EXPERT REVIEWS

The distinctive molecular, pathological and clinical characteristics of *BRAF*-mutant colorectal tumors

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Several clinical series have demonstrated a notably low overall survival for colorectal cancer patients diagnosed with a *BRAF*-mutant tumor. A potentially interesting predictive role has also been suggested for *BRAF*-mutant colorectal cancer receiving anti-EGFR monoclonal antibodies. Although a global consensus exists in indicating *BRAF* as a prognostic factor with a possible predictive activity, the clinical use of *BRAF* mutational status in colorectal tumors is still controversial. This article reviews the current knowledge on the use and implications of *BRAF* mutational status in colorectal tumors, in order to define its present role in the clinical practice. Also suggested are possible treatment strategies in this prognostically challenging group of patients. Finally, a comprehensive outlook on future developments for specifically directed anti-BRAF therapy is illustrated.

Keywords: *BRAF* • cetuximab • colon cancer • dabrafenib • encorafenib • panitumumab • trametinib • vemurafenib

The distinctive molecular profile of BRAF-mutant colorectal tumors

BRAF is one of the three RAF genes and its mutation has been reported in several human cancers, such as melanoma (50–60%), papillary thyroid carcinoma (30–70%), low-grade serous ovarian carcinoma (30%) and sporadic colorectal cancer (CRC; 10%) [1].

Frequent mutations in the *BRAF* gene have been detected in the two regions of the BRAF kinase domain: the G-loop in exon 11 and the activation segment in exon 15. The most common mutation is the single substitution missense mutation V600E where valine is substituted by glutamate at codon 600 of chromosome 7 within the activation segment of *BRAF*. This mutation occurs in >80% of cases and determines a constitutive activation of the BRAF kinase [1–3]. *BRAF* encodes a serine/threonine kinase acting downstream of *KRAS* [4,5]. Accordingly, mutations in these genes appear to be mutually exclusive [6].

Preclinical studies demonstrated that *BRAF* mutation increases the activity of the BRAF/mitogen-activated ERK kinase (MEK)/ERK pathway both *in vitro* and *in vivo*. The abnormal stimulation of the BRAF/MEK/ERK pathway eventually hinders programmed cell death mediated by the cytosolic caspase by inhibiting the release of cytochrome *c* from the mitochondria [1,3].

BRAF controls proliferation of tumor cells also through the regulation of cyclin D1 and cyclin-dependent kinase inhibitor $p27^{Kip1}$ [7,8]. In *BRAF*-mutant CRC cell lines, ERK1/2 phosphorylation, cyclin D1 expression and bcl-2 levels are reduced, whereas $p27^{Kip1}$ levels are increased [2].

Globally, this abnormal interaction with the molecular mechanisms of programmed cell death is thought to be the main reason responsible for the poor prognosis of *BRAF*-mutant colorectal tumors.

Notably, there is a striking difference in the frequency of *BRAF* mutations between tumors with and without mismatch repair deficiency.

Microsatellite instability (MSI) is observed in nearly all patients with hereditary non-polyposis colon cancer and in 15–20% of sporadic CRC cases. In the hereditary non-polyposis colon cancer syndrome, MSI is a biological consequence of a germline mutation in one of the mismatch repair genes, whereas it is mostly linked to

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hMLH1 promoter methylation in sporadic tumors [9–17]. *BRAF* mutations are more recurrent in MSI-high (MSI-H) tumors (13–78% of all MSI-H colorectal tumors). On the contrary, <10% of microsatellite stable tumors show a mutation in *BRAF* [18–23].

BRAF mutations occur frequently in sporadic cases with somatic *hMLH1* hypermethylation and more rarely in tumors with mismatch repair deficiency attributable to a germ-line mutation [24–31].

Both microsatellite stable and MSI-H tumors harboring a *BRAF* mutation are usually associated with a significantly poorer survival [21,24–31].

Given the distinct prognostic significance of *BRAF* mutation in CRC, there is also a growing interest in defining the clinicopathologic features of patients harboring this mutation.

BRAF mutation is frequently associated with proximal primary tumor location, T4 tumors and poor differentiation [32]. The prevalence of *BRAF* V600E is higher in older females (age >70 years) with *KRAS* wild-type, right-sided colon cancers, in patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 2, multiple metastatic sites and in tumors with mucinous histology [33,34]. *BRAF*-mutant colorectal tumors usually show a peculiar pattern of metastatic spread. These tumors are, in fact, significantly associated with a higher rate of peritoneal metastases, distant lymph node metastases and a lower rate of lung metastases [35].

