Published in final edited form as:
Clin Colorectal Cancer. 2014 September ; 13(3): 164–171. doi:10.1016/j.clcc.2014.06.001.

Progression-Free Survival Remains Poor Over Sequential Lines of Systemic Therapy in Patients with *BRAF*-mutated Colorectal Cancer

Van K. Morris[1], **Michael J. Overman**[2], **Zhi-Qin Jiang**[2], **Chris Garrett**[2], **Shweta Agarwal**[2], **Cathy Eng**[2], **Bryan Kee**[2], **David Fogelman**[2], **Arvind Dasari**[2], **Robert Wolff**[2], **Dipen Maru**[3], and **Scott Kopetz**[2]

[1]Department of Cancer Medicine, University of Texas – MD Anderson Cancer Center, Houston, Texas

[2]Department of Gastrointestinal Medical Oncology, University of Texas – MD Anderson Cancer Center, Houston, Texas

[3]Department of Pathology, University of Texas – MD Anderson Cancer Center, Houston, Texas

Abstract

Background—*BRAF* mutations occur in 5–10% of metastatic colorectal cancers and are biomarkers associated with a poor prognosis. However, the outcomes with standard chemotherapy over sequential lines of therapy in a large cohort of patients with *BRAF*-mutant tumors have not been described.

Methods—We searched the MD Anderson Cancer Center databases for patients with colorectal cancer patients and identified *BRAF* mutations between December 2003 and May 2012. Patients were analyzed for clinical characteristics, progression-free survival (PFS), overall survival (OS), and chemotherapeutic agents used. Survival was estimated according to the Kaplan-Meier method.

Results—Among the 1567 patients tested for *BRAF* mutations at our institution, 127 (8.1%) had tumors with *BRAF* mutations. The 71 patients who presented with metastatic disease received a median of 2 lines of chemotherapy. For the first three lines of chemotherapy, median progression-free survivals were 6.3 months (n=69 patients, 95% confidence interval (CI) of 4.9–7.7 months), 2.5 months (n=58, 95% CI of 1.8–3.0 months), and 2.6 months (n=31, 95% CI of 1.0–4.2 months), respectively. Median PFS was not affected by the backbone chemotherapeutic agent in the first-line setting, whether oxaliplatin-based or irinotecan-based (6.4 months vs. 5.4 months, respectively, p-value = 0.99).

Corresponding Author: Scott Kopetz, M.D., Ph.D., The University of Texas – MD Anderson Cancer Center, 1400 Holcombe Boulevard, Unit 426, Houston, TX 77030, Phone: (713) 792-2828, Fax: (713) 563-6764, skopetz@mdanderson.org.

Conflicts of Interest: Dr. Kopetz is supported by CA172670. The remaining authors report no conflicts of interest.

Conclusions—Progression-free survival is expectedly poor for patients with *BRAF*-mutated metastatic colorectal cancer. Despite the ascertainment bias present (with testing preferentially performed in patients suitable for clinical trials in refractory disease), these data provide historic controls suitable for future study design and support the idea that novel therapeutic options are essential in this population.

Introduction

Colorectal cancer is the second-leading cause of cancer-related mortality in the United States, with more than 50,000 deaths estimated in 2012.[1] Even so, survival for patients with metastatic colorectal cancer has improved owing to the advent of improved cytotoxic chemotherapeutic agents,[2–4] anti–vascular endothelial growth factor antibodies,[5,6] and the more frequent use of curative hepatic metastasectomies.[7–9] Additionally, greater understanding of the molecular pathways driving survival and proliferation of colorectal tumor cells has led to the approval of novel targeted therapies—namely, cetuximab and panitumumab—specifically tailored to inhibit epidermal growth factor receptor (EGFR) pathways and thereby thwart tumor growth and improve survival in patients with a wild-type *KRAS* oncogene.[10,11]

Despite such advances, patients with colorectal cancer harboring mutations in the *BRAF* oncogene (present in 5%–10% of all colorectal tumors[12,13]) have traditionally poor survival outcomes and low response rates when treated with the aforementioned therapies[14–16]. *BRAF* mutations, most commonly a valine to glutamic acid substitution of the 600th amino acid (V600E)[12], generate a conformational change of the RAF kinase, leading to constitutive activation of the BRAF kinase and the downstream MAPK pathway, which are implicated in tumor cell proliferation and anti-apoptotic behavior[17,18]. In a phase I trial of the mutated BRAF inhibitor vemurafenib, patients with *BRAF*-mutated metastatic colorectal cancers demonstrated a response rate of approximately 5% when treated with this drug as a single agent[19], much lower than the approximately 50% of patients with metastatic melanoma who responded to the same therapy in the seminal phase III trial[20,21]

To our knowledge, no prior studies have described progression-free survival (PFS) across sequential lines of chemotherapy among patients with *BRAF*-mutated metastatic colorectal cancer. To that end, we retrospectively evaluated the clinicopathologic features and survival of 127 patients with *BRAF*-mutated colorectal cancer treated at The University of Texas MD Anderson Cancer Center.

