Clinical Trial Protocol

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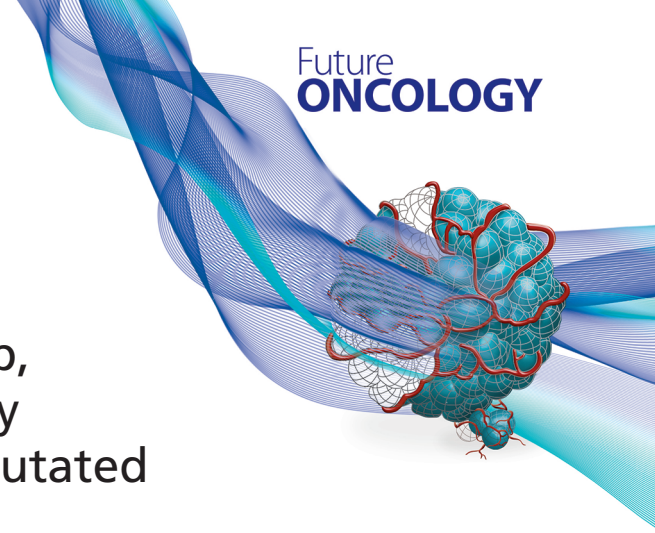

TRESBIEN (OGSG 2101): encorafenib, binimetinib and cetuximab for early recurrent stage II/III *BRAF* V600E-mutated colorectal cancer

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The *BRAF* V600E mutation accounts for approximately 5% of colorectal cancer (CRC) cases and is an extremely poor prognostic factor. However, there are no clear recommendations regarding first-line therapy for patients with early recurrent *BRAF* V600E-mutated CRC, during or after adjuvant chemotherapy. Recently, a novel combination of encorafenib, binimetinib and cetuximab, showed a higher response rate than standard chemotherapy in patients with *BRAF* V600E-mutated CRC. Here we describe our plan for the TRESBIEN study (OGSG 2101), which is an open-label, multicenter, single-arm, phase II study designed to evaluate whether encorafenib, binimetinib and cetuximab are effective for patients with early recurrent *BRAF* V600E-mutated colorectal cancer, during or after adjuvant chemotherapy. The planned number of subjects is 25.

Plain language summary: An ongoing study to evaluate encorafenib, binimetinib and cetuximab for people with early recurrent *BRAF* V600E-mutated colorectal cancer. *BRAF* V600E-mutated colorectal cancer (CRC) is a type of cancer caused by change (mutation) in a gene called *BRAF*. It is one of the most difficult types of CRC to treat because currently available drugs do not effectively treat the disease. Recently, two novel treatments, encorafenib and cetuximab, have been approved for use together in several countries for the treatment of advanced or metastatic *BRAF* V600E-mutated CRC. In Japan, these drugs are also approved to be given with another treatment called binimetinib, an approach called triplet therapy. This article describes the ongoing TRESBIEN study that is looking at how effective and how safe triplet therapy is for the treatment of people with early recurrent *BRAF* V600E-mutated CRC, during or after they have additional (adjuvant) chemotherapy. This study is ongoing, and the researchers are currently recruiting new participants. TRESBIEN will evaluate the percentage of participants whose tumors shrink with triplet therapy. The study will also look at any side effects.

Clinical Trial Registration: jRCTs051210152 (ClinicalTrials.gov) (Japan Registry of Clinical Trials https://jrct.niph.go.jp/search?language=en&page=1).

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Keywords: binimetinib (MEK inhibitor) • *BRAF* V600E • cetuximab • colorectal cancer • early recurrence • encorafenib (BRAF inhibitor) • triplet therapy

Colorectal cancer (CRC) is the second most common cause of cancer-related death, with approximately 900,000 fatalities worldwide each year [1]. The median overall survival (OS) without chemotherapy for unresectable or recurrent CRC is approximately 8 months. However, with advances in chemotherapy and molecular-targeted therapy, median OS is expected to exceed 30 months, even after the diagnosis of unresectable disease [2–4]. Nevertheless, the goal of chemotherapy is not to cure the disease, but to prolong survival time and control symptoms by slowing tumor progression; therefore, more effective treatment options are needed.

