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Mutational Landscape and Clinical Outcomes of BRAF-Altered Tumors in Patients with Metastatic Colorectal Cancer: A Review

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Abstract

BRAF-altered colorectal cancer is routinely described as a single poor-prognosis group, and reported as mutated or wild-type on the pathology form. Neither is accurate. The alterations fall into classes with different biochemistry, and the survival difference between them is larger than the difference between BRAF-mutant and BRAF-wild-type disease.

Objectives: *To review the published evidence on the distribution of BRAF alterations in metastatic colorectal cancer, the outcomes associated with V600E and non-V600 variants, and what targeted treatment has achieved in each group.*

Material and Methods: *Narrative review of randomised trials, trial biomarker analyses, sequencing cohorts and population-based series indexed in PubMed and the major oncology journals. Studies were eligible if they reported the prevalence or classification of BRAF alterations in colorectal cancer, outcomes stratified by BRAF variant, or the efficacy of BRAF-directed treatment. No new patient data were generated; every frequency, hazard ratio, response rate and survival estimate quoted is one published by the original investigators.*

Results: *BRAF is altered in roughly 8 to 12 per cent of metastatic colorectal cancers, and V600E accounts for the large majority of those. Non-V600 variants occur in about 2.2 per cent of cases and behave as a separate disease: median overall survival was 60.7 months against 11.4 months for V600E and 43.0 months for BRAF wild-type ($p < 0.001$), with non-V600 status independently associated with better survival (HR 0.18). Mutations at codons 594 and 596 showed the same pattern, with median survival of 62.0 against 12.6 months (HR 0.36). In previously treated V600E disease, encorafenib with cetuximab and binimetinib produced an objective response rate of 27 per cent against 2 per cent for chemotherapy with cetuximab, and median overall survival of 9.0 against 5.4 months. In the first-line setting, adding encorafenib and cetuximab to chemotherapy raised objective response from 40.0 to 60.9 per cent.*

Conclusion: *Reporting BRAF as a binary variable discards the distinction that matters most. V600E marks aggressive disease that now has an approved targeted option; non-V600 marks a group with survival measured in years for whom that option has not been shown to work. The two should be separated in reporting, in prognostic discussion and in trial eligibility.*

Abbreviations: *mCRC – Metastatic Colorectal Cancer, EGFR – Epidermal Growth Factor Receptor, MAPK – Mitogen-Activated Protein Kinase, MSI – Microsatellite Instability, MSI-H – Microsatellite Instability-High, dMMR – Deficient Mismatch Repair, MSS – Microsatellite Stable, CIMP – CpG Island Methylator Phenotype, ctDNA – Circulating Tumour DNA, ORR – Objective Response Rate, OS – Overall Survival, PFS – Progression-Free Survival, HR – Hazard Ratio, ICI – Immune Checkpoint Inhibitor.*

Keywords: *BRAF; Metastatic Colorectal Cancer; V600E; Encorafenib; Molecular Subtypes*

Introduction

BRAF encodes a serine-threonine kinase in the MAPK pathway, and activating mutations were identified across human cancers more than two decades ago [1]. In colorectal cancer the alteration has since acquired a settled reputation: uncommon, aggressive, resistant to chemotherapy, and until recently untreatable in any targeted sense.

That reputation is accurate for the variant most patients carry, and misleading for the rest. The V600E substitution produces a kinase that signals as a monomer, independently of upstream RAS, and it accounts for the great majority of BRAF alterations in this disease. But a minority of tumours carry mutations elsewhere in the gene, with different biochemistry and, as the clinical data show, very different outcomes [2,3].

The distinction has practical consequences that are easy to miss. A sequencing report that says BRAF mutation detected, without the

variant, will be read by most clinicians as indicating the poor-prognosis group. If the variant is in fact non-V600, that reading is wrong by a wide margin, and it may lead to an approved BRAF-directed regimen being offered to a patient in whom it has never been shown to work [2,4].

At the same time, the therapeutic position for V600E disease has changed materially. A randomised trial established a targeted option in previously treated patients [5], and a subsequent first-line trial has reported substantially higher response rates than chemotherapy alone [6]. The aim of this review is to set out the mutational landscape of BRAF in metastatic colorectal cancer, the outcomes reported for each group, and what treatment has achieved in each.

Material and Methods

Search strategy: PubMed and the archives of the major oncology journals were searched for studies of BRAF alterations in colorectal cancer. Search terms combined BRAF and V600E with metastatic colorectal cancer, non-V600, class II, class III, prognosis, overall survival, encorafenib, cetuximab and microsatellite instability. Reference lists of retrieved trials and reviews were screened by hand for further primary sources.