Methods

Identification of Patients with BRAF-Mutated Colorectal Cancer

The MD Anderson institutional computerized database were searched to identify patients with a diagnosis of colorectal cancer who were evaluated and assessed for treatment at our institution between December 2003 and May 2012. Tumors were classified and staged according to clinical and pathologic information (American Joint Committee on Cancer [AJCC] Cancer Staging Manual, 7th edition)[22].

Patients with colorectal cancer were included for analysis in this series only if their pathology reports revealed a *BRAF* mutation in either the primary tumor or a metastasis, (depending on the tissue available). To determine whether a *BRAF* mutation was present, DNA was extracted from sections of microdissected paraffin-embedded blocks and analyzed by both polymerase chain reaction and pyrosequencing from codons 595 to 600 of the *BRAF* oncogene. This assay has the sensitivity to detect approximately 1 in 10 mutation-bearing cells in the microdissected area.

Microsatellite Testing

Microsatellite stability or instability was determined by one of two methods: (1) DNA was extracted from paraffin-embedded sections of microdissected tumor and adjacent sections of non-neoplastic colorectal tissue surrounding the tumor and analyzed by polymerase chain reaction followed by capillary electrophoretic detection of microsatellite repeats. Here, a panel of seven microsatellite markers (BAT25, BAT26, BAT40, D2S123, D5S346, D17S250, and TGFB2) was evaluated to detect changes in the numbers of microsatellite repeats in tumor tissue compared with the adjacent normal tissue from the same patient. Tumors bearing five or more markers with higher numbers of microsatellite repeats relative to the normal tissue controls were deemed to exhibit microsatellite instability; or, (2) tumor samples were tested with immunohistochemical stains using antibodies against the proteins MLH1, MSH2, MSH6, and PMS2. Microsatellite instability was defined as the loss of one or more of these proteins in the tumor tissue compared with the adjacent normal tissue.

Statistical Analyses

Once those patients with *BRAF* mutations had been identified, their medical records were retrospectively reviewed to obtain demographic, clinicopathologic, treatment, and outcome data according to an institutional review board–approved protocol. Descriptive statistics were used to characterize the patient population. OS was defined as the time between the date of diagnosis and date of death or date of last follow-up. PFS was defined as the time between the date of treatment initiation and either the date of radiographic disease progression (as determined by the interpreting radiologist at our institution) or the date of death. Survival curves were generated using the Kaplan-Meier method, and the differences between curves were calculated with the log-rank test. The effects of patient demographics, disease, and treatment characteristics on survival outcomes were analyzed using the methods of Kaplan and Meier with a two-sided p-value of less than 0.05 considered significant. Hazard ratios were estimated with univariate Cox proportion hazard models.

Results

Patient Demographics

Among the 1567 patients with colorectal cancer tested for activating *BRAF* mutations, 127 patients (8.1%) were found to have *BRAF*–mutant tumors. Table 1 summarizes the demographic characteristics of these 127 patients and the clinicopathologic features of their disease. The median age at diagnosis was 60.0 years (range, 27–73 years). Most tumors (59.8%) were located in the right colon and were of moderate or poor histologic grade (2–3).

94% of the patients had tumors which carried a V600E mutation in the *BRAF* oncogene. Six tumors had D594G mutations, and one had a G496R mutation.

Characteristics of Patients with Stages I–III Disease at Diagnosis

All fifty-six patients with stage I-III disease at diagnosis underwent surgical resection of their primary tumors. The median OS for this group was 62.6 months, and was strongly associated with stage (Figure 1, $p<0.001$). Higher T stages and higher N stages were associated with shorter median OS (Table 2; $p=0.04$ and $p=0.0006$, respectively). Microsatellite stability testing was performed in 36 of these patients. Right-sided primary tumors were more likely to demonstrate microsatellite instability when compared to tumors arising from the left colon/rectum (OR 85.7, $p=0.004$) (Table 3). In fact, all patients with microsatellite-high (MSI-H) tumors had primary tumors located in the right colon.

Among the stage I–III patients, 39 (69.6%) developed recurrent disease after undergoing initial surgical resection (Table 4). Those with recurrent disease had a median OS of 27.1 months and were less likely to be alive at the time of data analysis ($p<0.001$) than those without disease recurrence, all of whom were still alive at the same time of data analysis (median follow-up of 24.8 months, range 5.3–110.8 months). The primary tumor site was not associated with survival in patients with recurrent disease. Recurrent disease was observed in 94% of patients with microsatellite-stable (MSS) tumors and was more strongly associated with MSS-tumors when compared to the population with MSI-H tumors (OR 60.0, $p< 0.001$).