The *BRAF* V600E mutation accounts for approximately 5% of CRC cases [5–7] and is an extremely poor prognostic factor [8,9]. Although the standard-of-care for early recurrent *BRAF* V600E-mutated CRC during or after adjuvant chemotherapy has not been established, the combination of fluorouracil plus levofolinate, oxaliplatin and irinotecan (FOLFOXIRI) plus bevacizumab (BEV) has been considered the optimal treatment based on the results of a subgroup analysis of the TRIBE trial [10,11]. However, a subsequent meta-analysis of five trials, including TRIBE, found no difference in survival between fluorouracil plus levofolinate and either oxaliplatin or irinotecan (FOLFOX/FOLFIRI) plus BEV or FOLFOXIRI plus BEV [12]. EGFR antibodies, which show significant efficacy in *RAS* wild-type CRC, have limited efficacy in *BRAF* V600E-mutated CRC and are not recommended [13]. Based on the above, FOLFOXIRI plus BEV or FOLFOX/FOLFIRI plus BEV is usually considered for early recurrent *BRAF* V600E-mutated CRC, depending on individual characteristics (performance status, organ function etc.).

Recently, a novel combination of molecular-targeted agents – encorafenib (BRAF inhibitor), binimetinib (MEK inhibitor) and cetuximab (anti-EGFR monoclonal antibody) – significantly prolonged OS and showed a higher response rate than the standard-of-care in patients with previously treated metastatic CRC with the *BRAF* V600E mutation [14]. Furthermore, in first-line chemotherapy for *BRAF* V600E-mutated CRC, triplet therapy showed a promising tumor shrinkage and disease control rate (DCR) [15]. These results suggest that triplet therapy may be effective even in early recurrent *BRAF* V600E-mutated CRC during or after adjuvant chemotherapy; however, there are no prospective data demonstrating its efficacy in this population. To investigate this possibility, we designed the phase II TRESBIEN study (OGSG 2101) to investigate whether encorafenib, binimetinib and cetuximab are effective first-line treatments in patients with early recurrent *BRAF* V600E-mutated CRC during or after adjuvant chemotherapy. Here we describe the protocol for the phase II TRESBIEN study.

Methods & design

Study design & treatment

The TRESBIEN study is an open-label, multicenter, single-arm, phase II study designed to evaluate whether encorafenib, binimetinib and cetuximab are effective in patients with early recurrent *BRAF* V600E-mutated CRC, during or after adjuvant chemotherapy (Figure 1). The study was approved by the Clinical Research Review Board of the Osaka General Medical Center and is currently ongoing at 21 medical facilities in Japan (version 1.1 protocol approved on 17 August 2022). The main inclusion criteria were histologically confirmed *RAS* wild-type and *BRAF* V600E-mutated stage II/III adenocarcinoma of the colon or rectum after radical resection; imaging evidence of recurrence during or within 6 months of adjuvant chemotherapy; no prior treatment with encorafenib, binimetinib or cetuximab; age ≥20 years; Eastern Co-operative Oncology Group performance status 0–2; measurable lesions based on the Response Evaluation Criteria in Solid Tumors guidelines (v. 1.1); adequate organ function; and sufficient oral ingestion function. Regimens of adjuvant chemotherapy are not fixed and vary between institutions. The complete list of inclusion and exclusion criteria is given in Table 1. *RAS* and *BRAF* testing are performed locally. Patients will receive oral encorafenib at 300 mg daily, oral binimetinib at 45 mg orally twice daily and intravenous cetuximab weekly at 250 mg/m^2 after the first dose of 400 mg/m^2. Treatment will continue until disease progression, unacceptable toxicity, death, patient refusal or investigator's decision. There are no prescribed treatments following completion or discontinuation of the protocol treatment. The planned enrollment period is

