

Case Study Series

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Cases in the Management of Metastatic Colorectal Cancer: Sequencing Therapies in a Patient With the *BRAF* V600E Mutation



Tanios S. Bekaii-Saab, MD

Professor, Mayo Clinic College of Medicine and Science
Program Leader, GI Program, Mayo Clinic Cancer Center
Consultant, Mayo Clinic
Phoenix, Arizona

Case 1 of a 3-Part Series

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Sequencing Therapies in a Patient With the *BRAF* V600E Mutation

Tanios S. Bekaii-Saab, MD

Patient Case

The patient is a 49-year-old man who began to experience recurrent abdominal pain accompanied by low-grade fevers and night sweats (Table 1). He also noticed darkening in his stools. After these symptoms continued for nearly 2 months, the patient presented to his primary care physician. Laboratory tests showed mild anemia (hemoglobin, 11.4 g/dL). Based on this finding, as well as the apparently new onset of melena, the primary care physician referred him to a gastroenterologist.

After an initial visit, the patient underwent a colonoscopy that revealed a suspicious mass in the ascending colon. Pathologic examination of the biopsy specimens taken during colonoscopy confirmed a poorly differentiated adenocarcinoma. Positron emission tomography/computed tomography (PET/CT) of the chest and pelvis showed no remarkable findings. The gastroenterologist recommended that the patient undergo immediate surgical resection. A right ileocectomy was performed with tumor staging (stage 2A [T3 N0 M0]). Notably, of 36 lymph nodes examined during surgery, none were positive for tumor cells. Genomic testing indicated that the tumor was microsatellite stable. The patient was screened for germline mutations and was found to have no evidence of hereditary cancer syndromes.

After a discussion with his gastroenterologist, the patient decided not to proceed with adjuvant therapy because his risk of recurrence was very low. He was closely followed with routine surveillance scans and laboratory tests. After approximately 1.5 years, a surveillance scan revealed multiple suspicious peritoneal lesions. Blood work

showed a rise in his carcinoembryonic antigen (CEA) level to 4.9 µg/L. An examination further revealed ascites, and the patient reported increased fatigue and loss of appetite. His physician rated his Eastern Cooperative Oncology Group (ECOG) performance status as 0.

A peritoneal lesion biopsy confirmed metastatic recurrence of the original adenocarcinoma. The biopsy specimen was sent for next-generation sequencing, which showed evidence of mismatch repair (MMR) proficient (microsatellite stable), *RAS* wild-type disease and a *BRAF* V600E mutation. The tumor mutation burden was low.

After further discussion between the patient and his medical oncologist, it was decided that treatment would begin with fluorouracil plus leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab. The patient tolerated treatment very well, achieving a rapid partial response. FOLFOXIRI plus bevacizumab was continued for a total of 4 months. Upon completion of his induction therapy—and in the absence of a complete response and owing to the aggressive nature of his tumor—the patient began maintenance treatment with capecitabine plus bevacizumab. Unfortunately, after 2 months of maintenance therapy, the patient's disease progressed significantly, as evidenced by ascites and additional widespread lesions appearing in his liver and lungs. The patient reported significant abdominal pain. Additionally, his CEA level rose to 6.4 mg/L.

Based on a discussion with his physician, the patient understood that, given the rapid progression of his disease, his tumor was likely resistant to the FOLFOXIRI regimen used as first-line therapy. It was decided that the next course of therapy would shift away from chemo-

On the Cover

Confocal light micrograph of cultured colorectal cancer cells dividing. The cellular proteins are indicated by fluorescent markers: DAPI (blue, cell nuclei), tubulin (green), and GM1 (red). The central island of flat cells (green) contains dividing cells and is surrounded by differentiated cells.

Credit: AMMRF, University of Sydney/Science Source.

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Table 1. Key Points of the Case

Initial Clinical Presentation
<ul style="list-style-type: none"> • 49-year-old man • Abdominal pain, fever, anemia, ascites
Pathology
<ul style="list-style-type: none"> • T3 N0 M0 adenocarcinoma • MMR-proficient; low tumor mutation burden • <i>RAS</i> wild-type; <i>BRAF</i> V600E mutation
Initial Diagnosis
<ul style="list-style-type: none"> • Stage 2A colon cancer
Primary Treatment
<ul style="list-style-type: none"> • Surgery • No adjuvant chemotherapy
Lines of Therapy for Metastatic Disease
<ul style="list-style-type: none"> • First line: FOLFOXIRI plus bevacizumab • Second line: Encorafenib plus cetuximab • Third line: Dose-escalated regorafenib

FOLFOXIRI, fluorouracil plus leucovorin, oxaliplatin, and irinotecan; MMR, mismatch repair.

therapy, and he began treatment with encorafenib plus cetuximab. The patient's tumor showed a rapid response, with a significant drop in his CEA level (to 2.9 µg/L).