Characteristics of Patients with Stages IV Disease at Diagnosis

Seventy-one patients had metastatic disease at diagnosis (Table 5). The liver was the most common site of metastasis at diagnosis, with metastases detected in 43 (60.6%) patients (Table 4). Of the 43 patients with liver metastases, eight (18.6%) were able to undergo hepatic metastasectomy. After a median follow up of 14.3 months, 63% of patients had disease recurrence, with a median recurrence-free survival of 9.1 months following hepatic resection. Other sites of metastases detected at diagnosis were the lungs (13 patients), distant/non-regional lymph nodes (28), and the peritoneum (20).

Characteristics of patients initially diagnosed with stage I–III disease whose tumors recurred were compared with those of patients who had stage IV disease at the time of diagnosis. Patients with recurrent tumors were most likely to develop oligometastatic disease in the peritoneum **and**/or at the site of their initial surgical resection (24 of 39 patients who developed recurrent disease); peritoneal disease was more common in patients with recurrent tumors than in those with metastatic disease detected at diagnosis (21 of 39 patients vs. 20 of 71 patients, respectively; $p<.01$).

Survival Outcomes of Patients with Metastatic Disease

The patients with stage IV disease had a median OS of 20.1 months, with a 2-year OS rate of 42.5% (Figure 1). No associations between OS and age, sex, or site of the primary tumor were found in patients with metastatic disease. However, 67 patients (94.3%) with metastatic disease had V600E *BRAF* mutations. The remaining four patients with D594G

mutations were still alive 2 years after their initial diagnosis, with a median OS of 42.2 months, whereas patients with V600E mutations had a median OS of 20.0 months (hazard ratio for death among those with D594G mutations=0.45, p=0.04).

Sixty-nine of the 71 patients with metastatic disease received systemic therapy (Table 6). The performance status of the remaining two patients did not allow treatment initiation. The median number of lines of systemic therapy was two. The type of systemic therapy used (e.g., oxaliplatin-based or irinotecan-based) did not significantly affect PFS in any line of treatment. Most patients (61 of 69) received an oxaliplatin-based regimen as their first-line treatment, and irinotecan-based therapies were most common in the second-line setting (39 of 58). The median progression-free survivals for patients after one, two, and three lines of therapy were 6.3 months, 2.5 months, and 2.6 months, respectively (Figure 2). Although a short duration of benefit was noted with first-line treatment, the median PFS in patients who received two or three lines of therapy corresponded to the time of the first restaging scans. In the second-line setting, 28 of the 39 patients treated with irinotecan concomitantly received an anti-EGFR monoclonal antibody (cetuximab or panitumumab). No difference in PFS was observed for those patients receiving an anti-EGFR monoclonal antibody when compared to those patients who did not.

Of note, despite the poor prognosis of the majority of patients with *BRAF*-mutant metastatic tumors, a rare subset of patients had prolonged disease control with systemic chemotherapy and a more indolent course, as represented by an approximate 15% two-year PFS with first-line therapy. A trend toward an improved survival was noted among the eleven patients who underwent metastectomy (8 liver resections, 1 lung resection, 1 lymph node dissection, and 1 brain resection) relative to those who did not proceed to metastectomy (median OS 34.8 versus 17.9 months, respectively; p=0.066). However, the small sample size does not allow better characterization of this subset. With the exception of the majority of patients with D594G *BRAF* mutations found within this group, no other clinicopathologic parameters (age at presentation, gender, ethnicity, site of primary tumor, distribution of metastases) were unique to this population demonstrating the prolonged survival.

Discussion

To our knowledge, no previous studies have quantified progression-free survival outcomes across multiple lines of therapy specifically for patients with *BRAF*-mutant metastatic colorectal cancer. With a median PFS of 6.3 months, patients seemed to receive some survival benefit from the first line of systemic therapy upon treatment initiation for metastatic disease. However, the median PFS of patients who underwent second and third lines of treatment were both approximately 2.5 months and correspond to the time of first restaging. That these tumors grew without any apparent radiographic improvement in the second- and third-line settings reinforces the notion that refractory *BRAF*-mutant metastatic colorectal cancer does not respond well to traditional chemotherapy regimens. Those with metastatic disease tolerated a median of two lines of treatment before having to discontinue therapy permanently. Collectively, these results reinforce the notion that this disease responds very poorly to systemic treatment.

The 71 patients with metastatic disease in this single-institution study had a longer median OS (20.1 months) from the time of diagnosis than those of other cohorts of patients with metastatic, *BRAF*-mutated colorectal cancer[13,23–28]. This result may reflect an ascertainment bias present in our cohort representing a group of patients with a robust performance status able to travel for clinical trials. Indeed, we have previously reported median OS of 10.4 months for a retrospective population cohort without the *BRAF* ascertainment bias[23]. Nonetheless, a subset analysis of a phase II study of frontline FOLFOXIRI chemotherapy in combination with bevacizumab for patients with metastatic colorectal cancer showed a median PFS of 12.8 months and an OS of 23.8 months for those with *BRAF* mutations[29]. Although only ten highly selected patients with BRAF mutations were included in this study, the median OS is similar to what we report and reinforces the notion that patients able to withstand aggressive systemic treatments may demonstrate benefit despite the presence of a *BRAF* mutation.