Eligibility: Studies were included if they reported the prevalence or variant-level distribution of BRAF alterations in a defined colorectal population, clinical outcomes stratified by BRAF variant or class, or the efficacy of BRAF-directed or anti-EGFR treatment in BRAF-altered disease. Randomised trials and their prespecified biomarker analyses were included preferentially. Preclinical work is cited only where it explains a clinical observation.

Data extraction and handling: Design, sample size, variant definition, assay platform and reported effect estimates with their confidence intervals were extracted as published. No pooling or re-analysis was performed and no patient-level data were obtained. Prevalence figures are reported with the population attached, since BRAF-mutant frequency differs between screened populations and referred trial cohorts. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How common the alteration is, and in whom: Reported prevalence of BRAF mutation in metastatic colorectal cancer clusters around 8 to 12 per cent, with the range across published series running wider [4,5]. A population-based reflex-testing study of 1,898 patients found an all-stage prevalence of 12.5 per cent, which did not differ significantly between early and metastatic stages, and a prevalence among metastatic cases of 10.6 per cent [7]. V600E accounts for the substantial majority of BRAF mutations in this disease [2,3].

The clinicopathological associations are consistent across cohorts. V600E disease is enriched among older patients, women, right-sided primaries, poorly differentiated and mucinous histology, and peritoneal spread; it arises through the serrated pathway and is closely associated with the CpG island methylator phenotype and with MLH1 promoter methylation, which is why a proportion of these tumours are also mismatch-repair deficient [3,8,9].

Non-V600 variants are a different disease: The most consequential single finding in this literature comes from a sequencing series in which 208 of 9,643 patients with metastatic colorectal cancer carried a non-V600 BRAF mutation, a prevalence of about 2.2 per cent. Median overall survival was 60.7 months in that group, against 11.4 months for V600E and 43.0 months for BRAF wild-type disease ($p < 0.001$) (Figure 1). On multivariable analysis, non-V600 status was independently associated with improved survival, with a hazard ratio of 0.18 ($p < 0.001$) [2].

These patients also differ clinically: younger, more often male, more often left-sided and microsatellite stable, with lower-grade tumours and less peritoneal spread than the V600E group [2,4]. An independent series confined to mutations at codons 594 and 596 reported the same direction of effect, with median overall survival of 62.0 months against 12.6 months for V600E (HR 0.36, 95% CI 0.20-0.64, $p = 0.002$); those tumours were more often rectal, non-mucinous, without peritoneal spread and uniformly microsatellite stable [10].

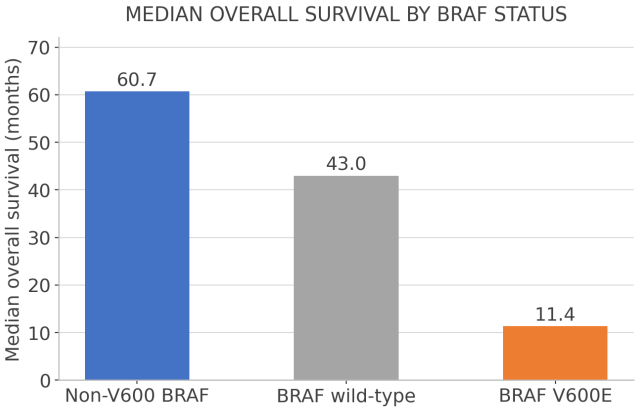

Figure 1: Median overall survival by BRAF status in metastatic colorectal cancer, from a sequencing series of 9,643 patients [2]

Study	n	Design	Principal reported finding
Jones et al. 2017 [2]	9,643	Sequencing	Non-V600 median OS 60.7 vs 11.4 months for V600E
Cremolini et al. 2015 [10]	—	Cohort	Codon 594/596 median OS 62.0 vs 12.6 months
Kopetz et al. 2019 [5]	665	Phase 3 RCT	Triplet ORR 27% vs 2%; OS 9.0 vs 5.4 months
Kopetz et al. 2025 [6]	—	Phase 3 RCT	First-line ORR 60.9% vs 40.0% for standard care
Seligmann et al. 2017 [11]	2,530	Pooled trials	Confirms poor outcomes of BRAF-mutant disease

Table 1: Principal studies reviewed, with design and the finding as reported by the original investigators

Why the classes behave differently: The biochemical account is that BRAF alterations divide by how the mutant kinase signals. V600 mutants, designated class I, are active as monomers and independent of upstream RAS. Class II mutants signal as RAS-independent dimers with intermediate to high kinase activity. Class III mutants have low intrinsic kinase activity and depend on upstream RAS input, which is why they co-occur with KRAS and NRAS mutations far more often than V600E does [2,4]. That dependency also explains why the anti-EGFR data differ between the groups, since class III signalling can be interrupted upstream in a way class I signalling cannot [12,13,14].