Several authors also investigated the grade of concordance of *BRAF* status between primary tumors and related metastatic sites. Most of the analyses reported an identical mutational pattern of *BRAF* in primary tumors and matching metastases, with an overall concordance rate of around 90% [36–41].

A study by Kopetz *et al.* demonstrated that *BRAF* mutational status had a concordance rate similar to *KRAS* (89%). Interestingly, the concordance rates were lower for *PIK3CA* and other genes such as *FGFR3*, *STK11* and *FBXW7* (53 and 64%, respectively) [42]. Recent studies also showed the occurrence of *BRAF* mutations during therapy with anti-EGFR inhibitors in patients who originally responded to treatment.

Bettegowda *et al.* used circulating tumor DNA to detect the onset of new mutations in 24 metastatic CRC patients who initially responded to EGFR blockade and then progressed. In this study, the authors observed the onset of a *BRAF* V600E mutation in one patient [43]. Spindler *et al.* analyzed circulating free DNA, *KRAS* and *BRAF* in 108 metastatic CRC patients during third-line treatment with cetuximab and irinotecan. Final data showed that among five patients with primary wild-type disease, three developed a *KRAS* mutation and two developed a *BRAF* mutation during treatment [44].

Prognostic & predictive role of BRAF mutational status in colorectal tumors

BRAF mutation has been extensively investigated as a prognostic factor in metastatic CRC treated with anti-EGFR monoclonal antibodies.

Tol *et al.* conducted a retrospective analysis of the *BRAF* V600E mutational status in patients with metastatic CRC included in a Phase III trial comparing chemotherapy, bevacizumab and cetuximab (the CBC regimen) versus chemotherapy and bevacizumab (the CB regimen) [45]. A *BRAF* mutation was detected in 45 (8.7%) out of 519 tested tumors. Patients with *BRAF*-mutant tumors had a significantly shorter median progression-free survival (mPFS) and median overall survival (mOS) compared to patients with wild-type *BRAF* (WT-*BRAF*) tumors in both groups (CB regimen: mPFS of 12.2 months in WT-*BRAF* vs 10.4 months in mut-*BRAF*, mOS of 24.6 months in WT-*BRAF* vs 15.0 months in mut-*BRAF*; CBC regimen: mPFS of 10.4 months in WT-*BRAF* vs 6.6 months in mut-*BRAF*, mOS of 21.5 months in WT-*BRAF* vs 15.2 months in mut-*BRAF*). No difference in response rates was observed. This study showed that *BRAF* mutation is a negative prognostic marker in patients with metastatic CRC, independent of the chemotherapy and the biological agent used.

Further data have been derived from a study by Di Nicolantonio *et al.* who performed a retrospective analysis of 113 tumor samples treated with cetuximab or panitumumab with or without chemotherapy [46]. Seventy-nine patients with *KRAS*-WT were identified. In this cohort, 11 (13.9%) patients were *BRAF* mutants. None of them reported an objective tumor response.

In the CRYSTAL study, 9% (59 of 625) of patients had a *BRAF* mutation. These patients showed a shorter mOS in both the FOLFIRI (10.3 months) and FOLFIRI/cetuximab (14.1 months) arms, compared with the *KRAS*-WT/*BRAF*-WT population in which the survival was 21.6 and 25.1 months, respectively. The authors concluded that *BRAF* mutation was an indicator of poor prognosis, without a predictive role for cetuximab efficacy [47].

A meta-analysis based on combined results from the OPUS and CRYSTAL trials indicated that in *KRAS*-WT patients, the use of cetuximab in combination with chemotherapy was more prominently beneficial for *BRAF*-WT patients. *BRAF* mutation was found to be a strong negative prognostic marker [48].

In a retrospective pooled study from the European Consortium including 761 chemorefractory patients treated with cetuximab plus chemotherapy, De Roock *et al.* reported a 4.7% mutation rate for *BRAF*. *BRAF*-mutant patients had a significantly lower response rate (RR) (8.3 vs 38% for *BRAF*-WT; odds ratio [OR] = 0.15; $p = 0.0012$), a shorter mPFS (8 vs 26 weeks in *BRAF*-WT; hazard ratio [HR] = 3.74; $p < 0.0001$) and a shorter mOS (26 weeks vs 54 weeks in *BRAF*-WT; HR = 3.03; $p < 0.0001$) [49].

