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COMMENTARY

BRAF^{V600E} Metastatic Colorectal Cancer: Perspective from a Patient, a Caregiver, and an Oncologist

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ABSTRACT

This article has been co-authored by a patient with right-sided *BRAF*^{V600E} metastatic colorectal cancer (mCRC), his caregiver, and an oncologist. Here the patient and caregiver discuss their personal experiences struggling with cancer, including their fears, expectations, and attitudes as the disease progresses. The oncologist describes how patients with *BRAF*^{V600E} mCRC are treated and how the management strategy can be balanced to mitigate any side effects. Improved diagnostic techniques and the availability of numerous treatment options, including various chemotherapy schemes and molecular-targeted drugs, can aid rapid implementation of treatment algorithms. The pivotal roles of patients' associations in the general support of patients and those close to them, and in facilitating the link with healthcare professionals, are highlighted in this perspective piece.

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PLAIN LANGUAGE SUMMARY

This article has been co-authored by a French patient with *BRAF*^{V600E} metastatic colorectal cancer since December 2020, his caregiver, and an oncologist, a French physician currently based at the Institut Paoli-Calmettes in Marseille. Metastatic colorectal cancer is characterized by a high number of genetic mutations, each being associated with a different prognosis and response to treatment. Around 8–12% of patients with metastatic colorectal cancer will present with a *BRAF* mutation in their tumour, the majority of which are V600E, leading to a poor response to standard chemotherapy and short overall survival. The patient and caregiver discuss their personal experiences of struggling with *BRAF*^{V600E} metastatic colorectal cancer, including their fears and expectations, as the disease progresses. The patient is currently receiving immunotherapy as his fifth line of treatment, while his caregiver actively communicates with patients' associations to understand more about the disease and identify new treatment possibilities. The treatment lines received by the patient did not follow the usual treatment algorithms proposed in France for

patients with *BRAF*^{V600E}-mutated metastatic colorectal cancer. The caregiver sought a clinical trial for the patient's third-line treatment from information provided by patients' associations. Thus, patients' associations play a key role in the general support of patients and those close to them, and in facilitating the link with healthcare professionals.

Keywords: *BRAF*^{V600E} metastatic colorectal cancer; Metastatic; Oncology; Patient perspective; Caregiver

Key Summary Points

This article has been co-authored by a patient with right-sided *BRAF*^{V600E} metastatic colorectal cancer (mCRC), his caregiver, and an oncologist.

The patient and caregiver describe their personal experiences, the history of the illness, the various treatments received, and the difficulties encountered.

The physician describes the main characteristics of *BRAF*^{V600E} mCRC and discusses which treatments were used for the patient.

The importance of shared decision-making and the pivotal role of patients' associations in the general support of patients and those close to them, and in facilitating the link with healthcare professionals, are highlighted.

PATIENT AND CAREGIVER'S PERSPECTIVES

Guillaume (patient): I am a 45-year-old man who was working in information technology before I became ill. I am married to Laure and we have two young children. The first symptom of colorectal cancer (CRC) was a very intense abdominal pain, which appeared in December 2020. This pain initially resolved after a good night's sleep, but shortly returned on New Year's Eve where it became so unbearable and persistent that I headed straight to the emergency room. I had a computerized tomography (CT) scan and was referred to a surgeon, who told me that I had an occlusion that required emergency surgery as there was an 80% probability that my pain was related to a tumour in my colon. I had the surgery and was told that it had taken several hours longer than expected, but the surgeon remained rather vague about the result. Looking back, he was probably just trying to protect me—he told my wife that I had metastatic colon cancer associated with peritoneal carcinomatosis.

Laure (caregiver): This was a time of immense stress and disorientation for me. I was terrified—I was breastfeeding our second child, had a 2-year-old daughter, and had just been told that my husband might die. I was completely panic-stricken, but the priority was for Guillaume to recover, so I did not tell him anything at the surgeon's request. For 5 months, I could see that Guillaume did not really want to be fully informed; he just received information in small amounts, only fully understanding his actual situation in May/June 2021. In February, when Guillaume was already receiving chemotherapy, we learned that the right-sided tumour harboured a *BRAF*^{V600E} mutation; we already knew that the tumour was microsatellite stable (MSS). The oncologist did not tell us how this mutation would worsen the prognosis and Guillaume did not want to know how serious the news was.