In addition, the choice of an oxaliplatin- or an irinotecan-based regimen did not affect PFS. Prior studies of this subset of patients with colorectal cancer have failed to demonstrate significant differences in response between different types of treatments used[30,31], a finding reinforcing the idea that the presence of a *BRAF* mutation is not predictive of response to the currently available therapies.

In our cohort, the four patients with D594G mutations showed a longer OS than those with V600E mutations. Scant information regarding outcomes of patients with metastatic D594G *BRAF*-mutated colorectal cancer has been reported thus far, with one study citing a lone patient demonstrating an objective response to systemic treatment.[32] In vitro work with melanoma cells has shown the D594G *BRAF* mutation generates a significantly less active BRAF kinase and thereby confers less constitutive activation of the MAPK pathway that is readily triggered by the V600E-mutant BRAF kinase[17,33]. These clinical results further corroborate the notion that non- V600E mutations may display different clinical phenotypes from those of the more common V600E *BRAF*-mutated tumors; if these findings are validated prospectively, patients harboring D594 mutations may need to be studied prospectively and independently from patients whose tumors contain *BRAF* V600E mutations.

Of the 56 patients with non-metastatic disease at the time of diagnosis, 39 (69.6%) eventually developed recurrence. Among these patients, the median OS did not significantly differ from that of the patients with metastatic disease at the time of diagnosis (27.1 months vs. 21.0 months, respectively; p=0.18). Prior series have shown that patients with *BRAF*-mutant colorectal cancer who are initially diagnosed with stage II or III disease have poor survival after recurrence[34] and worse OS[16] relative to similar patients with wild-type *BRAF* tumors. Thus, when compared to patients with *BRAF*-mutated tumors whose disease was metastatic at initial presentation, it is not surprising that the patients in our cohort who recurred displayed similarly poor outcomes and did not respond well to available therapeutic options.

Microsatellite status and recurrence were clearly related. All patients with left colon or rectal primary tumors that were tested for microsatellite instability had microsatellite-stable

tumors, and all these patients developed recurrent disease. Likewise, primary tumors arising in the right colon that demonstrated microsatellite instability were less likely to recur. Our findings are consistent with prior findings that patients with *BRAF*-mutated tumors with microsatellite stability are associated with worse survival outcomes relative to those with microsatellite instability.[16,34,35] Large efforts are underway to better define the prognostic role of BRAF mutation in stage II/III colon cancer and the interaction of this prognostic effect with microsatellite instability and tumor location.

We recognize that many of the metastatic patients described here were initially screened for a *BRAF* mutation because they were being considered for participation in a clinical trial and thus had a performance status suitable for trial eligibility. Therefore, our OS results likely overestimate the survival of all patients with metastatic *BRAF*-mutated colorectal cancer, as many patients with more aggressive phenotypes would have died before being evaluated for study eligibility. Nonetheless, even with survival outcomes superior to prior reports, this group of patients not only had poor disease response to available systemic chemotherapy and biologic agents but also proved unable to withstand sequential lines of treatment. Treatment of these patients with all available standard-of-care therapies is unlikely to be possible due to declining performance status, and appears to provide little or no improvement in progression-free survival for most patients. Early engagement in the many open or planned studies for this specific population is warranted. In the absence of access to such studies, a regimen of 5-FU, oxaliplatin, and irinotecan may be considered in selected good performance status patients based on the prior report[29]. Thus, therapeutic options remain poor for patients with *BRAF*-mutated colorectal cancer, and our findings reinforce the need for a greater understanding of the activated pathways driving these tumors that could be translated into more effective treatment.

Conclusion

Progression-free survivals across sequential lines of systemic therapy are poor in patients with *BRAF*-mutated metastatic colorectal cancer, and by the second line of treatment, correspond to the time of first restaging scans. Our data provide historical controls for which responses to therapies used in the treatment of trial-eligible *BRAF*-mutated metastatic colorectal cancer patients can be compared in the future. As patients with this subset of disease do not respond well to currently available traditional treatment options, these results reinforce the notion that additional prospective studies are necessary in order to offer more effective options to patients.

Acknowledgments

The University of Texas MD Anderson Cancer Center is supported in part by the National Institutes of Health through Cancer Center Support Grant CA16672.

Funding: The University of Texas MD Anderson Cancer Center is supported in part by the National Institutes of Health through Cancer Center Support Grant CA16672.