Following initiation of encorafenib plus cetuximab, there was quick and nearly complete resolution of the patient's ascites, and his pain improved significantly. He did experience grade 1 rash and diarrhea, but no vision changes. Overall, he seemed to tolerate the treatment extremely well. The first follow-up scan, taken 8 weeks after he started the regimen, revealed complete dissolution of most lesions and significant shrinking of the remaining lesions. The patient continued treatment with encorafenib plus cetuximab for nearly a year.

Unfortunately, a follow-up PET/CT scan at that time revealed that the disease had again progressed, with a significant increase in the number and size of lesions throughout the chest and lungs. Interestingly, this progression was not accompanied by the onset of symptoms, such as dyspnea. The patient had only a minor dry cough. The scan also showed new lesions throughout the peritoneum, as well as a resurgence of ascites. Overall, the patient's performance status remained good. A discussion ensued about his next course of therapy. Both trifluridine/tipiracil and regorafenib were considered. Ultimately, regorafenib was favored for several reasons, including the fact that it is a multikinase inhibitor that likely has improved activity earlier in the refractory setting. In addition, the patient's younger age and performance status made him a good candidate for this treatment.

Regorafenib was initiated according to a dose-

escalation strategy. Treatment began at a dose of 80 mg during week 1, then increased to 120 mg during week 2. Initiation of regorafenib coincided with the COVID-19 epidemic. Therefore, the patient was followed closely by video consult to monitor for the onset of adverse reactions. The patient tolerated treatment well, with no apparent toxicities during the first 2 weeks of regorafenib dose escalation. After the dose was escalated to 160 mg during week 3, the patient reported hand-foot syndrome and diarrhea, both of which appeared to be grade 1 in severity. He was able to maintain his activities of daily living. Loperamide effectively controlled his diarrhea. By cycle 2, the hand-foot syndrome was nearly resolved with local application of a corticosteroid cream. The patient continued to receive regorafenib at the 160-mg dose. A CT scan of the chest, abdomen, and pelvis administered after the completion of the second cycle of regorafenib indicated stable disease. The image showed significant cavitation in the lung lesions, a suggestion that regorafenib had activity within the lungs. Additionally, the patient's CEA level decreased.

Based on his response to and overall tolerance of this regimen, it was decided that the patient would continue this dose of regorafenib into cycle 3. He remains on this dose and is doing well.

Rationale for the Treatment Decisions

FOLFOXIRI Plus Bevacizumab

For many years, the most widely adopted first-line treatment of metastatic colorectal cancer was fluorouracil plus leucovorin with either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). Both of these chemotherapy regimens are typically administered in combination with the vascular endothelial growth factor (VEGF)-targeting monoclonal antibody bevacizumab for the majority of patients.

The more intense triple-drug combination of FOLFOXIRI showed high activity in phase 2 studies.^{1,2} A phase 3 study conducted by the Gruppo Oncologico Nord Ovest showed that 12 cycles of treatment with FOLFOXIRI was associated with a superior response rate, progression-free survival, and overall survival compared with the standard of care (12 cycles of FOLFIRI).³ Additionally, a phase 2 study suggested that the clinical activity of FOLFOXIRI could be increased even further with the addition of bevacizumab, with no additional toxicity compared with FOLFOXIRI alone.⁴

The open-label, randomized phase 3 TRIBE2 study compared first-line FOLFOXIRI followed by reintroduction of the same regimen after disease progression vs a sequence of modified FOLFOX6 (fluorouracil, leucovorin, and oxaliplatin) and FOLFIRI doublets, in combination with bevacizumab, in patients with unresectable,

metastatic colorectal cancer.⁵ The trial was conducted in 58 Italian centers, and enrolled patients ages 18 to 75 years with an ECOG performance status of 2. The primary endpoint was progression-free survival 2, which was defined as the time from randomization to disease progression during any treatment administered after first disease progression, or death, as analyzed in the intention-to-treat population.