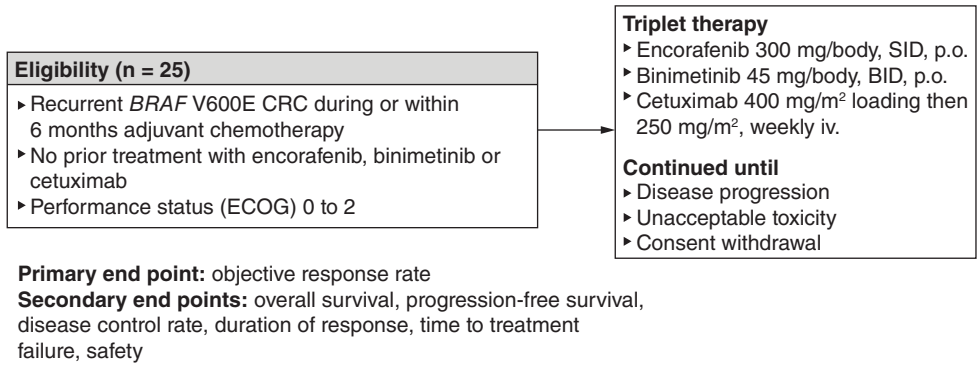

Figure 1. TRESBIEN study design.
BID: Bis in die (twice a day); CRC: Colorectal cancer; ECOG: Eastern Co-operative Oncology Group; iv.: Intravenous; p.o. : Per os; SID: Semel in die (once a day).

from January 2022 to December 2024, and the observation period will include a 1-year follow-up period from the time the last patient is enrolled. No interim analyses will be performed.

End points & assessments

The primary objective of this study is to determine whether encorafenib, binimetinib and cetuximab are effective in patients with early recurrent *BRAF* V600E-mutated CRC in terms of objective response rate (ORR) assessed by central review. The secondary end points are OS, progression-free survival (PFS), DCR, duration of response (DoR), time-to-treatment failure (TTF) and rate of adverse events (AEs). Disease assessment is performed every 8 weeks using computed tomography scanning and/or MRI. Responses are determined based on the Response Evaluation Criteria in Solid Tumors (v. 1.1). The ORR is defined as the percentage of patients relative to the total number of enrolled subjects who achieved a complete or partial response based on imaging. A central review will be performed to evaluate ORR following our established procedure. OS is defined as the time from study enrolment to the date of death due to any cause; PFS is defined as the time from study enrolment to first disease progression or death, whichever occurs first; DCR is defined as the percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease to a therapeutic intervention; duration of response is defined as the time from first response to time of progression; and time to treatment failure is defined as the interval from initiation of chemotherapy to its premature discontinuation. All AEs observed during the study treatment period will be appropriately registered in the subjects' medical records and electronic case report forms. All serious AEs, namely fatal or life-threatening AEs, those requiring hospitalization or resulting in persistent or significant disability/incapacity, must be disclosed by the investigator following the guideline for Good Clinical Practice. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (v. 5.0).

Target sample size & statistical analyses

The primary end point of this study is the ORR. There are no specific data on the effect of ORR on early recurrence of *BRAF* V600E-mutated CRC. In a large phase III trial (the BEACON CRC study), the encorafenib, binimetinib and cetuximab combination showed better ORR (26.1%; 95% CI: 18.2–35.3) compared with cetuximab and irinotecan or cetuximab and FOLFIRI (1.9%; 95% CI: 0.2–6.6) in *BRAF* V600E-mutated metastatic CRC as second- or third-line treatment [14]. Based on these results, the expected ORR in this study was 26.0%. To achieve 90% power to show a significant response benefit with a one-sided α level of 0.05, and assuming a threshold ORR of 6.0%, we estimated that 23 patients would be necessary. Considering dropouts, a total of 25 patients were planned for enrolment. The following hypothesis will be tested using the exact binomial test, and the CIs for the response rates calculated using the Clopper–Pearson exact method. The sample size was calculated using PASS v. 21.0.3 (NCSS, LLC, UT, USA).

Discussion

Since the 1990s the standard adjuvant therapy has been 6 months of fluoropyrimidine-based monotherapy or a combination with oxaliplatin [16]. However, persisting neurosensory toxicity caused by oxaliplatin has been a serious

Table 1. Patient inclusion and exclusion criteria.