REFERENCES

1. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J. Clin. 2012 Jul-Aug;62(4):220–241. [PubMed: 22700443]
2. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008 Mar 22; 371(9617):1007–1016. [PubMed: 18358928]
3. Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. Eur. J. Cancer. 1999 Sep; 35(9):1343–1347. [PubMed: 10658525]
4. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J. Clin. Oncol. 2007 Oct 20; 25(30):4779–4786. [PubMed: 17947725]
5. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J. Clin. Oncol. 2003 Jan 1; 21(1):60–65. [PubMed: 12506171]
6. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N. Engl. J. Med. 2004 Jun 3; 350(23):2335–2342. [PubMed: 15175435]
7. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. J. Clin. Oncol. 1997 Mar; 15(3):938–946. [PubMed: 9060531]
8. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann. Surg. 2002 Jun; 235(6):759–766. [PubMed: 12035031]
9. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J. Clin. Oncol. 2009 Aug 1; 27(22):3677–3683. [PubMed: 19470929]
10. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N. Engl. J. Med. 2009 Apr 2; 360(14):1408–1417. [PubMed: 19339720]
11. Douillard J-Y, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab (pmab) with FOLFOX4 for first-line metastatic colorectal cancer (mCRC). J. Clin. Oncol. 2010; 29(suppl):3510.
12. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature. 2002 Jun 27; 417(6892):949–954. [PubMed: 12068308]
13. Tie J, Gibbs P, Lipton L, et al. Optimizing targeted therapeutic development: analysis of a colorectal cancer patient population with the BRAF(V600E) mutation. Int. J. Cancer. 2011 May 1; 128(9):2075–2084. [PubMed: 20635392]
14. Yokota T, Ura T, Shibata N, et al. BRAF mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer. Br. J. Cancer. 2011 Mar 1; 104(5):856–862. [PubMed: 21285991]
15. Price TJ, Hardingham JE, Lee CK, et al. Impact of KRAS and BRAF Gene Mutation Status on Outcomes From the Phase III AGITG MAX Trial of Capecitabine Alone or in Combination With Bevacizumab and Mitomycin in Advanced Colorectal Cancer. J. Clin. Oncol. 2011 Jul 1; 29(19): 2675–2682. [PubMed: 21646616]
16. Ogino S, Shima K, Meyerhardt JA, et al. Predictive and prognostic roles of BRAF mutation in stage III colon cancer: results from intergroup trial CALGB 89803. Clin. Cancer Res. 2012 Feb 1; 18(3):890–900. [PubMed: 22147942]
17. Wan PT, Garnett MJ, Roe SM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell. 2004 Mar 19; 116(6):855–867. [PubMed: 15035987]
18. Pritchard C, Carragher L, Aldridge V, et al. Mouse models for BRAF-induced cancers. Biochem. Soc. Trans. 2007 Nov; 35(Pt 5):1329–1333. [PubMed: 17956344]
19. Kopetz S, Desai J, Chan E, et al. PLX4032 in metastatic colorectal cancer patients with mutant BRAF tumors. J. Clin. Oncol. 2010; 28(15 Suppl):a3534.

20. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N. Engl. J. Med. 2011 Jun 30; 364(26):2507–2516. [PubMed: 21639808]
21. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N. Engl. J. Med. 2012 Feb 23; 366(8):707–714. [PubMed: 22356324]
22. Enge, S.; Byrd, D.; Comptom, C.; Fritz, A.; Green, F.; Trotti, A. Cancer Staging Manual. 7th ed.. Nwe York, NY: Springer; 2010.
23. Tran B, Kopetz S, Tie J, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer. 2011 Oct 15; 117(20):4623–4632. [PubMed: 21456008]
24. Samowitz WS, Sweeney C, Herrick J, et al. Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. Cancer Res. 2005 Jul 15; 65(14):6063–6069. [PubMed: 16024606]
25. Tol J, Nagtegaal ID, Punt CJ. BRAF mutation in metastatic colorectal cancer. N. Engl. J. Med. 2009 Jul 2; 361(1):98–99. [PubMed: 19571295]
26. Souglakos J, Philips J, Wang R, et al. Prognostic and predictive value of common mutations for treatment response and survival in patients with metastatic colorectal cancer. Br. J. Cancer. 2009 Aug 4; 101(3):465–472. [PubMed: 19603024]
27. Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet. 2011 Jun 18; 377(9783):2103–2114. [PubMed: 21641636]
28. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J. Clin. Oncol. 2008; 26(35):5705–5712. [PubMed: 19001320]
29. Masi G, Loupakis F, Salvatore L, et al. Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial. Lancet Oncol. 2010 Sep; 11(9):845–852. [PubMed: 20702138]
30. Richman SD, Seymour MT, Chambers P, et al. KRAS and BRAF Mutations in Advanced Colorectal Cancer Are Associated With Poor Prognosis but Do Not Preclude Benefit From Oxaliplatin or Irinotecan: Results From the MRC FOCUS Trial. J. Clin. Oncol. 2009 Dec 10; 27(35):5931–5937. [PubMed: 19884549]
31. Hutchins G, Southward K, Handley K, et al. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. J. Clin. Oncol. 2011 Apr 1; 29(10):1261–1270. [PubMed: 21383284]
32. De Roock W, Claes B, Bernasconi D, et al. Effects of< i>KRAS, BRAF, NRAS</i>and< i>PIK3CA</i>mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. The lancet oncology. 2010; 11(8):753–762. [PubMed: 20619739]
33. Smalley KS, Xiao M, Villanueva J, et al. CRAF inhibition induces apoptosis in melanoma cells with non-V600E BRAF mutations. Oncogene. 2009 Jan 8; 28(1):85–94. [PubMed: 18794803]
34. Gavin PG, Colangelo LH, Fumagalli D, et al. Mutation Profiling and Microsatellite Instability in Stage II and III Colon Cancer: An Assessment of Their Prognostic and Oxaliplatin Predictive Value. Clin. Cancer Res. 2012 Dec 1; 18(23):6531–6541. [PubMed: 23045248]
35. Phipps AI, Buchanan DD, Makar KW, et al. BRAF mutation status and survival after colorectal cancer diagnosis according to patient and tumor characteristics. Cancer Epidemiol. Biomarkers Prev. 2012 Oct; 21(10):1792–1798. [PubMed: 22899730]