More recently, a meta-analysis of nine Phase III trials and one Phase II trial (six first-line and two second-line trials, plus two trials involving chemorefractory patients) including >450 CRC patients treated with an anti-EGFR monoclonal antibody (cetuximab or panitumumab) in combination with chemotherapy was presented [50]. Unsurprisingly, the addition of cetuximab or panitumumab in the *BRAF*-mutant subgroup did not significantly improve the progression-free survival (PFS) (HR = 0.88; $p = 0.33$), OS (HR = 0.91; $p = 0.63$) and RR (1.31; $p = 0.25$), compared to control regimens. A further meta-analysis was also in line with these findings [51].

Table 1. Main studies investigating the role of *BRAF* in metastatic colorectal cancer patients receiving anti-EGFR monoclonal antibodies.

Author (year)	*BRAF* mutant (%)	RR (%)	PFS (months)	OS (months)	Notes	Ref.
Di Nicolantonio *et al.* (2008)	13	0 vs 32 (p = 0.02)	1.6 vs 3.6 (p = 0.001)	6 vs 12 (p < 0.0001)	(1), (2), (3), (4)	[46]
De Roock *et al.* (2011)	4.7	8.3 vs 38 (p = 0.001)	2 vs 6.5 (p < 0.0001)	6.5 vs 13.5 (p < 0.0001)	(1), (2), (4)	[49]
Park *et al.* (2011)	9	0 vs 23 (p = 0.5)	1.5 vs 4.6 (p = 0.06)	2.4 vs 7.5 (p = 0.9)	(1), (2), (4)	[39]
Bokemeyer *et al.* (2012)	9	Not reported	8.0 vs 10.9	14.1 vs 25.1	(2), (5)	[48]

(1) Control group absent.
(2) Retrospective analysis.
(3) *KRAS* status not significant for either PFS or OS.
(4) Second- or third-line chemotherapy.
(5) First-line chemotherapy.
OS: Overall survival; PFS: Progression-free survival; RR: Response rate.

BRAF mutation was shown as a negative prognostic factor in the recent PRIME trial also. In fact, patients with all *RAS*-WT (*KRAS* plus *NRAS*) but *BRAF*-mutant tumors had a worse PFS and OS, compared with subjects with both *RAS* and *BRAF*-WT disease. In the *RAS*-WT/*BRAF*-mutant subgroup, the addition of panitumumab to chemotherapy produced, in fact, only a small, statistically not significant benefit in term of disease free survival and OS [52].

The prognostic role of *BRAF* mutations was also investigated in an elderly CRC population. In this study, 28 elderly patients treated with the TEGAFOX-E schedule (cetuximab, oxaliplatin and oral uracil/ftorafur (UFT) were analyzed according to *KRAS*, *BRAF*, *NRAS* and *TP53* mutations. The authors found a trend toward an increase in RR (83 vs 33%; p = 0.063) and longer PFS in patients without any mutations, with *BRAF* representing the most relevant factor along with *RAS* status [53].

The Phase III PICCOLO trial evaluated the addition of panitumumab to single-agent irinotecan as second- or subsequent-line treatment in 1198 prospectively tested *KRAS*-WT metastatic CRC patients. *BRAF*-mutant tumors (13.6%) showed a worse OS. Interestingly, the addition of panitumumab to irinotecan had a detrimental effect on survival (HR = 1.84; 95% CI: 1.10–3.08; p = 0.029) [54].

A recent meta-analysis evaluated the possible predictive value of additional biomarkers in the RAS–RAF–MAPK and phosphatidylinositol-3 kinase (PI3K)–Akt–mTOR pathways, including *BRAF*, in determining the clinical benefit from anti-EGFR treatment. The authors investigated the correlation between alterations in *KRAS* (exons 3 and 4), *BRAF*, *PIK3CA* and *PTEN* and the clinical outcome during anti-EGFR treatment in 2395 patients from 22 studies. All mutations significantly predicted poor RR (OR = 0.26, OR = 0.29, OR = 0.39 and OR = 0.41, respectively), shorter PFS (HR = 2.19, HR = 2.95, HR = 2.30 HR = 1.88, respectively) and shorter OS (HR = 1.78, HR = 1.85, HR = 2.52 and HR = 1.43, respectively) [55].