Results were reported for 679 patients: 339 in the investigative arm and 340 in the control arm. After a median follow-up of 35.9 months, the median progression-free survival 2 was 19.2 months (95% CI, 17.3-21.4) in the investigative arm vs 16.4 months (95% CI, 15.1-17.5) in the control arm (HR, 0.74; 95% CI, 0.63-0.88; $P=.0005$). During first-line treatment, the most frequent all-cause grade 3/4 adverse events in the investigative arm were diarrhea (17% vs 5% in the control arm), neutropenia (50% vs 21%), and arterial hypertension (7% vs 10%). Serious adverse events were reported in 25% of the investigative arm vs 17% of the control arm. After first disease progression, the only grade 3/4 adverse event substantially more common in the investigative arm was neurotoxicity, which occurred in 5% of patients (vs no patients in the control arm). The authors concluded that upfront FOLFOXIRI plus bevacizumab followed by the reintroduction of the same regimen after disease progression appeared to be superior to sequential administration of chemotherapy doublets, in combination with bevacizumab, in this setting.

Encorafenib Plus Cetuximab

The patient's metastatic colorectal cancer tumor was known to harbor the *BRAF* V600E mutation, which is reported in approximately 5% to 10% of patients with metastatic colorectal cancer.^{6,7} *BRAF* V600E mutation-positive metastatic colorectal cancer has a particularly poor prognosis, with minimal response to standard chemotherapy regimens.^{8,9} As a result, patients with *BRAF* V600E mutation-positive metastatic colorectal cancer tend to have rapidly progressive disease and decreased overall survival.

Unlike in other tumor types, BRAF inhibitors alone do not show significant activity in *BRAF* V600E mutation-positive metastatic colorectal cancer. In preclinical studies in colon cancer cells, BRAF inhibition triggered rapid feedback activation of the epidermal growth factor receptor (EGFR) signaling pathway.¹⁰⁻¹² Based on these findings, phase 1 and phase 2 clinical trials were designed to clinically validate the combined inhibition of the BRAF and EGFR signaling pathways.¹³⁻¹⁵ The clinical activity observed in these early studies led to the design of a phase 3 trial evaluating the combination of the BRAF inhibitor encorafenib with the anti-EGFR antibody cetuximab.¹⁶

BEACON CRC was a global, multicenter, randomized, active-controlled, open-label study that evaluated the activity of the combination of encorafenib plus cetuximab with or without the addition of the MEK inhibitor binimetinib in previously treated metastatic colorectal cancer.¹⁶ The trial enrolled patients with confirmed *BRAF* V600E mutation-positive metastatic colorectal cancer who had developed disease progression after 1 or 2 prior therapies.

Patients were randomly assigned to treatment with encorafenib plus cetuximab (n=220) or the investigator's choice of either cetuximab plus irinotecan or cetuximab plus FOLFIRI (n=221). A third arm randomly assigned patients to a triplet regimen of encorafenib, cetuximab, and binimetinib (n=224). Stratification factors included ECOG performance status (0 or 1), prior use of irinotecan (yes or no), and cetuximab formulation (US-licensed or European-approved). The treatment was administered in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, or death. Patient crossover was not permitted before the data cutoff date.

The triplet regimen of encorafenib, binimetinib, and cetuximab did not perform better than encorafenib plus cetuximab.¹⁶ The addition of binimetinib increased toxicity. This triplet regimen treatment arm will not be discussed in detail here. This summary will focus on the approved doublet regimen of encorafenib plus cetuximab compared with the control doublet of irinotecan plus cetuximab.

After a median follow-up for survival of 7.8 months, the median overall survival was 8.4 months (95% CI, 7.5-11.0) with encorafenib plus cetuximab vs 5.4 months (95% CI, 4.8-6.6) with irinotecan plus cetuximab.¹⁶ The risk of death was significantly lower in the encorafenib/cetuximab arm compared with the control arm (HR, 0.60; 95% CI, 0.45-0.79; $P<.001$).

The median follow-up for progression-free survival was 5.4 months.¹⁶ Progression-free survival, as assessed by central review, was 4.2 months with encorafenib plus cetuximab vs 1.5 months with irinotecan plus cetuximab (HR, 0.40; 95% CI, 0.31-0.52; $P<.001$).