Targeted treatment in V600E disease: Single-agent BRAF inhibition failed in this disease. A phase II study of vemurafenib in BRAF-mutated metastatic colorectal cancer produced responses in only a small minority, in contrast with melanoma, because feedback reactivation of EGFR restores MAPK signalling [15]. Combining BRAF and EGFR blockade was the response, and it was tested in a three-arm randomised trial in previously treated V600E disease. Objective response was 27 per cent with encorafenib, binimetinib and cetuximab, 20 per cent with encorafenib and cetuximab, and 2

per cent with cetuximab plus irinotecan-based chemotherapy (Figure 2) [5].

Survival moved with response but by a smaller margin. Median overall survival in the initial analysis was 9.0 months with the triplet against 5.4 months in the control arm (HR 0.52, 95% CI 0.39-0.70). An updated analysis reported 9.3 months with the doublet against 5.9 months (HR 0.61) (Figure 3) [5]. The doublet became the approved regimen, the triplet having added toxicity without a clear survival gain over it.

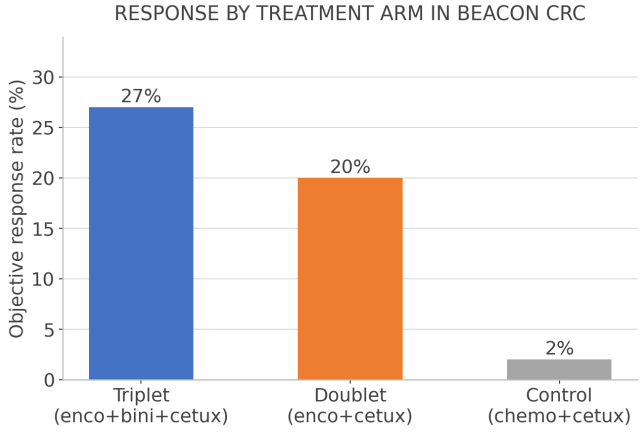

Figure 2: Objective response rate by treatment arm in previously treated BRAF V600E metastatic colorectal cancer [5]

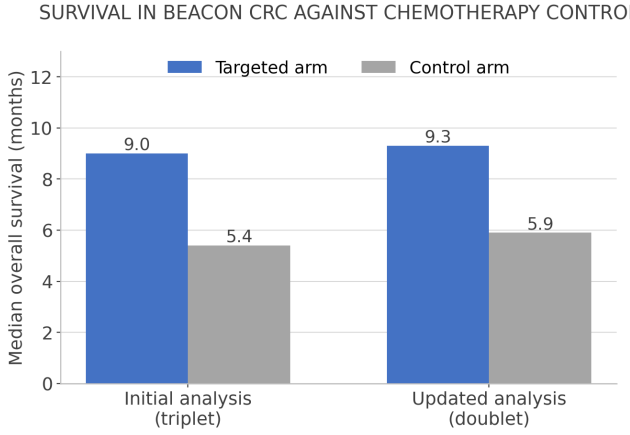

Figure 3: Median overall survival for the targeted arms against the chemotherapy control in the same trial [5]

Moving the combination into first line: A subsequent phase 3 trial added encorafenib and cetuximab to first-line mFOLFOX6 in previously untreated V600E disease. Objective response was 60.9 per cent against 40.0 per cent for standard care (odds ratio 2.443, 95% CI 1.403-4.253, one-sided p = 0.0008), with median duration of response of 13.9 against 11.1 months (Figure 4). The co-primary progression-free survival endpoint was not mature at the reported data cutoff [6]. A single-arm phase II study of the triplet in untreated patients had earlier suggested activity in this setting [16].