Inclusion criteria
1. Histologically diagnosed adenocarcinoma of the colon or rectum (excluding appendiceal cancer and anal canal cancer)
2. Patients with *RAS* wild-type and *BRAF* V600E mutation proved by tumor tissue
3. Patients who received postoperative adjuvant chemotherapy after stage II/III radical resection and fulfill any of the following criteria:
a. Recurrence during adjuvant chemotherapy
b. Recurrence within 6 months after postoperative adjuvant chemotherapy due to AEs
c. Recurrence within 6 months after scheduled adjuvant chemotherapy
4. No prior treatment with encorafenib, binimetinib or cetuximab
5. Measurable lesions based on RECIST v1.1
6. Performance status (ECOG) 0–2
7. Age ≥20 years
8. Patients who can take oral medication
9. Fulfill all of the following conditions:
a. Neutrophil count ≥1200/mm^3
b. Hemoglobin ≥9.0 g/dl (no blood transfusion within 14 days prior to registration)
c. Platelet count ≥75,000/mm^3
d. Total bilirubin ≤2.0 mg/dl
e. ALT ≤100 IU/l, AST ≤100 IU/l (≤200 IU/l in patients with liver metastasis)
f. Serum creatinine ≤1.5 mg/dl or creatinine clearance calculated by the Cockcroft–Gault equation or measured directly is ≥50 ml/min
10. Patients are expected to survive for at least 12 weeks
11. With written informed consent
Exclusion criteria
1. Synchronous or metachronous active malignancies with a disease-free interval of 5 years or less
2. Symptomatic brain metastasis or meningitis
3. Women who are pregnant, breastfeeding or who wish to conceive; men who wish to conceive
4. Unrecovered grade 2 or higher (CTCAE v. 5.0) AEs related to previous treatment (excluding anemia, alopecia, skin pigmentation and oxaliplatin-induced peripheral neuropathy and proteinuria)
5. Patients with active infections (fever of ≥38°C)
6. History of myocardial infarction, severe/unstable angina, NYHA class III or IV symptomatic congestive heart failure within the past 6 months from the date of enrollment
7. Poorly controlled hypertension with a systolic blood pressure of 150 mm Hg or diastolic blood pressure of 100 mm Hg or higher, even with medication
8. Poorly controlled active hepatitis B with detectable HBV DNA despite the administration of nucleic acid analogs, active hepatitis C with positive HCV RNA, or known HIV infection
9. Ascites, pleural effusion or pericardial effusion requiring continuous drainage on the date of enrollment
10. Patients with a history of, or currently suffering from, retinal vein occlusion, or at risk for such occlusion
11. Patients with concomitant psychosis or psychiatric symptoms that make it difficult to participate in clinical research
12. Patient treated with any of the following within a certain period of time prior to the start of protocol treatment:
a. Extensive surgery within 4 weeks (excluding central venous port placement)
b. Stoma surgery within 2 weeks
13. Other cases in which physicians judge that the subject is inappropriate for this clinical research

AE: Adverse event; ALT: Alanine aminotransferase; AST: Aspartate transaminase; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Co-operative Oncology Group; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NYHA: New York Heart Association; RECIST: Response Evaluation Criteria In Solid Tumors.

concern [17]. Based on the result of pooled analysis comparing 3 versus 6 months of fluoropyrimidine and oxaliplatin (the IDEA consortium), 3 months of capecitabine and oxaliplatin is preferred in low-risk stage III (T1–3/N1) CRC [18]. Conventionally, adjuvant chemotherapy for *BRAF* V600E-mutated CRC is performed similarly to that for wild-type tumors. Exploratory analyses of the correlation between genetic mutations and prognosis have been performed in several past clinical trials on perioperative chemotherapy [19–22]. Indeed, a meta-analysis including these trials showed that *BRAF* V600E-mutated stage II/III CRC had poorer OS (hazard ratio [HR]: 1.42; 95% CI: 1.25–1.60; $p < 0.00001$) and PFS (HR: 1.26; 95% CI: 1.07–1.48; $p = 0.006$) than the wild-type tumors [23].

Based on the results of meta-analyses, including the TRIBE trial [12], FOLFOX/FOLFIRI or FOLFOXIRI plus BEV has been applied to recurrent *BRAF* V600E-mutated CRC according to patient characteristics. Although

there are no reports of detailed outcomes for the subgroup of early recurrent *BRAF* V600E-mutated CRC during or after adjuvant chemotherapy, the outcomes of first-line chemotherapy in early recurrence can be considered to approximate those of second-line chemotherapy. In a retrospective report comparing the outcomes of first-, second- and third-line chemotherapy for *BRAF* V600E-mutated CRC, the median PFS for first-line chemotherapy was 6.3 months (95% CI: 4.9–7.7), while that for second-line chemotherapy was worse at 2.5 months (95% CI: 1.8–3.0) [24]. Another single-center retrospective report from Japan also showed that *BRAF* V600E-mutated CRC patients had a poor PFS of 2.5 months (95% CI: 1.91–4.11) and OS of 6.5 months (95% CI: 4.30–9.63) with second-line chemotherapy, while the response rate to conventional cytotoxic chemotherapy was reported to be 0% [25]. The development of novel therapies for *BRAF* V600E-mutated CRC is urgently required.