For my part, as a scientist by training, I need to understand things in order to be able to deal with them. I think that with a disease like this, you can find serenity in information. Knowing what causes the symptoms—no matter how serious the disease is—provides a certain peace of mind and a strength to fight. As I wanted to know what was going on, I searched for the best oncologists immediately after the surgery in order to learn more. I remember asking our local oncologist what the *BRAF*^{V600E} mutation meant in terms of the aggressiveness of the cancer. The oncologist remained vague and told me that it would not change the treatment strategy. I felt

that this was not good news. After searching the internet, I realised that carrying the *BRAF* mutation and having a peritoneal carcinomatosis was often catastrophic, with very poor survival outcomes. Around 6 months after the diagnosis, I had managed to identify three oncologists to advise us on Guillaume's case: one in Nancy and two in Paris. Later, I added in a Spanish oncologist who is a specialist in the $BRAF^{V600E}$ mutation. I liaise between the four specialist oncologists to discuss options and ensure the best decision is made with each progression of the disease. Since Guillaume has been ill, I have given up my job and spent a lot of time looking for new treatment options for him. We have had to reorganise our whole life.

Guillaume: Since the surgery to remove my primary tumour, I have received five lines of treatment. Unfortunately, my peritoneal carcinomatosis could not be resected because it was already too extensive, and the treatments did not help to reduce it. My treatments have been chemotherapy-based (first- and fourth-line), targeted therapies (second- and third-line), and a combination of targeted therapy and immunotherapy (fifth-line). Some of these were so-called experimental treatments, since I was deemed to be fit enough to enter clinical trials that Laure was finding in her online searches. In all lines of treatment, there was always disease stability at first, but then progression. During the two lines of chemotherapy, I was stable for 4 months with first-line treatment and for 6 months with fourth-line treatment. Lung metastasis appeared at the end of first-line treatment and continued to grow. The chemotherapies were heavy-going in terms of side effects, particularly in the first week of each cycle; I spent a lot of time vomiting, was extremely tired, and also suffered from neuropathic pain in my feet. Unfortunately, during first-line treatment, we did not know that using ice could reduce the neuropathy, so I suffered more than I needed to.

The targeted therapies stabilized the tumour for three and a half months during second-line treatment, and for five and a half months during third-line treatment. With those treatments, side effects were acceptable, with only a small amount of fatigue. However, in order to enter a clinical trial, I was told to stop all treatments, including an antibiotic to prevent rash. I had a grade 3 rash for a week, which was extremely hard to live with as it prevented me from sleeping; this really affected me. I later found out that this was a medical error, and I could have continued the antibiotic. This shows that even in this kind of situation, where everything is monitored very closely, there is still the risk of error. I have now just moved onto fifth-line treatment (September 2022). This is very hard physically, of course, as it has all taken a toll on me. There is also a psychological side, with lots of stress every time a new treatment line begins. Fortunately, I am very lucky to have Laure by my side, who is fully involved in the search for treatment options.

Laure: I regularly ask Guillaume to share his feelings so that we are clear on his physical and psychological status. So far, Guillaume has always asked me to keep looking for treatment options (which oncologists do not always have time to do) and I will continue to do this for as long as he wants.