Main results from studies investigating the role of *BRAF* in metastatic CRC patients receiving anti-EGFR treatment have been also summarized in Table 1.

Radical surgery of liver or lung metastases may offer to selected CRC patients a 40% chance for long-term survival and even cure. It is uncertain, however, whether the molecular biology of the underlying colorectal disease and, in particular, *BRAF* mutational status should be considered in the selection process for such strategic procedure. Patients diagnosed with advanced CRC with *BRAF* V600E mutation have, in fact, a worse clinical outcome and usually present with (or soon develop) nodal and peritoneal metastases. As a consequence, it has been hypothesized that the presence of *BRAF* mutations might attenuate the potential benefit of salvage surgery.

Teng *et al.* evaluated the clinical impact of *KRAS* and *BRAF* mutational status on OS in 292 CRC patients undergoing liver metastasectomy. The authors found a *BRAF* mutation in approximately 2% of liver specimens analyzed. A prognostic independent and significant role for *BRAF* mutation (HR = 5.181; p = 0.002) was evident even after adjustment for potentially confounding clinicopathologic variables (number of liver metastases: HR = 1.983, p = 0.009; concomitant extrahepatic disease: HR = 1.858, p = 0.014; surgical margin: HR = 3.241, p < 0.001) [56].

Additional data from a retrospective study confirmed that *BRAF* mutation is an independent prognostic biomarker in CRC patients undergoing liver metastasectomy [57].

Recently, a French study evaluated the prognostic role of *KRAS* and *BRAF* mutational status in 180 patients with CRC who underwent a lung metastasectomy. *BRAF*-mutant patients (about 10% of the total population) had a significantly worse 5-year OS compared to mutated *KRAS* patients (0 and 44%, respectively; p < 0.0001). Median OS was 15 and 55 months, respectively (p < 0.0001). Multivariate analysis confirmed these findings (HR: 0.005; p < 0.0001) [58].

Globally, *BRAF* mutation seems to represent a strong prognostic factor rather than a negative predictive marker for anti-EGFR efficacy. *BRAF*-mutant patients have, in fact, a worse survival than *BRAF*-WT patients, irrespective of the treatment received. Nonetheless, available data in *BRAF*-mutant patients

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receiving cetuximab or panitumumab still seem to suggest a careful evaluation of treatment aims before using an anti-EGFR therapy in these patients. We should also underscore that first-line, registrative Phase III randomized trials generally failed to demonstrate a negative predictive value of *BRAF* mutations. Most studies suggesting that *BRAF*-mutant tumors are associated with resistance to anti-EGFR monoclonal antibodies are, in fact, retrospective.

Further data are mandatory to confirm the possible predictive role of *BRAF* and to identify new treatment strategies to overcome the intrinsic tumor resistance linked to this peculiar molecular profile [59–61].

The use of BRAF mutational status as a guide for treatment strategy: current options & future developments

BRAF mutational status is probably the strongest independent prognostic factor for survival in patients with metastatic CRC. Even in the era of combination chemotherapy and targeted therapies, the median survival of patients with *BRAF*-mutant cancer remains, in fact, disappointingly poor, ranging between 10 and 12 months [62,63].

These patients usually have a rapidly progressive multi-site disease with a lower chance to receive a second or subsequent line of treatment, compared to those with *BRAF*-WT tumors.

The close correlation between *BRAF* mutation and the unfavorable outcome should then drive the treatment strategy, especially in the first-line setting [63]. It is unclear whether *BRAF*-mutant CRC patients are less likely to benefit from standard chemotherapy agents because of intrinsic resistance. Although in a randomized Phase III trial the outcome results of *BRAF*-mutant CRC patients exposed to standard chemotherapy and bevacizumab were concordantly inferior to those seen in *BRAF*-WT patients in terms of response rate, PFS and OS [64], in the MRC FOCUS trial, the mutational status did not seem to impact on irinotecan or oxaliplatin's effect either on PFS or OS [65]. Similarly, the efficacy of FOLFOXIRI and bevacizumab reported in the TRIBE trial was independent from *BRAF* mutational status [66].

Despite an increasing knowledge of biology and clinical characterization of *BRAF*-mutant tumors, a clear effective treatment strategy has yet to be defined.