Grade 3 or higher adverse events occurred in 50% of the encorafenib/cetuximab arm and 61% of the irinotecan/cetuximab arm.¹⁶ Adverse events led to treatment discontinuation in 8% and 11% of patients, respectively. Fatal adverse events occurred in 3% and 4%, respectively. None of these events were determined to be related to treatment in the encorafenib/cetuximab arm. In the irinotecan/cetuximab arm, 2 deaths (1 from anaphylaxis and 1 from respiratory failure) were attributed to treatment.

At the 2020 American Society of Clinical Oncology Gastrointestinal Cancers (ASCO GI) Symposium, Kopetz

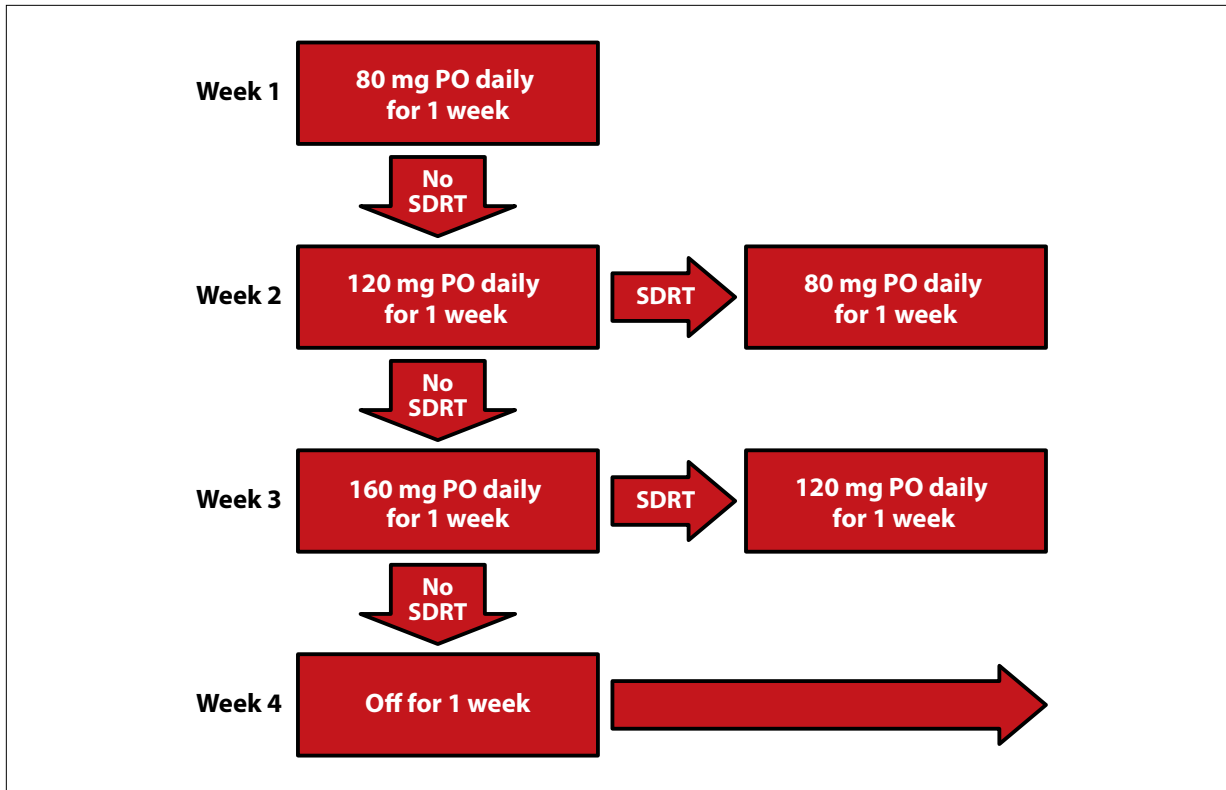


Figure 1. An incremental dose-escalation protocol for regorafenib can minimize toxicities. PO, by mouth; SDRT, significant drug-related toxicities. Reprinted from Grothey A. *Clin Adv Hematol Oncol*. 2015;13(8):514-517.³¹

and colleagues reported on the quality of life results in the BEACON CRC study.¹⁷ A higher quality of life was associated with encorafenib plus cetuximab.