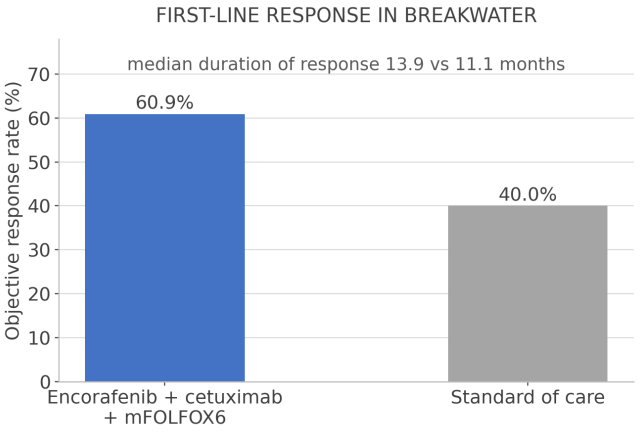

Figure 4: Objective response in previously untreated BRAF V600E metastatic colorectal cancer, first-line randomised comparison [6]

Class	Signalling	Typical variants	Clinical association
I	RAS-independent monomer	V600E	Poor prognosis; responds to BRAF plus EGFR blockade [5]
II	RAS-independent dimer	K601, G469, L597	Longer survival than V600E; no approved targeted option [2,12]
III	RAS-dependent, low kinase activity	D594, G596, G466	Frequent RAS co-mutation; favourable survival [10,12]

Table 2: Functional classification of BRAF alterations and the clinical associations reported for each

The mismatch repair overlap: Because V600E arises through a methylation-driven pathway that also silences MLH1, a proportion of these tumours are mismatch-repair deficient, and that changes the outlook considerably. Population-based data show that within BRAF V600E disease, deficient mismatch repair was associated with shorter median survival than proficient tumours in a chemotherapy-treated population (8.9 against 17.2 months) [7]. In earlier-stage disease the prognostic weight of BRAF also differs according to mismatch repair status rather than acting uniformly [17]. Because deficient mismatch repair opens access to checkpoint inhibition, which BRAF V600E does not preclude, mismatch repair status carries at least as much consequence for management as the BRAF variant in this subgroup.

Discussion

The evidence supports one main conclusion and one caution. The main conclusion is that BRAF should not be reported as a binary result in colorectal cancer. The survival gap between non-V600 and V600E disease, 60.7 against 11.4 months, is larger than the gap between BRAF-mutant and BRAF-wild-type disease [2]. A report that collapses those groups conveys the wrong prognosis to roughly one BRAF-mutant patient in five, and may route them toward a regimen tested only in the other group [2,4,5].

The caution concerns how much the targeted advance has actually delivered. The response difference in previously treated disease is large, 27 per cent against 2 per cent, but the survival difference is 9.0 against 5.4 months [5]. That is a real gain in a population with few options, and it is not a transformation. The first-line data are more encouraging on response, though the survival endpoint was immature when reported [6].

Implications for reporting and trials

Three things follow. Variant-level reporting should be standard, since the information is already in the sequencing output and only the summary discards it. Trial eligibility written as BRAF-mutant rather than BRAF V600E will enrol a minority of patients with a different disease and a much better baseline prognosis, which biases the result. And mismatch repair status should be reported alongside BRAF in every case, because it determines whether checkpoint inhibition is available and, where it is, materially alters what is available to the patient [7,17].

Study limitations

The limitations belong to the evidence base. Non-V600 disease is rare enough that the survival estimates rest on a few hundred patients assembled retrospectively from sequencing databases, with the referral and testing biases that implies; the finding that non-V600 survival exceeds BRAF wild-type survival is itself surprising and has been flagged as needing confirmation [2,4]. Prevalence figures differ systematically between population-based screening and trial populations, and the population-based data suggest outcomes are worse than trial cohorts imply because of attrition between treatment lines [7]. The functional classification into classes rests substantially on preclinical work, and the clinical data supporting class-specific treatment decisions remain thin [12,13].

Two gaps deserve naming. No randomised trial has tested BRAF-directed treatment in non-V600 disease, so the absence of benefit there is inferred from biochemistry rather than demonstrated. And the first-line survival data for the encorafenib combination were not mature at the time of the report reviewed here, so the durability of the response advantage is not yet established [6].

Conclusion

BRAF alteration is present in roughly a tenth of metastatic colorectal cancers and is not one entity. V600E defines an aggressive subtype with median survival close to a year on chemotherapy, for which combined BRAF and EGFR blockade now offers a reproducible if modest gain and a substantially higher first-line response rate. Non-V600 variants occur in about one BRAF-mutant patient in five and carry survival measured in years, with no evidence that the approved targeted regimen benefits them. The clinically useful step is unglamorous and immediate: report the variant rather than the gene, and report mismatch repair status alongside it.

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Credit for the underlying work belongs to the trial groups and sequencing consortia cited throughout. This article adds no observations of its own to what they reported.

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Conflict of Interest

No author holds an interest that bears on this work.

Ethics Statement

The sources behind this article were all in the public literature before it was written. No patient records were opened and no volunteers recruited, placing it outside ethical review.

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