In preclinical models, the combination of BRAF and EGFR inhibition synergistically suppresses the MAPK pathway, leading to tumor regression in *BRAF* V600E-mutated CRC [26,27]. To suppress MAPK signaling more robustly, the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib was administered in *BRAF* V600E-mutated CRC as well as in malignant melanoma and non-small-cell lung cancer [28,29]. The response rate of this combination was 12%, which was better than that of a single agent, although pre- and post-biopsy specimens showed that suppression of the MAPK pathway was insufficient even with RAF/MEK dual inhibition. To control *BRAF* V600E-mutated CRC, inhibition of RAS activation via EGFR is important [30].

Fueled by these molecular biological findings, the phase III BEACON CRC study was recently published, in which 665 patients with *BRAF* V600E-mutated metastatic CRC who had disease progression after one or two previous treatment regimens were randomized (1:1:1) to receive encorafenib, binimetinib and cetuximab (triplet therapy) versus encorafenib and cetuximab (doublet therapy) versus irinotecan plus FOLFIRI and cetuximab as control therapy [31]. This study showed that both triplet and doublet therapies have clinical benefits compared with the control group in second- or third-line treatment. In the updated analysis, median OS was 9.3 months (95% CI: 8.2–10.8) for triplet and 5.9 months (95% CI: 5.1–7.1) for control (HR: 0.60; 95% CI: 0.47–0.75). The median OS for doublet was 9.3 months (95% CI: 8.0–11.3) (HR: 0.61; 95% CI: 0.48–0.77). The confirmed ORR results by blinded independent review were 26.8% (95% CI: 21.1–33.1) for triplet, 19.5% (95% CI: 14.5–25.4) for doublet and 1.8% (95% CI: 0.5–4.6%) for control [31]**.** The ORR and depth of response tended to be better with triplet therapy than with doublet therapy, and the rates of treatment discontinuation due to AEs were similar in each group (8 and 7%, respectively). Regarding first-line chemotherapy for *BRAF* V600E-mutated CRC, the single-arm, phase II ANCHOR CRC study showed that triplet therapy had a promising response rate of 47.8% (95% CI: 37.3–58.5) and 88% disease control [15]. Additionally, other clinical trials have evaluated the efficacy of combined BRAF and EGFR inhibition, combined MEK and EGFR inhibition, and combined BRAF, EGFR and MEK inhibition (dabrafenib, panitumumab and trametinib) in patients with metastatic *BRAF* V600E-mutated CRC. The confirmed response rates in these groups were 10% (dabrafenib and panitumumab), 0% (panitumumab and trametinib) and 21% (triplet), respectively. The median PFS durations were 3.5 (95% CI: 2.8–5.8), 2.6 (95% CI: 1.4–2.8) and 4.2 months (95% CI: 4.0–5.6), respectively [32]. These clinical trials suggest that triplet therapy has promising efficacy in *BRAF* V600E-mutated CRC. Because early recurrent *BRAF* V600E-mutated CRC is anticipated to have a poor prognosis, we chose triplet therapy as the treatment protocol, expecting a higher ORR and deeper response. In addition, this study population includes patients with oligometastatic disease. The higher response rate of triplet therapy may contribute to an increase in curable conversion surgery rates.

The TRESBIEN study focuses on *BRAF* V600E-mutated CRC that recurred only during or within 6 months of adjuvant chemotherapy. Targeting *BRAF* V600E-mutated CRC, the BREAKWATER study, a phase III study comparing encorafenib and cetuximab with or without chemotherapy as first-line therapy with standard therapy is ongoing. Although the safety lead-in part of this study showed promising antitumor activity and tolerability of doublet with chemotherapy, patients with early relapse within 6 months were excluded from the study [33] As early recurrent cancer can be resistant to cytotoxic chemotherapy and can benefit from molecular-targeted agents, we planned to target this population.