An interesting observation is that the addition of the BRAF inhibitor to the EGFR inhibitor appears to improve the toxicity (particularly the skin toxicity) typically observed with cetuximab alone.¹⁸

The results of the phase 3 BEACON CRC study led to the 2020 approval by the US Food and Drug Administration (FDA) of encorafenib combined with cetuximab for patients with previously treated *BRAF* V600E mutation-positive metastatic colorectal cancer.^{19,20} In addition to this combination, the regimen of encorafenib with the alternative EGFR antibody panitumumab is also included in guidelines from the National Comprehensive Cancer Network (NCCN) in this setting.²¹

Dose-Escalated Regorafenib

In the third-line setting, regorafenib and trifluridine/tipiracil are approved by the FDA for patients previously treated with combination chemotherapy regimens consisting of fluorouracil, oxaliplatin, irinotecan, VEGF-targeted agents, and, when indicated, EGFR-targeted agents.^{22,23} Regorafenib and trifluridine/tipiracil do not

necessarily induce a significant tumor response, but they significantly prolong survival.

The CORRECT study was the pivotal trial that established the use of regorafenib in the third-line setting for patients with metastatic colorectal cancer.²⁴ The primary endpoint of median overall survival was 6.4 months with regorafenib vs 5.0 months with placebo (HR, 0.77; 95% CI, 0.64-0.94; $P=$.0052). The median progression-free survival, a secondary endpoint, was 1.9 months with regorafenib vs 1.7 months with placebo (HR, 0.49; 95% CI, 0.42-0.58; $P<$.0001), with curves on the Kaplan-Meier plot clearly separating after the median. No complete responses were observed, and the objective response rate was 1.0% with regorafenib and 0.4% with placebo ($P=$.19). The disease control rate, which included patients who achieved a partial response or stable disease, was 41% with regorafenib vs 15% with placebo ($P<$.0001). Importantly, in the CORRECT trial, adverse events leading to dose modification occurred in 67% of patients in the regorafenib arm (compared with 23% of the placebo arm). Among patients treated with regorafenib, 38% required a dose reduction and 61% required a dose interruption.

These results were confirmed in the similarly designed

CONCUR study,²⁵ which enrolled a broader population of Asian patients with refractory metastatic colorectal cancer compared with the CORRECT study.²⁴ In the CORRECT study, 111 of the 760 patients were Asian (90% of whom were Japanese). In the CONCUR study, the median overall survival was 8.8 months with regorafenib vs 6.3 months with placebo (HR, 0.55; 95% CI, 0.40-0.77; 1-sided $P=$.00016). The median progression-free survival was 3.2 months vs 1.7 months, respectively (HR, 0.31; 95% CI, 0.22-0.44; 1-sided $P<$.0001). As in the CORRECT trial, the objective response rate in CONCUR was low with regorafenib (4% vs 0% with placebo; 1-sided $P=$.045); all responses were partial.²⁵ The disease control rate (which included patients with either a partial response or stable disease) was 51% with regorafenib vs 7% with placebo (1-sided $P<$.0001). Treatment modifications (including treatment interruption, dose reduction, or both) owing to adverse events occurred in 71% of the regorafenib arm vs 16% of the placebo arm. Adverse events led to treatment discontinuation in 14% vs 6%, respectively.

As demonstrated in both the CORRECT and CONCUR studies,^{24,25} as well as by the real-world use of regorafenib,²⁶⁻²⁸ it is known that the standard dosing of regorafenib—160 mg once daily—is associated with a relatively high rate of toxicities, such as fatigue and hand-foot skin reaction. Thus, an alternative dosing strategy for regorafenib was compared with the standard dosing regimen in the randomized phase 2 ReDOS trial.²⁹ In both dosing regimens, regorafenib was administered orally for 21 consecutive days of a 28-day cycle. Among patients who received an alternative dosing strategy, regorafenib was initiated with 80 mg once daily on days 1 to 7 (Figure 1). In the absence of significant drug-related toxicities, the dose of regorafenib was escalated to 120 mg once daily on days 8 to 14, then to 160 mg once daily on days 15 to 21. In cycle 2 and thereafter, patients subsequently received the highest tolerated dose from cycle 1. The ReDOS study randomly assigned 123 patients to either the standard dose or dose escalation. The study provided data for 116 evaluable patients (defined as those who were eligible, who consented, and who received any protocol treatment) for the primary endpoint analysis.

At baseline, the patients' median age was 61.5 years (interquartile range, 53.0-68.0), and 61.5% of patients were male. The ECOG performance status was 1 in 63% of the study population. At baseline, 67.5% of patients had 3 or more metastatic sites, and 47% had *KRAS*-mutated disease.