In clinical trials, standard first-line treatment, including a doublet chemotherapy regimen and target therapy, usually showed discouraging results in terms of outcome [62,63,66].

In an exploratory *post-hoc* subgroup analysis from the FOIB trial, the authors focused on the role of *BRAF* mutational status among patients receiving FOLFOXIRI plus bevacizumab. The mPFS of *BRAF*-mutant patients was 12.8 months compared to 13.1 months in those with WT-BRAF. Similarly, the mOS was 23.8 and 30.9 months, respectively. These data suggested that the FOLFOXIRI plus bevacizumab combination might be a possible choice for *BRAF*-mutant patients [67]. In a prospective cohort including 15 *BRAF*-mutant, ECOG PS 0-1 CRC patients, RR was 60%, and the median PFS and median OS were 9.2 months (95% CI: 5.1–13.3) and 24.1 months (95% CI: 3.3–45.0), respectively [68]. In the pooled population of prospectively and retrospectively treated patients (24 in total), similar results were reported. Response rate was 72%, mPFS was 11.8 months, and mOS was 24.1 months.

Additional information came from the Phase III TRIBE trial. This study was planned to compare the benefit of FOLFOXIRI and bevacizumab versus FOLFIRI and bevacizumab, with PFS as the primary endpoint. A preplanned subgroup analysis confirmed the effectiveness of the triplet regimen in combination with bevacizumab in the *BRAF*-mutant subgroup [66]. Twenty-eight *BRAF*-mutant patients (7.5%) were identified among 375 *RAS* and *BRAF* evaluable cases. In this cohort, the mPFS was 5.5 months for those treated with FOLFIRI and bevacizumab compared to 7.5 months for those who received FOLFOXIRI and bevacizumab (HR: 0.55; 95% CI: 0.26–1.18). Consistently, an 8-month improvement in mOS was reported for *BRAF*-mutant patients assigned to the experimental arm (median OS: 19.1 months vs 10.8 months; HR: 0.55; 95% CI: 0.24–1.23).

This evidence seems to suggest that an intensive treatment could be a suitable upfront treatment approach for patients with *BRAF*-mutant advanced CRC with younger age (<75 years), adequate organ function and ECOG PS. Nonetheless, results from the TRIBE trial in *BRAF*-mutant patients should be interpreted with caution given the small sample size and the limitations of a subgroup analysis.

The FIRE-3 randomized study investigated the efficacy of FOLFIRI combined to either cetuximab or bevacizumab as first-line treatment for WT-*KRAS* metastatic CRC patients. Although the primary endpoint of the trial, response rate, was not met, a statistically significant prolongation of mOS was evident for the FOLFIRI plus cetuximab arm compared to FOLFIRI and bevacizumab arm. In *KRAS*-WT/*BRAF*-mutant CRC patients, however, no difference was seen in terms of either PFS or OS. In the FOLFIRI–cetuximab treatment group compared to those recruited in the FOLFIRI and bevacizumab arm, PFS was 4.9 and 6.0 months, respectively, and OS was 12.3 and 13.7 months, respectively [69].

The protein kinase BRAF plays an essential role in the RAS–RAF cellular signaling pathway that controls cell proliferation and survival. When RAF kinase triggers the MAPK signaling pathway, a subsequent downstream phosphorylation activates MEK [70]. Most of the *BRAF* mutations in CRC are a result of the single substitution of amino acid valine by glutamic acid at position 600 (V600E), which is located within the kinase domain of the gene. This amino acid shift results in a deregulated downstream signaling via MEK and ERK, which increases cell proliferation independently from external cellular signals [1].

Vemurafenib is a selective small molecule that potently inhibits *BRAF* [71]. This drug has been approved for the treatment of advanced melanoma in patients with *BRAF* V600E tumor mutation because of its high activity and efficacy [72]. In CRC, however, preclinical models suggest that *BRAF* mutation is not sufficient to predict vemurafenib activity [73]. Actually,

single-agent vemurafenib showed only a modest activity when used in patients with advanced *BRAF*-mutant CRC. In a Phase I extension trial of 19 pretreated patients, only one partial response and four minor responses were observed [74]. Also, a Phase I/II trial tested the combination of dabrafenib, a specific *BRAF* inhibitor, with trametinib, an MEK inhibitor. This association showed only a limited improvement of activity in *BRAF*-mutant metastatic CRC. Among the 43 enrolled, 12% of patients achieved partial response and one patient achieved a durable complete response; also, 51% of patients had stable disease [75]. Preclinical studies indicated the rapid feedback activation in the EGFR axis and the subsequent continuous tumor growth and progression, caused by *BRAF* V600E inhibition, as a possible hypothesis of poor response to vemurafenib [76].