As I work in higher education, I am used to reading scientific literature. Of course, this requires a lot of involvement and I spend most of my time reading research papers, talking to patients, contacting oncologists and researchers, along with oncological societies and patient associations, and attending online webinars and congresses (e.g., European Society for Medical Oncology and American Society of Clinical Oncology). While we have a good healthcare system in France, patients need to know their chance of a better prognosis depends on the energy they (and/or their caregivers) can put into finding treatment solutions. Patients are the main players in their disease, and their role, along with that of caregivers, is fundamental in care. I believe that a patient who is knowledgeable about his/her illness can work with his/her doctor on the treatment process by maintaining a sensible dialogue with him/her. Patients should be supported by a medical team, who can be consulted to better understand the functioning and evolution of the cancer, in order to make the best therapeutic choices for the next line of treatment. This is particularly important in $BRAF^{V600E}$ metastatic CRC

(mCRC) as it is very aggressive. In my view, it is also important for patients and caregivers to have an overview of all treatment options, including the most innovative ones, from an early disease stage. For patients with $BRAF^{V600E}$ mCRC, I would encourage oncologists to consider the possibility of them entering a clinical trial when discussing early lines of treatment with the patient. Guillaume was enrolled in a phase I clinical trial (NCT04294160) for his third-line treatment, which is not a typical option according to treatment algorithm recommendations. My connections with the COLONTOWN patients' organization helped me to find this trial. For me, this highlights the importance of referring patients to associations such as COLONTOWN (colontown.org) and mon reseau® cancercolorectal (monreseau-cancercolorectal.com) as sources of information (Table 1). Patients' organizations provide a supportive place to connect with other patients and caregivers/partners, and to exchange information about mCRC. Today, as a patient advocate and caregiver, I try to help and support other patients. Expert patients facilitate the link between the medical teams and the patient caregivers.

Unfortunately, Guillaume has an incurable disease. Therefore, I am also in contact with the local association 'Le jour d'après' that provides bereavement support for adults and children, to help us understand how best to look after our young children in this critical period. As children understand a lot, I think that it is necessary to support their knowledge and it is useful for us as parents to create the most accurate dialogue. This disease is like a tsunami that changes your life. Of course, family support and friends are there, but they cannot be there all the time. It is up to us to find solutions to keep moving forward.

ONCOLOGIST'S PERSPECTIVE

Worldwide, CRC is the third most common cancer and the second highest cause of cancer-related mortality [1]. This disease is characterized by a high prevalence of mitogen-activated protein kinase (MAPK)-signalling pathway mutations along with other rarer genetic alterations, each being associated with a different prognosis and response to targeted agents. Between 8% and 12% of patients with mCRC present with a $BRAF^{V600E}$ mutation in their tumour, which is associated with a poor response to standard chemotherapy and short overall survival (OS) [2–5]; in particular, the $BRAF^{V600E}$ mutation has been significantly correlated with adverse pathological features of CRC, along with distinct clinical characteristics [6]. Nearly 30% of $BRAF^{V600E}$ mCRC tumours also have genomic alterations called microsatellite instability (MSI) which are characterized by the presence of numerous insertions or deletions at repetitive DNA units [7]. For metastatic cancers, a mutational diagnosis searching for *BRAF* or *RAS* mutations and for MSI is critical in the first-line setting, as results will guide the treatment strategy, particularly the choice of targeted therapy combined with chemotherapy. Advances in mCRC molecular profiling have enabled the personalization of treatment(s) based on somatic biological features. For example, genomic profiling supports the selection of a suitable treatment so that more patients achieve a therapeutic benefit, while fewer are exposed to toxicity from ineffective therapies.

An important part of the initial communication with patients is devoted to explanations about the disease, its prognosis, and the treatment plan. Typically, the presence of somatic mutations can be tested for either in formalin-fixed paraffin embedded tissue (biopsies) or in the circulating blood (circulating tumour DNA). Patients are usually given test results from any molecular analysis at the beginning of the treatment in order for them to understand the therapeutic decision-making process. When patients know the disease and how treatment choices are made, they react more positively, feel more involved in their disease management, and are able to exchange information more easily. The second step in the decision process is to assess (as part of a multidisciplinary team [MDT] approach) whether or not the patient has clearly resectable or non-resectable metastatic disease. It is also important to assess the primary tumour resection status

Table 1 Patients' associations and communities providing resources and support connections for individuals with CRC