The primary endpoint was the proportion of evaluable patients initiating cycle 3. This endpoint was met by 43% of the dose-escalated arm vs 26% of the standard-dosing arm ($P=$.043).²⁹

The median overall survival was 9.8 months in the dose-escalated arm vs 6.0 months in the standard-dosing arm, but this difference did not reach statistical significance (HR, 0.72; 95% CI, 0.47-1.10; log-rank $P=$.12).²⁹ The median progression-free survival was 2.8 months in the dose-escalation arm compared with 2.0 months in the standard-dose arm (HR, 0.84; 95% CI, 0.57-1.24; log-rank $P=$.38).

The rates of grade 3 adverse events most frequently associated with regorafenib, such as fatigue, hand-foot skin reaction, hypertension, and diarrhea, were generally lower in the dose-escalation group compared with the standard-dose group in cycles 1 and 2 of treatment.²⁹ The most common grade 3 or 4 adverse events reported in the ReDOS trial were fatigue (13% in the dose-escalation arm vs 18% in the standard-dose arm), abdominal pain (17% vs 6%), hand-foot skin reaction (15% vs 16%), and hypertension (7% vs 15%). At least 1 drug-related serious adverse event occurred in 6 patients in the dose-escalation group and 8 patients in the standard-dose group. In a prespecified analysis of cycle 1, the incidence of grade 2 or 3 hand-foot skin reaction was lower in the dose-escalation group than in the standard-dose group.

At baseline, quality-of-life scores were similar between the dosing groups.²⁹ However, at week 2 of treatment, the mean quality-of-life scores (per the Brief Fatigue Inventory [BFI] questionnaire) were significantly better in the dose-escalation arm compared with the standard-dose arm for several measurements, including current fatigue, general activity interference, mood interference, walking ability interference, and normal work interference. At weeks 4, 6, and 8, no significant differences were found in quality-of-life scores between the dosing strategies.

Regorafenib is approved for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy.²² Based on the ReDOS trial data, the NCCN guidelines include this escalated dosing strategy as an appropriate alternative approach for administration of regorafenib.⁷

A recent network meta-analysis evaluated regorafenib and trifluridine/tipiracil in the treatment of metastatic colorectal cancer.³⁰ Both of these therapies were superior to best supportive care in this setting. With regard to progression-free survival, both standard-dose regorafenib (HR, 0.40; 95% CI, 0.26-0.63) and trifluridine/tipiracil (HR, 0.46; 95% CI, 0.40-0.52) were superior to best supportive care. Similar results were also reported for overall survival with both standard-dose regorafenib (HR, 0.67; 95% CI, 0.48-0.93) and trifluridine/tipiracil (HR, 0.67; 95% CI, 0.57-0.80). This analysis found no statistically significant difference between standard-dose regorafenib

and trifluridine/tipiracil for either endpoint. The dose-escalated regorafenib strategy was also evaluated, and found to be superior to best supportive care for both overall survival (HR, 0.44; 95% CI, 0.23-0.84) and progression-free survival (HR, 0.37; 95% CI, 0.21-0.66). Additionally, dose-escalated regorafenib was associated with a statistically nonsignificant improvement in both overall survival and progression-free survival compared with both trifluridine/tipiracil and standard-dose regorafenib.