In a recent study, Ahronian *et al.* identified different molecular alterations within MAPK pathway, including *RAS* alterations (*KRAS* mutation, *KRAS* amplification), *BRAF* amplification and *MEK1* mutation that lead to reactivation of MAPK signaling. Interestingly, these molecular alterations may drive the acquired resistance to simultaneous RAF/EGFR and RAF/MEK inhibition in *BRAF*-mutant CRC cells. These findings support a novel concept: the identification of MAPK pathway reactivating alterations represents a target for testing new options to overcome resistance in *BRAF*-mutant CRC (Figure 1) [77,78].

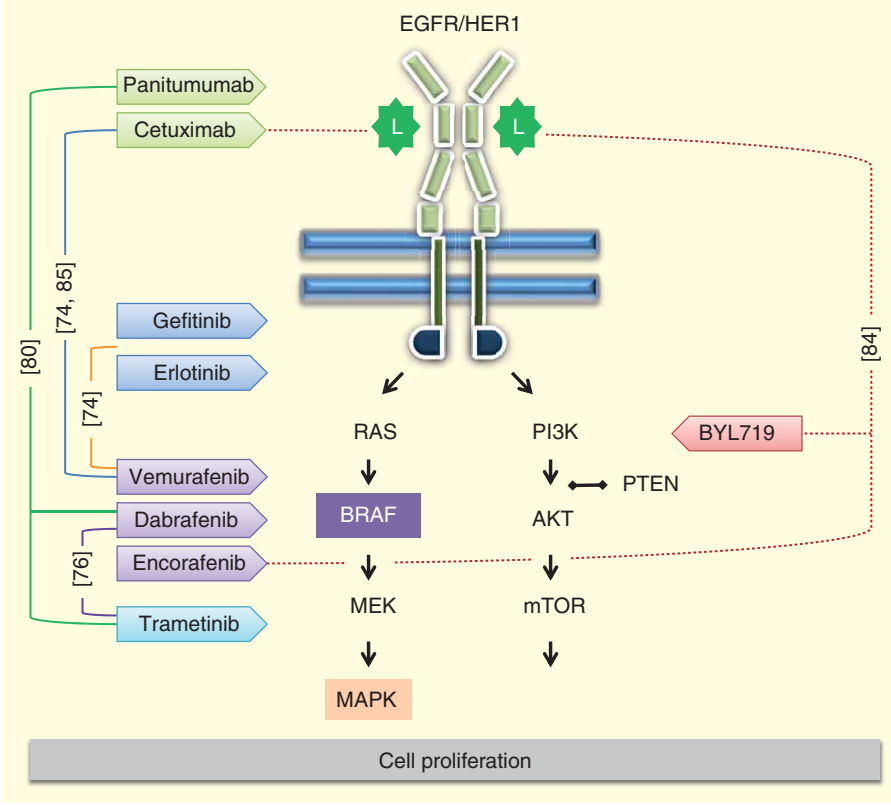

Figure 1. Novel treatment strategies for *BRAF*-mutant colorectal cancer patients testing double or triple inhibition directed multiple targets. Appropriate references are in square brackets.

Some *in vivo* evaluations provided the rationale for designing clinical trials that test the simultaneous BRAF and EGFR inhibition in colon cancer harboring *BRAF* V600E mutation. A strong synergism was observed when vemurafenib was associated to cetuximab, gefitinib or erlotinib, suggesting an increased antitumor activity and efficacy [76].

In a Phase I/II study, pretreated patients received dabrafenib and panitumumab with or without trametinib. In the triplet combination (dabrafenib, panitumumab and trametinib) arm, 15 patients had an RR of 40% with a disease control rate of 80%, with no unexpected toxicities. In particular, four partial remissions (PR) and two stable diseases were seen in six evaluable patients. In the doublet combination (dabrafenib and panitumumab) arm, the majority of patients achieved stable disease as the best response [79].