Name	Description	Website
mon reseau® cancer colorectal	Patient association for patients with CRC in France	https://www.monreseau-cancercolorectal.com/
COLONTOWN	Online community of more than 120 Facebook groups for patients with CRC, including survivors, and care partners	https://colontown.org/
Digestive Cancers Europe (DiCE)	Umbrella organization of various European national associations for digestive cancers	https://digestivecancers.eu/
Bowel Cancer UK	Bowel cancer charity based in the UK	https://www.bowelcanceruk.org.uk/
Fight Colorectal Cancer (Fight CRC)	Leading patient-empowerment and advocacy organization based in the USA	https://fightcolorectalcancer.org/
Colorectal Cancer Alliance/Blue Hope Nation (Facebook community)	Largest and oldest CRC non-profit organization in the USA	https://www.ccalliance.org/ https://www.facebook.com/groups/bluehopenation
Colorectal Cancer Canada	Not-for-profit CRC organization based in Canada	https://www.colorectalcancercanada.com/
#CRCTrialsChat	Twitter account about clinical trials for CRC	https://twitter.com/CrcTrialsChat

when considering the management of synchronous mCRC. For patients whose metastatic disease is deemed 'never to be resectable', the discussion between the medical oncologist and the patient is based on chemotherapy regimens, choice of targeted therapy, and their toxicity profiles. The pros and cons of various treatment approaches and sequences are also based on factors such as the duration of disease control and survival extent versus quality of life (QoL). It is also important to share with the patient any details of how a specific line of treatment is chosen, along with how the medical strategy will combine chemotherapy and targeted therapy, depending on the mutation profile. For patients with unresectable metastatic disease, the treatment goals are disease control and prolongation of survival, although cure is not possible at the current time. While the prognosis of patients with $BRAF^{V600E}$ mCRC is typically considered poor, it is of interest to note that most data suggesting poor survival are from relatively old studies, at a time when the disease management was not well guided by decision algorithms; patients, typically old, often did not receive chemotherapy and the disease was left to progress spontaneously in some cases. An improved disease prognosis can be expected in 2023 with the implementation of a specific therapeutic strategy, with new treatment options in $BRAF^{V600E}$ mCRC such as BRAF inhibitors (BRAFi) and immunotherapy (only approved for patients with defective mismatch-repair [dMMR]/MSI) mCRC). Furthermore, data

from several preclinical studies have suggested that *BRAF*/*MAPK* pathway inhibition may increase the tumour immune response, raising hope for combination therapies [8]. A recently published phase II trial reported interesting results with a combination of spartalizumab, dabrafenib (BRAFi), and trametinib (MAPK kinase [MEK] inhibitor [MEKi]) [9]. In this study, where most of the patients had proficient pMMR/MSS mCRC, the overall response rate (ORR) was 24.3% (95% confidence interval [CI] 11.9, 41.2) and the disease control rate was 70.3% (95% CI 53, 84.1). The benefit of adding a programmed death protein 1/programmed cell death ligand 1 inhibitor to a BRAFi and MEKi should now be investigated in a randomized study. Other emerging strategies for the treatment of $BRAF^{V600E}$ mCRC have been previously discussed [10, 11]. Concerning surgery at metastatic sites, the use of expert MDT assessment without segregation for mutational status is needed because important discrepancies have been shown in the literature between local and central evaluation of resectability in patients with *BRAF* mCRC (as high as 69% in a recent publication) [12]. Though they typically have a poor prognosis, patients with *BRAF* mCRC seem to derive long-term benefits from metastases resections [12, 13].