Disclosure

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References

- Falcone A, Masi G, Allegrini G, et al. Biweekly chemotherapy with oxaliplatin, irinotecan, infusional fluorouracil, and leucovorin: a pilot study in patients with metastatic colorectal cancer. *J Clin Oncol*. 2002;20(19):4006-4014.
- Masi G, Allegrini G, Cupini S, et al. First-line treatment of metastatic colorectal cancer with irinotecan, oxaliplatin and 5-fluorouracil/leucovorin (FOLFOXIRI): results of a phase II study with a simplified biweekly schedule. *Ann Oncol*. 2004;15(12):1766-1772.
- Falcone A, Ricci S, Brunetti I, et al; Gruppo Oncologico Nord Ovest. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOX-IRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25(13):1670-1676.
- 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;11(9):845-852.
- Cremolini C, Antoniotti C, Rossini D, et al. Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol*. 2020;21(4):497-507.
- Tol J, Nagtegaal ID, Punt CJ. *BRAF* mutation in metastatic colorectal cancer. *N Engl J Med*. 2009;361(1):98-99.
- Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor *KRAS* and *BRAF* mutation status. *J Clin Oncol*. 2011;29(15):2011-2019.
- Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med*. 2014;371(17):1609-1618.
- 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;117(20):4623-4632.
- Corcoran RB, Atreya CE, Falchook GS, et al. Combined *BRAF* and *MEK* inhibition with dabrafenib and trametinib in *BRAF* V600-mutant colorectal cancer. *J Clin Oncol*. 2015;33(34):4023-4031.
- Prahallad A, Sun C, Huang S, et al. Unresponsiveness of colon cancer to *BRAF*(V600E) inhibition through feedback activation of *EGFR*. *Nature*. 2012;483(7387):100-103.
- Mao M, Tian F, Mariadason JM, et al. Resistance to *BRAF* inhibition in *BRAF*-mutant colon cancer can be overcome with *PI3K* inhibition or demethylating agents. *Clin Cancer Res*. 2013;19(3):657-667.
- Corcoran RB, Ebi H, Turke AB, et al. *EGFR*-mediated re-activation of *MAPK* signaling contributes to insensitivity of *BRAF* mutant colorectal cancers to *RAF* inhibition with vemurafenib. *Cancer Discov*. 2012;2(3):227-235.
- Corcoran RB, André T, Atreya CE, et al. Combined *BRAF*, *EGFR*, and *MEK* inhibition in patients with *BRAF*V600E-mutant colorectal cancer. *Cancer Discov*. 2018;8(4):428-443.
- Tabernero J, Van Geel R, Guren TK, et al. Phase 2 results: encorafenib (ENCO) and cetuximab (CETUX) with or without alpelisib (ALP) in patients with advanced *BRAF*-mutant colorectal cancer (*BRAF* mCRC) [ASCO abstract 3544]. *J Clin Oncol*. 2016;34(15 suppl).
- Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in *BRAF* V600E-mutated colorectal cancer. *N Engl J Med*. 2019;381(17):1632-1643.
- Kopetz S, Grothey A, Van Cutsem E, et al. Encorafenib plus cetuximab with or without binimetinib for *BRAF* V600E-mutant metastatic colorectal cancer: quality-of-life results from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC) [ASCO GI abstract 8]. *J Clin Oncol*. 2020;38(4 suppl).
- Mondaca S, Lacouture M, Hersch J, Yaeger R. Balancing *RAF*, *MEK*, and *EGFR* inhibitor doses to achieve clinical responses and modulate toxicity in *BRAF* V600E colorectal cancer. *JCO Precis Oncol*. 2018. doi:10.1200/PO.18.00088.
- Braftivo [package insert]. Boulder, CO: Array BioPharma Inc; 2020.
- US Food and Drug Administration. FDA approves encorafenib in combination with cetuximab for metastatic colorectal cancer with a *BRAF* V600E mutation. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-combination-cetuximab-metastatic-colorectal-cancer-braf-v600e-mutation#:~:text=On%20April%208%2C%202020%2C%20the,approved%20test%2C%20after%20prior%20therapy>. Updated April 9, 2020. Accessed October 18, 2020.
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer. Version 4.2020. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Updated June 15, 2020. Accessed October 27, 2020.
- Stivarga [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2020.
- Lonsurf [package insert]. Princeton, NJ: Taiho Oncology, Inc; 2019.
- Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.
- Li J, Qin S, Xu R, et al; CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2015;16(6):619-629.
- Ducreux M, Petersen LN, Öhler L, et al; CORRELATE Investigators. Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer in routine clinical practice in the prospective, observational CORRELATE study. *Eur J Cancer*. 2019;123:146-154.
- Yamaguchi K, Komatsu Y, Satoh T, et al. Large-scale, prospective observational study of regorafenib in Japanese patients with metastatic colorectal cancer in a real-world clinical setting. *Oncologist*. 2019;24(7):e450-e457.
- Kopeckova K, Buchler T, Bortlick Z, et al. Regorafenib in the real-life clinical practice: data from the Czech registry. *Target Oncol*. 2017;12(1):89-95.
- Bekaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. *Lancet Oncol*. 2019;20(8):1070-1082.
- Sonbol MB, Benkhadra R, Wang Z, et al. A systematic review and network meta-analysis of regorafenib and TAS-102 in refractory metastatic colorectal cancer. *Oncologist*. 2019;24(9):1174-1179.
- Grothey A. Regorafenib in metastatic colorectal cancer: optimal dosing and patient selection recommendations. *Clin Adv Hematol Oncol*. 2015;13(8):514-517.