Conclusion

The TRESBIEN study is the first trial to evaluate the efficacy of triplet therapy in early recurrent *BRAF* V600E-mutated CRC. The planned enrolment period is from January 2022 to December 2024. Five patients have already been enrolled in the study.

Executive summary

***BRAF* V600E-mutated colorectal cancer**

- The *BRAF* V600E mutation accounts for approximately 5% of colorectal cancer (CRC) cases and is an extremely poor prognostic factor.

BEACON triplet therapy

- Recently, a novel combination of encorafenib, binimetinib and cetuximab showed a higher response rate than standard chemotherapy in patients with *BRAF* V600E-mutated CRC.

TRESBIEN study (OGSG 2101)

- The TRESBIEN study (OGSG 2101) is an open-label, multicenter, single-arm phase II study in Japan designed to evaluate whether encorafenib, binimetinib and cetuximab are effective for patients with early recurrent *BRAF* V600E-mutated CRC, during or after adjuvant chemotherapy. The planned number of subjects is 25.

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Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The current study has been approved by the clinical research review board of Osaka General Medical Center (T2021002), and permission for conducting the study has been obtained from the managements of all participating facilities. Written informed consent for participation will be obtained from all participants. This trial has been registered in the Japan Registry of Clinical Trials (jRCTs051210152).

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Sung H, Ferlay J, Siegel RL *et al.* Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 71(3), 209–249 (2021).
2. Miyamoto Y, Suyama K, Baba H. Recent advances in targeting the EGFR signaling pathway for the treatment of metastatic colorectal cancer. *Int. J. Mol. Sci.* 18(4), 752 (2017).
3. Baraniskin A, Buchberger B, Pox C *et al.* Efficacy of bevacizumab in first-line treatment of metastatic colorectal cancer: a systematic review and meta-analysis. *Eur. J. Cancer* 106, 37–44 (2019).

4. Glimelius B, Stintzing S, Marshall J, Yoshino T, de Gramont A. Metastatic colorectal cancer: advances in the folate–fluoropyrimidine chemotherapy backbone. *Cancer Treat. Rev.* 98, 102218 (2021).
5. Yokota T, Ura T, Shibata N *et al. BRAF* mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer. *Br. J. Cancer* 104(5), 856–862 (2011).
6. Kawazoe A, Shitara K, Fukuoka S *et al.* A retrospective observational study of clinicopathological features of *KRAS, NRAS, BRAF* and *PIK3CA* mutations in Japanese patients with metastatic colorectal cancer. *BMC Cancer* 15, 258 (2015).
7. Ikoma T, Shimokawa M, Kotaka M *et al.* Clinical and prognostic features of patients with detailed *RAS*/*BRAF*-mutant colorectal cancer in Japan. *BMC Cancer* 21(1), 518 (2021).
8. Schirripa M, Bergamo F, Cremolini C *et al. BRAF* and *RAS* mutations as prognostic factors in metastatic colorectal cancer patients undergoing liver resection. *Br. J. Cancer* 112(12), 1921–1928 (2015).
9. 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.* 18(23), 6531–6541 (2012).
10. Loupakis F, Cremolini C, Salvatore L *et al.* FOLFOXIRI plus bevacizumab as first-line treatment in *BRAF* mutant metastatic colorectal cancer. *Eur. J. Cancer* 50(1), 57–63 (2014).
11. Cremolini C, Loupakis F, Antoniotti C *et al.* FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol.* 16(13), 1306–1315 (2015).
12. Cremolini C, Antoniotti C, Stein A *et al.* Individual patient data meta-analysis of FOLFOXIRI plus bevacizumab versus doublets plus bevacizumab as initial therapy of unresectable metastatic colorectal cancer. *J. Clin. Oncol.* doi:10.1200/JCO.20.01225(2020) (Epub ahead of print).

• **FOLFOXIRI+bevacizumab is a powerful regimen but does not prolong survival in patients with *BRAF* V600E mutation.**

13. 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.* 26(35), 5705–5712 (2008).
14. Kopetz S, Grothey A, Yaeger R *et al.* Encorafenib, binimetinib, and cetuximab in *BRAF* V600E-mutated colorectal cancer. *N. Engl. J. Med.* 381(17), 1632–1643 (2019).