Algorithms for the management of patients with $BRAF^{V600E}$mCRC are available and help clinicians in the routine clinical practice [14]. For the first-line treatment, a chemotherapy regimen (5-fluorouracil-based doublet [FOLFOX or FOLFIRI] or triplet [FOLFOXIRI]) is usually associated with an anti-angiogenic agent (bevacizumab). While a meta-analysis showed no superiority of triplet chemotherapy + bevacizumab over doublet + bevacizumab, Moretto et al. reported real-life data supporting the use of FOLFOXIRI + bevacizumab in a subgroup of patients with right-sided $BRAF^{V600E}$ mCRC (versus left-sided tumours) [15, 16]. For patients with a dMMR/MSI tumour, pembrolizumab has shown a benefit both in ORR and progression-free survival (PFS) over chemotherapy in the first-line metastatic setting, regardless of *BRAF* status [17]. As the prognosis of patients with $BRAF^{V600E}$ mutations may be poor, regular follow-ups including CT scans must be done every 2 months during first-line treatment, in order to be able to change treatment as early as possible, where needed. In the second-line setting, a BRAFi combined with an anti-epidermal growth factor receptor (EGFR) is now widely used since it has shown improved tumour response rate, PFS, and OS in the randomized phase III BEACON trial [18, 19]; while adverse events are generally mild (mostly grade 1 or 2 in severity) and rarely lead to treatment discontinuation, they typically affect more than 50% of patients, with dermatological and digestive adverse events, pyrexia, and arthralgia mostly reported. Management strategies can be employed to help mitigate the impact of any adverse events. A dedicated nurse may be helpful in educating patients and caregivers on the disease, and possible adverse events of the treatment [20].

The choice of third-line treatments in patients with $BRAF^{V600E}$ mCRC depends on previously received treatment lines. If the patient received chemotherapy as first-line treatment, it is generally reintroduced in the third line, particularly if the PFS with this chemotherapy-based regimen was prolonged. If immunotherapy was given as first-line treatment (in dMMR/MSI mCRC), then a BRAFi combined with an anti-EGFR can be used for the second line and chemotherapy is introduced in the third line. In later lines of treatment, where more importance is placed on improving QoL, two oral therapies, regorafenib and trifluridine/tipiracil, have both demonstrated survival benefits [21, 22]. The recently published SUNLIGHT phase III trial established the combination therapy of trifluridine-tipiracil and bevacizumab as a new standard in patients with refractory mCRC [23]. Patients may also be offered the chance to participate in a clinical trial.

The treatment lines received by Guillaume do not follow the usual treatment algorithms proposed in France for patients with right-sided $BRAF^{V600E}$-mutated mCRC [14, 24]. In particular, Guillaume received immunotherapy, which is normally only prescribed to patients who have a dMMR/MSI tumour. In my view, the case of Guillaume illustrates the important role of the involvement of the patient and/or caregiver in understanding the disease and available

treatments in order to accelerate or facilitate access to innovative therapeutic approaches used in clinical trials. In daily practice, oncologists do not systematically discuss the possibility of entering a clinical trial from the early lines of treatment and there are several reasons for this. At the first consultation, the oncologist typically presents a huge amount of information to the patient. For most patients, this causes a massive amount of psychological distress, including uncertainty, disbelief, despair, vulnerability, fear, and anxiety; it can take a long time to process. As we interact with the patients at a high emotional level, too much information can generate additional stress and anxiety, so it is important to get the balance right. Therefore, a discussion about clinical trials requires a dedicated consultation. Another issue is that physicians are cautious regarding preliminary results from treatment candidates that have sometimes only been tested in phase I or II trials in a limited number of patients. Their concern is that promising efficacy may not be confirmed in a larger cohort within a phase III trial. Should the patient say at the first consultation "I would like to take part in a clinical trial", then we would of course discuss all possible options. However, for $BRAF^{V600E}$ mCRC, time is of the essence and there is a need to treat the patient symptoms (such as pain, fever, and risk of occlusion) as quickly as possible. It may be not reasonable to wait several weeks to get the patient to move to another institution to facilitate inclusion in a clinical trial. Moreover, oncologists may not be aware of ongoing clinical trials in the field of $BRAF^{V600E}$ mCRC in their vicinity. Indeed, in digestive oncology, physicians are not full-time specialists for only one specific cancer type and they have to deal with many different pathologies. Thus, it is unrealistic for all physicians to be fully up to date with all clinical trials in digestive oncology worldwide, including those for $BRAF^{V600E}$ mCRC.