Several evidences showed that colon cell lines have higher levels of PI3K/Akt signaling compared to melanoma cells [80]. *In vitro* experiments showed that the concurrent presence of *PTEN* or *PI3K* mutations in *BRAF*-mutated CRC cells caused reduced sensitivity to vemurafenib. In *BRAF* and *PI3K* double mutant colon cancer cells (such as RKO, HT-29, NCI-H508 or WiDr), the inhibition of both pathways seemed to be synergistic [81,82]. A recent Phase I study investigated the simultaneous inhibition of *BRAF*, *EGFR* and *PI3K*. Twenty CRC patients treated with a triple combination including encorafenib, cetuximab and BYL719 (a potent inhibitor of the alpha subunit of PI3K) had an RR of 30% and disease control in 90% of the cases [83].

Also, the combination of targeted therapies with standard chemotherapy agents was studied in this challenging patient population. In a recent Phase Ib study, the combination of vemurafenib, cetuximab and irinotecan produced noteworthy clinical benefit (100% of disease control rate, with 50% of PR) [84]; the Phase II trial enrolling 78 patients is ongoing [85]. Recently, Yaeger *et al.* reported the findings of a pilot trial assessing the response rate and safety of vemurafenib combined with panitumumab in 15 patients with *BRAF*-mutant metastatic CRC. Results were encouraging with tumor regressions in 10 out of 12 evaluable patients and partial responses in 2 patients [86].

Aim of the current clinical trials is to identify which combination of different drugs and which different pathway inhibitions are particularly effective in *BRAF*-mutant CRC patients. Since previous findings suggest that the simultaneous BRAF and EGFR inhibition may be an encouraging treatment strategy, it is important to draw clinical trials investigating future combinations with vemurafenib or dabrafenib and other target

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and chemotherapy agents to provide an increased clinical benefit. However, secondary resistance to these novel combinations, eventually caused by the amplification of different genes, should be considered a potential hurdle to long-term efficacy.

Expert commentary

Clinical series demonstrated that *BRAF* gene is mutated in approximately 10% of all colorectal tumors. Along with the prognostic impact in the advanced disease, *BRAF* mutational status is becoming increasingly relevant also for the direct implications on the clinical management. Since *BRAF*-mutant CRC is usually linked to a unique aggressive clinical profile, it is mandatory that these patients be managed accordingly. When clinically feasible, we propose that *BRAF*-mutant CRC patients should receive a triplet chemotherapy regimen in combination with biological therapy. In this view, the FOLFOXIRI plus bevacizumab regimen might represent a possible choice for these patients. *BRAF* mutational status should also have a role in guiding the clinical evaluation for surgical resection of metastases.

Five-year view

We can speculate that the clinical management of *BRAF*-mutant colorectal tumors will change radically in the next few years, as the therapeutic strategies that are under investigation at the moment will hopefully introduce new options for these patients.

Preliminary results with the use of *BRAF*-directed therapy are, in fact, encouraging, with this treatment opportunity probably representing the next scientific frontier for these patients.

The efficacy of *BRAF* inhibitors in *BRAF*-mutant CRC is substantially limited by the early occurrence of escape mechanism involving the activation of the EGFR, PI3K and MEK–driven molecular pathways. As a result, the strategies being explored now are those employing a multiple inhibition approach combining a simultaneous pharmacological blockade of BRAF, EGFR and/or PI3K and/or MEK.

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Key issues

- A *BRAF* mutation is present in approximately 10% of all colorectal tumors.
- *BRAF*-mutant tumors represent a distinct biological and molecular group among colorectal cancer patients.
- Clinical series unanimously reported that patients harboring a *BRAF*-mutant colorectal tumor experienced an impressively worse clinical outcome, particularly median overall survival.
- Therapeutic strategies for *BRAF*-mutant colorectal cancer patients are limited by the aggressiveness of this disease determining resistance to therapy, early progression and death.
- When clinically feasible, a therapeutic approach using a triplet chemotherapy regimen in combination with biologicals such as the FOLFOXIRI plus bevacizumab regimen might be a possible option in carefully selected cases.
- The efficacy of *BRAF* inhibitors in *BRAF*-mutant colorectal cancer is limited by the early occurrence of resistance mechanism involving the activation of the EGFR, PI3K and MEK–driven molecular pathways.
- The novel treatment strategies now explored are those combining a simultaneous pharmacological blockade of BRAF, EGFR and/or PI3K and/or MEK.

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