Title
Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer

Journal
New England Journal of Medicine, 382(9)

ISSN
0028-4793

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Publication Date
2020-02-27

DOI
10.1056/nejmc1915676

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TO THE EDITOR: Kopetz et al. (Oct. 24 issue)[1] found an overall survival benefit of triplet therapy (encorafenib, binimetinib, and cetuximab) as compared with control therapy (cetuximab with either irinotecan or FOLFIRI [folinic acid, fluorouracil, and irinotecan]) among patients with *BRAF*-mutated colorectal cancer. The trial also included a third group that received doublet therapy (encorafenib and cetuximab). Although the trial was not powered to compare the triplet-therapy group with the doublet-therapy group, a number of observations favor the doublet-therapy group.

First, among more than 200 patients in each group, the median progression-free survival was similar in the doublet-therapy group and the triplet-therapy group (4.2 months and 4.3 months, respectively). Second, another measure of treatment efficacy, disease control (complete or partial response or stable disease), was similar in the doublet-therapy group and the triplet-therapy group (74% and 68% of patients, respectively) (Table 2 of the article). Third, among patients with a response, the percentage of those who had the response maintained for 6 months or longer was higher in the doublet-therapy group than in the triplet-therapy group (43% vs. 24%) (Table 2 of the article). In addition, the incidence of adverse events of grade 3 or higher was lower in the doublet-therapy group than in the triplet-therapy group (50% vs. 58%) (Table 3 of the article).

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No potential conflict of interest relevant to this letter was reported.

1. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in *BRAF* V600E–mutated colorectal cancer. N Engl J Med 2019;381:1632-43.

DOI: 10.1056/NEJMc1915676

TO THE EDITOR: The investigators in the BEACON CRC (Binimetinib, Encorafenib, and Cetuximab Combined to Treat *BRAF*-Mutant Colorectal Cancer) trial report an overall survival advantage with encorafenib, binimetinib, and cetuximab over control treatment (investigator's choice of irinotecan-containing chemotherapy plus cetuximab). The interpretation of these results requires additional information that was not provided in their article or in the protocol or Supplementary Appendix (which are available with the full text of the article at NEJM.org). What percentage of patients received adjuvant therapy? What adjuvant therapies were given, at what frequency, and for how many cycles? What drugs, as part of what regimens, at what frequency, and for how many cycles, were given for the first-line treatment of metastatic disease? What was the median time from the diagnosis of metastatic colorectal cancer to enrollment in the trial? What post-protocol therapies were given, line by line, at what frequency? Can the authors report the pre-trial and post-trial chemotherapy received by patients according to geographic region of enrollment?

Finally, can the authors post a version of the protocol that does not contain redactions, which occur in the inclusion criteria and end-points sections of the document?

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Editor's note: The correct version of the protocol was posted with the full text of the article at NEJM.org as soon as we learned that an incorrect redacted version was online.

No potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc1915676

TO THE EDITOR: The results of the BEACON CRC trial of triple or dual targeted combination therapies in patients with *BRAF*-mutated metastatic colorectal cancer are practice-changing. Given the high prevalence (approximately 30%) of microsatellite instability among patients with *BRAF*-mutated metastatic colorectal cancer, it would be useful to know the results of retrospective analyses of both the triplet and doublet experi-

mental therapies as compared with the control therapy according to subgroups of microsatellite instability status, in terms of overall survival, progression-free survival, and objective response rate (which was one of the primary end points).

Despite the clear need for new treatment options for patients with microsatellite-stable, *BRAF*-mutated metastatic colorectal cancer, immune checkpoint inhibitors have provided long-term disease control in patients with metastatic colorectal cancer with a high level of microsatellite instability. The availability of these immunotherapy drugs could explain the relatively low prevalence (<10%) of microsatellite instability among patients enrolled in this trial. It is important to know the relative efficacy of targeted combination therapies in this molecular subgroup, since poorer outcomes and rapid onset of resistance have been reported in trials of first-line therapy with anti–epidermal growth factor receptor (EGFR) agents in patients with cancer without *RAS* or *BRAF* mutations.[1,2]

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Dr. Pietrantonio reports receiving consulting fees and lecture fees from Servier, Merck Serono, Eli Lilly, Roche, Amgen, Sanofi, and Bayer and grant support from Bristol-Myers Squibb. No other potential conflict of interest relevant to this letter was reported.

1. Innocenti F, Ou FS, Qu X, et al. Mutational analysis of patients with colorectal cancer in CALGB/SWOG 80405 identifies new roles of microsatellite instability and tumor mutational burden for patient outcome. J Clin Oncol 2019;37:1217-27.
2. Morano F, Corallo S, Lonardi S, et al. Negative hyperselection of patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer who received panitumumab-based maintenance therapy. J Clin Oncol 2019;37:3099-110.

DOI: 10.1056/NEJMc1915676

THE AUTHORS REPLY: We agree with Sharma and Vanidassane that the BEACON CRC trial was not powered to evaluate the triplet-therapy group against the doublet-therapy group. We are not able to make a definite conclusion regarding the relative benefits of the doublet or triplet regimen owing to limited follow-up at the time of publication.