I should add that some oncologists are not familiar with clinical trials at all. Indeed, all patients should be able to receive care in the facility of their choice and have the opportunity to be referred to an expert centre, where needed (and if that is what they want). This is the best way to guarantee the patient's choice of a specific therapeutic strategy, which could be an innovative treatment undergoing testing within a clinical trial.

The QoL of patients with mCRC and their caregivers is dramatically affected, as we can see in Guillaume and Laure's case. Oncologists are well aware that treatments have side effects that can add to the disease-associated symptoms which are already affecting the lives of our patients. Therefore, the therapeutic strategy is to have a balance between the advantages and disadvantages of treatments. Shared decision-making process includes a discussion of the potential impact on QoL and rate of adverse events associated with treatments. Regular discussions should cover the intensity of any undesirable effects in relation to the benefit that can be seen on a scan or via the improvement of symptoms. While we try to mitigate any side effects by using additional treatments (e.g., anti-emetics or emollient creams), treatment doses may sometimes need to be reduced or temporarily stopped. Alternative approaches such as aromatherapy, sophrology, and the use of cannabis for therapeutic purposes can be suggested to those patients whose side effects (e.g., nausea, anxiety) cannot be reduced by conventional treatments.

A focus on supportive care with nutrition and physical activity is important given that cases of $BRAF^{V600E}$ mCRC are frequently associated with peritoneal carcinomatosis. This is a rare form of cancer affecting the peritoneum and its presence means that digestive disorders may lead to undernutrition. Additional psychological and/or social care may also be needed for those patients who are isolated and/or who need financial assistance. Studies have demonstrated the value of effective communication between a patient and their healthcare team and provider [25–27]. Patients' needs remain important: early referral to palliative and supportive care services can benefit patients' psychological and physical well-being and also improves survival, while caregivers can also benefit.

As mentioned by Laure above, patients' associations are an essential element in the care pathway and in the general support of patients and those close to them. Therefore, I inform

patients of these groups as soon as possible, but not usually at the first consultation as it is often hard for them to assimilate lots of information about the disease and treatments. There are dedicated services in many hospitals—Espace de Rencontres et d'Information (ERI)—where patients and their families can also find information about what they are about to experience during the course of the disease. The ERI enables patients to be directed to patients' associations and/or other professionals in order to cope and benefit from the most individualized follow-up. Patients' associations can support and accompany patients and caregivers, not only helping them to develop their skills but also in searching for information; they actively contribute to the quality of care of these patients. Today, expert patients facilitate the link between medical teams and caregivers, and we would gain more by collaborating further with patients' associations, for example, in the development of clinical trials, treatment recommendations, and decision algorithms.

CONCLUSION

In recent years, improved diagnostic techniques and the availability of multiple treatments, including various chemotherapy schemes and molecular-targeted drugs, have lowered mortality and improved prognosis in CRC. Research in this field has made considerable progress and it is important for treatment algorithms to be implemented. Today, new treatments offer a level of hope: some strategies are based on blocking the signalling pathway at different downstream or upstream sites other than *BRAF*, with combined treatment strategies also in clinical development. While the prognosis of $BRAF^{V600E}$ mCRC is typically worse than a cancer without this mutation, not all mutated cancers have such a bad prognosis and there is still considerable work to do at a medical and scientific level. For example, there is an ongoing need to apply criteria in clinical practice to determine which patients have the worst prognosis, along with identification of those who may achieve better outcomes. In addition, as some $BRAF^{V600E}$ tumours are resistant to anti-*BRAF*-based treatments, there is a lot of research needed to understand the underlying biological processes (e.g., additional mutations or tumour modification) in order to develop effective treatments. The identification of novel prognostic (such as plasma circulating tumour DNA [28]) and predictive biomarkers [29] to guide individualized treatment plans is also critical to overcoming therapeutic resistance. In parallel with this, it is essential to consider the knowledge that patients and their caregivers have of their disease and treatments, along with the impact on QoL. Patients' associations have a major role to play here, in the general support of patients and those close to them, and in facilitating the link with healthcare professionals.

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