Clinical Practice Points

- Mutations in the *BRAF* oncogene are a poor prognostic marker in patients with metastatic colorectal cancer. Responses to standard therapies are poor and are of short duration.
- Enrollment into clinical trials is appropriate for these patients prior to exhausting all available standard-of-care therapies.
- Patients with MSS/*BRAF*-mutated tumors are more likely to develop disease recurrence than those with MSI-H/*BRAF*-mutated tumors.
- In the metastatic setting, patients with D594G *BRAF* mutations may not have as aggressive a disease as patients with V600E *BRAF* mutations.

(A)

Stage	Overall Survival (months)
I	106.7
II	104.3
III	43.9
IV	20.1

(B)

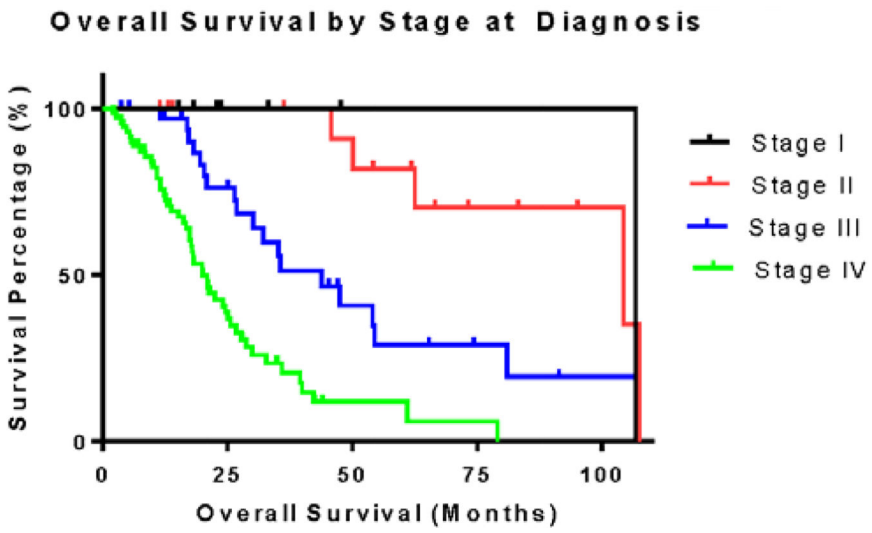

Figure 1.
Overall Survival According to Stage at Diagnosis

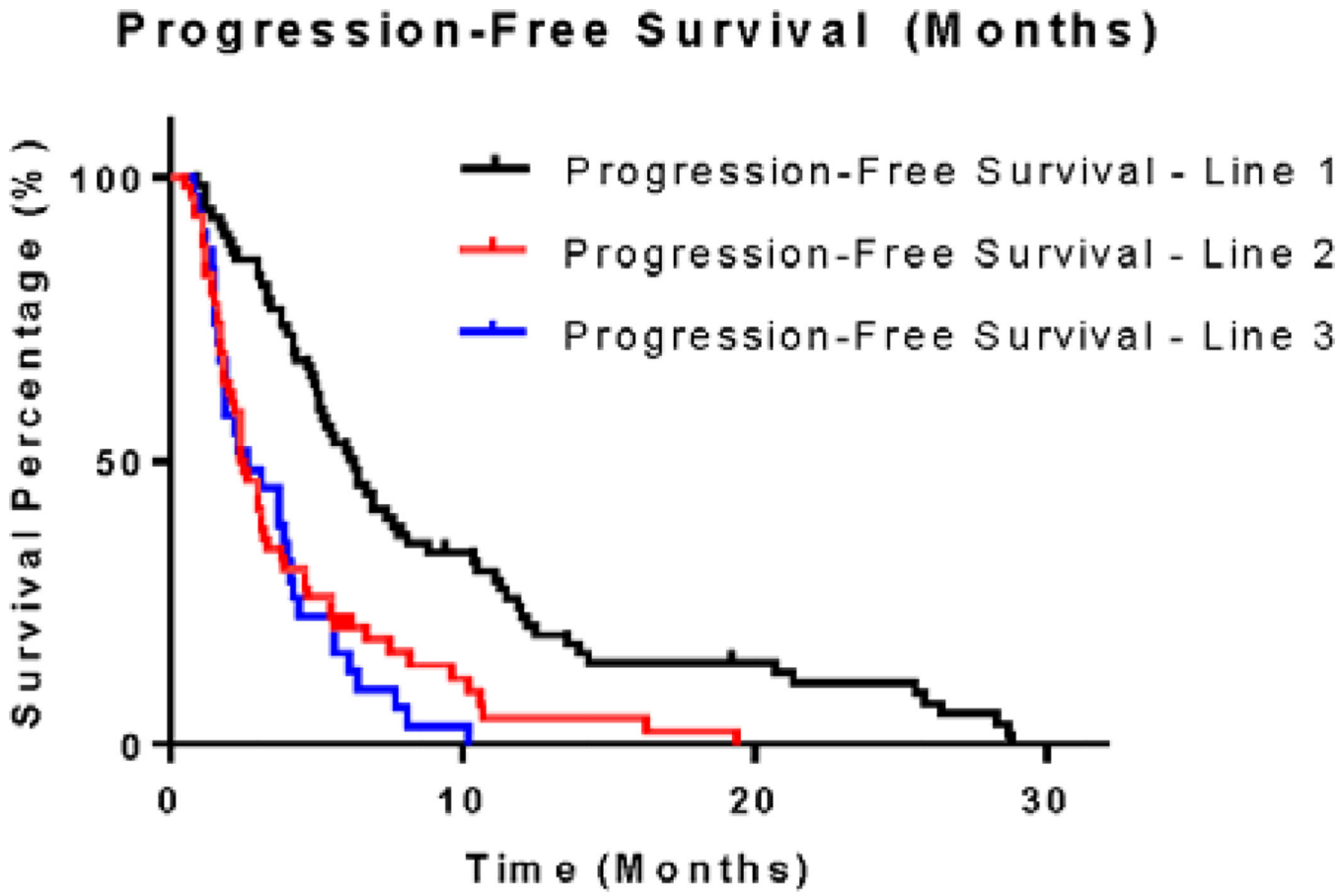

Figure 2.
Progression-Free Survival by Line of Therapy

TABLE 1

PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS

Characteristic	Stage I–III (n=56)	Stage IV (n=71)
Median Age at Diagnosis (years)	61	59
Sex (%)		
Male	26 (46.4%)	39 (54.9%)
Female	30 (53.6%)	32 (45.1%)
Race/Ethnicity (%)		
Caucasian	49 (87.5%)	60 (84.5%)
African American	5 (8.9%)	2 (2.8%)
Hispanic	1 (1.8%)	2 (2.8%)
Asian	1 (1/8%)	7 (9.9%)
Stage at Diagnosis (%)		
I	8 (14.3%)	--
II	15 (26.8%)	--
III	33 (58.9%)	--
IV	--	71
T Stage (%)		
T1	0	0
