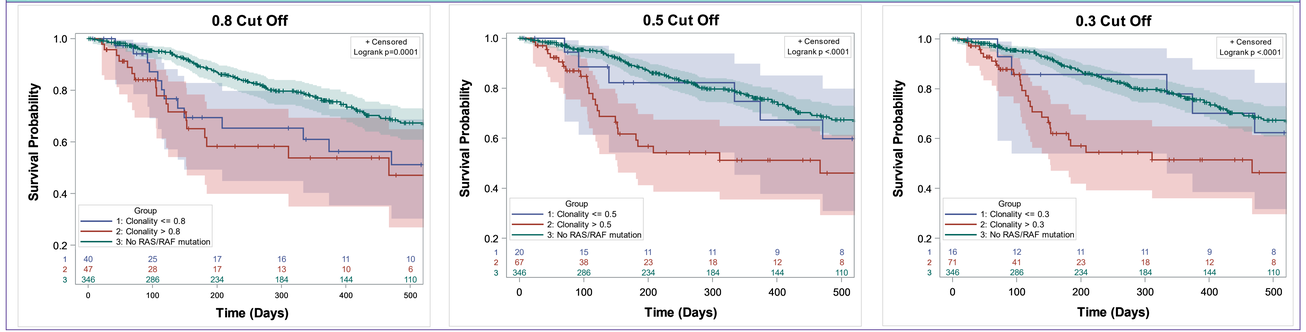


Figure 2. Kaplan Meier Curves for Overall Survival Outcome by Clonality Cut-Offs



CONCLUSIONS

- **Using a liquid biopsy-based clinical-genomic dataset, we demonstrate that patients harboring sub-clonal RAS or BRAF mutations benefit from anti-EGFR therapy to a degree similar to wild-type patients.**
- **Given the limited patient numbers, this finding warrants additional investigation into the utility of ant-EGFR therapies as a treatment option for this subgroup of CRC patients. Using 0.3 value as clonality cut off is recommended as a starting point, given additional support from clinical evidence.[2]**

REFERENCES

[1]Klein-Scory *et al*. Evolution of RAS Mutational Status in Liquid Biopsies During First-Line Chemotherapy for Metastatic Colorectal Cancer. *Front Oncol.* 2020; 10:1115.

[2]Nakamura *et al*. Clinical utility of circulating tumor DNA sequencing in advanced gastrointestinal cancer: SCRUM-Japan GI-SCREEN and GOZILA studies. *Nat Med*. 2020; 26:1859-1864.

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