•• **Pivotal phase III trial which showed survival benefit with molecular-targeted combination therapy in *BRAF* V600E-mutated colorectal cancer.**

15. Cutsem EV, Taieb J, Yaeger R *et al.* O-10 ANCHOR CRC: results from a single-arm, phase 2 study of encorafenib, binimetinib plus cetuximab in previously untreated *BRAF* V600E-mutant metastatic colorectal cancer. *Ann. Oncol.* 32(Suppl. 3), S222 (2021).

• **The triplet combination is effective in first-line *BRAF* V600E-mutated colorectal cancer treatment.**

16. Moertel CG, Fleming TR, Macdonald JS *et al.* Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N. Engl. J. Med.* 322(6), 352–358 (1990).
17. André T, Boni C, Navarro M *et al.* Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J. Clin. Oncol.* 27(19), 3109–3116 (2009).
18. Grothey A, Sobrero AF, Shields AF *et al.* Duration of adjuvant chemotherapy for stage III colon cancer. *N. Engl. J. Med.* 378(13), 1177–1188 (2018).
19. French AJ, Sargent DJ, Burgart LJ *et al.* Prognostic significance of defective mismatch repair and *BRAF* V600E in patients with colon cancer. *Clin. Cancer Res.* 14(11), 3408–3415 (2008).
20. Roth AD, Delorenzi M, Tejpar S *et al.* Integrated analysis of molecular and clinical prognostic factors in stage II/III colon cancer. *J. Natl Cancer Inst.* 104(21), 1635–1646 (2012).
21. Sinicrope FA, Mahoney MR, Yoon HH *et al.* Analysis of molecular markers by anatomic tumor site in stage III colon carcinomas from adjuvant chemotherapy trial NCCTG N0147 (Alliance). *Clin. Cancer Res.* 21(23), 5294–5304 (2015).
22. André T, de Gramont A, Vernerey D *et al.* Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to *BRAF* mutation and mismatch repair status of the MOSAIC study. *J. Clin. Oncol.* 33(35), 4176–4187 (2015).
23. Zhu L, Dong C, Cao Y *et al.* Prognostic role of *BRAF* mutation in stage II/III colorectal cancer receiving curative resection and adjuvant chemotherapy: a meta-analysis based on randomized clinical trials. *PLOS ONE* 11(5), e0154795 (2016).

• **Stage II/III *BRAF* V600E-mutated colorectal cancer patients have poorer overall survival than those with *BRAF* wild-type tumors.**

24. Morris V, Overman MJ, Jiang Z-Q *et al.* Progression-free survival remains poor over sequential lines of systemic therapy in patients with *BRAF*-mutated colorectal cancer. *Clin. Colorectal Cancer* 13(3), 164–171 (2014).
25. Mitani S, Taniguchi H, Sugiyama K *et al.* The impact of the Glasgow Prognostic Score on survival in second-line chemotherapy for metastatic colorectal cancer patients with *BRAF* V600E mutation. *Ther. Adv. Med. Oncol.* 11, 1758835918820298 (2019).
26. 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.* 2(3), 227–235 (2012).

27. Prahallad A, Sun C, Huang S *et al.* Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature* 483(7387), 100–103 (2012).

28. Flaherty KT, Infante JR, Daud A *et al*. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N. Engl. J. Med.* 367(18), 1694–703 (2012).

29. Planchard D, Besse B, Groen HJM *et al*. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol.* 17(7), 984–993 (Year).

30. 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.* 33(34), 4023–4031 (2015).

31. Tabernero J, Grothey A, Cutsem EV *et al.* Encorafenib plus cetuximab as a new standard of care for previously treated *BRAF* V600E-mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON study. *J. Clin. Oncol.* 39(4), 273–284. (2021).

32. Corcoran RB, André T, Atreya CE *et al.* Combined BRAF, EGFR, and MEK inhibition in patients with *BRAF* V600E-mutant colorectal cancer. *Cancer Discov.* 8(4), 428–443 (2018).

33. Tabernero J, Yoshino T, Kim TW *et al*. LBA26 – BREAKWATER safety lead-in (SLI): encorafenib (E)+cetuximab (C)+chemotherapy (chemo) for *BRAF* V600E metastatic colorectal cancer (mCRC). *Ann. Oncol.* 33(Suppl. 7), S808–S869 (2022).

- **Although a small number of cases, encorafenib + cetuximab + chemotherapy showed promising efficacy and safety.**