Genomic landscape of *ERBB2/3* alterations in colorectal cancer: co-mutations, immuno-oncology biomarkers and consensus molecular subtypes

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INTRODUCTION

ERBB2 is a rapidly emerging therapeutic target for a subset of colorectal cancer (CRC) patients harboring oncogenic alterations in this gene.[1-3] Oncogenic *ERBB3* mutations have been reported in various cancers including CRC, but little is known about its functional impact. A growing number of studies confirmed *ERBB2* as a driver of carcinogenesis with reproducible role both as a prognostic and a predictive biomarker in CRC. Importantly, several new *ERBB2* targeting experimental arms have now been added to the ASCO TAPUR study, highlighting the need to better describe the prevalence of HER2 overexpressing tumors in GI cancers. Optimal targeting of this pathway requires better understanding of the genomic context in which somatic *ERBB2/3* alterations occur in a real-world CRC population.

METHODS

We analyzed 7,688 de-identified records from CRC patients that underwent next generation sequencing with the Tempus xT assay (DNA-seq of 648 genes at 500x coverage; full transcriptome RNA-seq). We assessed the prevalence and association of *ERBB2/3* alterations with demographics, co-occurring alterations, immuno-oncology biomarkers (microsatellite instability [MSI], tumor mutational burden [TMB], PD-L1 expression), and consensus molecular subtype (CMS, available for a subgroup with primary biopsies and RNA data [n=2,686]).

REFERENCES

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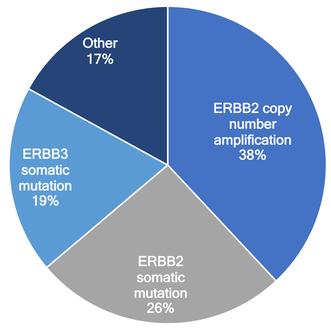
SIGNIFICANCE

ERBB2/3 mutated CRC are **more likely to be MSI-H, TMB-high and harbor *KRAS* alterations** compared with *ERBB2*-amplified or *ERBB2/3*-WT tumors. These results highlight the need for more detailed **inquiry into the relationships between *ERBB2/3* alterations and genomic alterations of other genes**—such as *BRAF, TP53, CDK12, PIK3CA*, and *TOP2A*—which may help to advance the clinical development of HER2-targeted therapies.

RESULTS

Figure 1: Types and distribution of *ERBB2 and ERBB3* genomic aberrations among 376 CRC tumors with *ERBB2/3* alterations

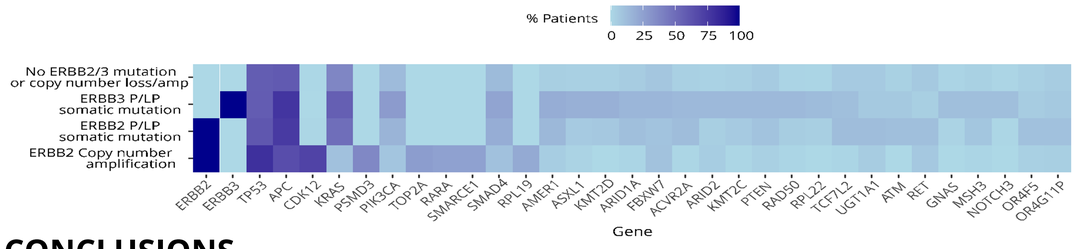


Overall, 5% (376/7688) of CRC tumors harbored an *ERBB2* or *ERBB3* alteration. Of these, 1.9% (n=143) were *ERBB2*-amplified, 1.3% (n=97) were *ERBB2*-mutated, 0.9% (n=72) were *ERBB3*-mutated, and <1% derived from other combinations (excluded from analyses). There were no significant differences in baseline demographics (age of onset, race or gender) between groups.

Table 1: Biomarkers & Co-Mutations of interest among *ERBB2/ERBB3*-altered CRC tumors

	***ERBB2* amplified (n=143)**	***ERBB2* mutated (n=97)**	***ERBB3* mutated (n=72)**	***ERBB2/3* WT (n=7,312)**	***p-value***
Biomarkers					
MSI-H	0 (0%)	12 (12%)	15 (21%)	404 (5.6%)	<0.001
TMB ≥10	4 (3.0%)	17 (18%)	20 (28%)	675 (9.4%)	<0.001
PD-L1+	4 (6.6%)	1 (3.3%)	3 (10%)	205 (7.5%)	0.8
Co-mutated genes					
TP53	115 (80%)	59 (61%)	42 (58%)	4,234 (58%)	<0.001
CDK12	101 (71%)	1 (1.0%)	0 (0%)	37 (0.5%)	<0.001
KRAS	15 (10%)	48 (49%)	41 (57%)	2,764 (38%)	<0.001
PIK3CA	12 (8.4%)	16 (16%)	20 (28%)	950 (13%)	<0.001
BRAF	1 (0.7%)	5 (5.2%)	2 (2.8%)	525 (7.2%)	0.010
TOP2A	39 (27%)	0 (0%)	0 (0%)	5 (<0.1%)	<0.001

Figure 2: Heatmap of co-mutations among *ERBB2*/ERBB3-altered CRC tumors



Selection criteria of co-mutated genes were based on 10% or more co-mutation exhibited among at least one of the four cohorts. *P = pathogenic; LP = likely pathogenic*

CMS classification by cohort did not identify significant differences; *ERBB2* alterations compared to wild-type (CMS1: 8.6% vs 13%; CMS2: 24% vs 26%; CMS3: 20% vs 17%; CMS4: 30% vs 34%; p=0.12) and *ERBB3* alterations compared to wild-type (CMS1: 24% vs 13%; CMS2: 12% vs 26%; CMS3: 16% vs 17%; CMS4: 40% vs 34%; p=0.3).

CONCLUSIONS

Consistent with previous reports, our analyses suggest that all *ERBB2*-amplified tumors are microsatellite stable. In contrast, patients with *ERBB2/3* mutations are more likely to have MSI-high and TMB-high status, compared with *ERBB2/3* wild-type tumors, suggesting a potential role for combination strategies with immunotherapy. *TP53* mutations appear to be more prevalent in *ERBB2*-amplified tumors than *ERBB2/3*-mutated or wild-type tumors. Furthermore, significant differences were observed in co-occurring gene alterations among *ERBB2/3*-altered and wild-type tumors. Further analyses including clinical outcome to HER-2 targeted therapy are required to elucidate the mechanism of resistance and to assess the clinical significance of these co-mutations.

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