T2	11 (14.3%)	4 (5.6%)
T3	35 (62.5%)	20 (28.2%)
T4	10 (17.9%)	25 (35.2%)
TX	0	22 (31.0%)
N Stage (%)		
N0	23 (41.1%)	3 (4.2%)
N1	15 (26.8%)	14 (19.7%)
N2	18 (32.1%)	31 (43.7%)
NX	0	23 (32.4%)
Tumor Grade (%)		
1 (well differentiated)	1 (1.8%)	0
2 (moderately differentiated)	35 (62.5%)	36 (50.7%)
3 (poorly differentiated)	20 (35.7%)	35 (49.3%)
Site of Primary Tumor (%)		
Right	35 (62.5%)	41 (57.8%)
Left	12 (21.4%)	15 (21.1%)
Rectal	9 (16.1%)	15 (21.1%)
BRAF Mutation Type (%)		
V600E	53 (94.6%)	67 (94.4%)
D594G	2 (3.6%)	4 (5.6%)
G496R	1 (1.8%)	0

TABLE 2

SURVIVAL CHARACTERISTICS OF PATIENTS WITH STAGES I-III DISEASE AT DIAGNOSIS

Characteristic	N	Events	Median Overall Survival (months)	Two-Year Overall Survival Rate (%)	p-value
Overall Survival	56	22	62.6	86.8	
Age at Diagnosis					
Age < 50 years	8	3	104.3	83.3	0.87
Age ≥ 50 years	48	21	54.5	85.4	
Sex					
Male	26	12	62.6	78.5	0.66
Female	30	12	54.5	95.7	
T Stage					
T1	--	--	--	--	0.04
T2	11	1	106.7	100.0	
T3	35	17	54.1	86.7	
T4	10	5	45.8	64.3	
N Stage					
N0	23	6	104.3	100.0	<0.01
N1	15	6	54.5	83.3	
N2	18	11	32.2	67.2	
Site of Primary Tumor					
Right	35	11	54.5	88.7	0.78
Left	12	8	45.8	64.1	
Rectal	9	5	62.6	100.0	
BRAF Mutation Type					
V600E	53	20	54.5	86.2	0.76
D594G/N	2	1	62.6	100.0	
G496R	1	1	45.8	100.0	

Clin Colorectal Cancer. Author manuscript; available in PMC 2015 September 01.