Prasad requests additional information about the patients' backgrounds. A total of 11% of the patients in the trial had received adjuvant therapy previously. First-line therapy for patients who had undergone randomization in our trial reflected existing patterns of care, with more than 90% of patients having received a fluoropyrimidine and oxaliplatin previously. Patients were stratified according to previous irinotecan use, and results from the trial suggested that patients benefited from the triplet or doublet therapy regardless of previous irinotecan treatment. Therapies administered after disease progression were consistent with the absence of meaningfully active therapy, with the most common being fluorouracil and irinotecan. All these factors were well balanced across the groups and would not be expected to affect this trial of salvage therapy because these characteristics have not been shown to influence the natural history in patients with relapsed *BRAF*-mutated metastatic colorectal cancer.

Pietrantonio requests a retrospective efficacy analysis according to microsatellite instability subgroups. A review of the literature of the prevalence of microsatellite instability in *BRAF*-mutated metastatic colorectal cancer, including a meta-analysis and data from a recent randomized trial, suggests that less than 20% of patients who have tumors with a *BRAF* V600E mutation have a high level of microsatellite instability and deficient mismatch repair[1,2] — findings that are consistent with those of our trial. Our article showed that the hazard ratio for death was 0.52 (95% confidence interval [CI], 0.39 to 0.70) in the general population and 0.67 (95% CI, 0.26 to 1.76) in the subgroup with a high level of microsatellite instability.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal

cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res 2014;20:5322-30.
2. Kopetz S, McDonough SL, Lenz H-J, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406) J Clin Oncol 2017;35:15 Suppl:3505. abstract.

DOI: 10.1056/NEJMc1915676

Medicine and the Mind

TO THE EDITOR: In the Perspective article by Gardner and Kleinman (Oct. 31 issue),[1] the authors present concerns regarding the current state of psychiatry. They lament the "checklist" approach that characterizes too much of modern psychiatric practice in lieu of consideration of the full biopsychosocial picture of the complex person seeking care. As director of the National Institute of Mental Health (NIMH), whose mission it is to support basic and clinical research to combat mental illnesses, I share the authors' concerns and their understanding of the importance of diverse approaches to address the problems our patients face.

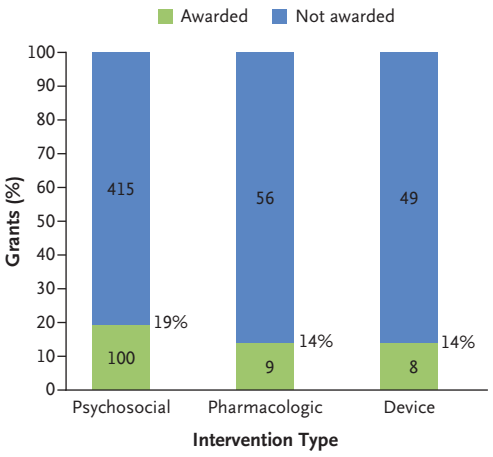

Figure 1. NIMH Clinical Trial Applications and Awards in Fiscal Years 2015 through 2018, According to Intervention Type.

Shown are the total numbers of clinical trial applications received by the National Institutes of Mental Health (NIMH) and grants awarded in fiscal years 2015 through 2018, according to intervention type. These data were presented at the open session of the National Advisory Mental Health Council May 2019 meeting (data source: National Institutes of Health Query, View, Report system, with manual curation by subject-matter experts; data were accessed on May 16, 2019).[4] Each application, regardless of version, counted as an instance of an award in the given period. The NIMH solicits clinical trial applications primarily through the Clinical Trial Pipeline Funding Opportunity Announcements (FOAs)[3]; thus, only clinical trial research grant applications that responded to those FOAs were included in this analysis.

The NIMH vigorously supports a broad portfolio of excellent science. To improve mental health care, the NIMH spends more than 80% of its research dollars on disease-focused research, with about half directed toward therapeutics and services research.[2] We continue to robustly support psychosocial research — the majority of currently funded clinical trials have been testing such approaches (Fig. 1).[3] These studies have had immediate and powerful effects, including nationwide implementation of coordinated specialty care for first-episode psychosis and formal recognition of the efficacy of psychotherapy-based prevention of perinatal depression.

Meanwhile, the NIMH also supports basic research to generate the knowledge and tools needed for future transformative treatments. This research has already started to pay off: in the spring of 2019, the Food and Drug Administration approved two new antidepressant medications (brexanolone and esketamine), the development of which resulted from long-term investments in basic neuroscience.

At the NIMH, we have the privilege and the responsibility to consider the full spectrum of research needed by the populations we serve. We meet these needs by funding excellent science, whether in the areas of neurobiology or psychology, clinical trials or molecular genetics, or psychotherapy or psychopharmacology. We need to continue investing in a comprehensive portfolio of research extending across diverse time frames if we are going to improve mental health care now and transform it in the future.