TABLE 3

MICROSATELLITE TESTING RESULTS ACCORDING TO SITE OF PRIMARY TUMOR

	MSS	MSI-H
Stage I–III: No Recurrent Disease		
Left Colon/Rectum	0	0
Right Colon	1	16
Stage I–III: Recurrent Disease		
Left Colon/Rectum	11	0
Right Colon	4	4
Stage IV at Presentation		
Left Colon/Rectum	16	0
Right Colon	17	3

TABLE 4

CHARACTERISTICS OF PATIENTS WITH RECURRENCE AFTER SURGICAL RESECTION

Characteristic	No Recurrence (Stage I-III)	p-value[1]	Recurrence (Stage I-III)	p-value[2]	Stage IV
Number of Patients	17		39		71
Sex					
Male	5	0.36 (0.10)	21	0.96 (0.91)	39
Female	12		18		32
Primary Tumor Site					
Right	17	40.7 (0.01)	18	0.63 (0.24)	41
Left	0		12		15
Rectum	0		9		15
Site of Recurrence/Metastasis					
Lung	--		5	0.66 (0.46)	13
Liver	--		7	0.08 (<0.01)	43
Peritoneum	--		21	2.98 (<0.01)	20
Lymph Nodes	--		10	0.53 (0.15)	28
Rectum	--		3	--	--
Survival (months)					
Overall	Not reached		27.1	0.18	21.0
Right			23.4		
Left			17.0		
Rectum			37.5		
Vital Status at Time of Analysis					
Alive	17	68.7 (<0.01)	13	1.10 (0.83)	21
Deceased	0		26		50
Stage at Diagnosis					
I	5		2		--
II	7		8		--
III	5		29		--
IV	--		--		71

Characteristic	No Recurrence (Stage I-III)	p-value[1]	Recurrence (Stage I-III)	p-value[2]	Stage IV
Microsatellite Status[3]					
Stable	1	0.02 (<0.01)	15		
Unstable	16		4		

[1] Compares the recurrence and no recurrence groups

[2] Compares the recurrence and stage IV groups

[3] Only 36 of the patients with initial non-metastatic disease had tissue available for microsatellite testing.

TABLE 5

CHARACTERISTICS OF PATIENTS WITH STAGE IV DISEASE AT DIAGNOSIS

Characteristic	N	Events	Median Overall Survival Time (months)	Two–Year Overall Survival Rate (%)	p-value
Overall Survival	71	50	20.1	42.5	
Age at Diagnosis					
Age < 50	19	15	17.4	28.9	0.38
Age ≥ 50	52	35	24.1	47.3	
Sex					
Male	39	27	21.2	42.7	0.23
Female	32	23	21.0	45.5	
T Stage					
T1	0	--	--	--	0.17
T2	4	4	12.5	25.0	
T3	20	15	12.4	34.1	
T4	25	18	22.5	43.7	
N Stage					
N0	3	3	12.4	0	0.34
N1	14	10	34.5	71.4	
N2	31	23	17.4	25.6	
Site of Primary Tumor					
Right	41	28	21.0	41.0	0.88
Left	15	11	24.6	53.6	
Rectal	15	11	17.8	37.5	
BRAF Mutation					
Type					
V600E	67	47	20.0	40.0	0.04
D594G	4	3	47.2	100.0	

TABLE 6

PROGRESSION-FREE SURVIVAL BY LINE OF TREATMENT AND BY TREATMENT REGIMEN EMPLOYED

Line of Treatment	N	Progression-Free Survival (months; 95% confidence interval)	p-value
Line 1[1]	69	6.3 (4.9–7.7)	
Oxaliplatin-based	61	6.4	0.63
Irinotecan-based	6	5.4	
5-FU[2]-based	2	4.6	
Line 2	58	2.5 (1.8–3.0)	
Oxaliplatin-based	7	3.0	0.18
Irinotecan-based	39	3.0	
5-FU[2]-based	4	3.1	
Clinical trial	4	3.6	
Other	4	1.7	
Line 3	31	2.5 (1.0–4.2)	
Oxaliplatin-based	5	3.1	0.19
Irinotecan-based	8	3.1	
5-FU[2]-based	7	6.1	
Clinical trial	11	3.7	
Other	8	1.6	

[1] Two patients were too ill at presentation to receive systemic therapy.

[2] 5-fluorouracil without oxaliplatin or irinotecan.