



The evolving treatment paradigm for BRAF V600 mutant colorectal cancer

Jeremy D. Kratz¹, Dustin A. Deming^{1,2,3}

¹Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; ²Department of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; ³University of Wisconsin Carbone Cancer Center, Madison, WI, USA

Correspondence to: Dustin A. Deming, MD. 6507 Wisconsin Institutes for Medical Research, 1111 Highland Ave, Madison, WI 53705, USA.
Email: ddeming@medicine.wisc.edu.

Provenance: This is an invited article commissioned by the Academic Editor, Dr. Chun-Dong Zhang, PhD (Department of Gastrointestinal Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan).

Comment on: Van Cutsem E, Huijberts S, Grothey A, *et al*. Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E-Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study. *J Clin Oncol* 2019;37:1460-9.

Submitted Nov 01, 2019. Accepted for publication Dec 10, 2019.

doi: 10.21037/atm.2019.12.61

View this article at: <http://dx.doi.org/10.21037/atm.2019.12.61>

Introduction

Metastatic colorectal cancer (CRC) is now being better understood as a collection of diseases with each distinguished by distinct molecular profiles. *BRAF* mutant cancers are an important CRC subtype composing about 10% of metastatic CRCs. Of those with a mutation in the *BRAF* gene, 80% possess the V600E mutation (1). This alteration results in a constitutively active kinase which activates the downstream MEK/ERK signaling pathway. *BRAF*^{V600} mutant cancers are more commonly on the right side of the colon and have a higher prevalence in women (2). These cancers have a preponderance for extensive nodal disease, peritoneal disease, and a very poor prognosis, with a median survival for patients with *BRAF*^{V600} mutant metastatic CRC of less than 2 years (3-5).

BRAF^{V600} mutations are associated with relative chemotherapy resistance and rapid progression in the setting of chemotherapy resistance. For patients with appropriate performance status, combination cytotoxic chemotherapy remains the consensus standard of care. FOLFOX and FOLFIRI regimens are commonly utilized (6). *BRAF* mutations are associated with a lack of survival benefit from the anti-epidermal growth factor receptor (EGFR) inhibitors, cetuximab and panitumumab (5,7-9), but *BRAF* mutant cancers can still benefit from

bevacizumab (10). Given the poor prognosis and decreased performance status, many patients with *BRAF* mutant CRC are not candidates for second-line therapy. This has led to interest in using FOLFOXIRI and bevacizumab in the first-line setting. The TRIBE study investigated this regimen in a post-hoc analysis of small cohort (n=28) of patients demonstrating an improvement in overall survival from 10.7 to 19 months when compared to FOLFIRI and bevacizumab, although not statistically significant with hazard ratio (HR) 0.54 (0.24, 1.20) (4).

In contrast to *BRAF* mutant melanoma, *BRAF* mutant CRCs are largely resistant to single agent *BRAF* targeted therapies (11-13). Preclinical studies have revealed feedback signaling results in increased EGFR signaling mediated downstream by direct activation of CRAF or by the transactivation of *BRAF*-CRAF heterodimers (14). This has led to combination EGFR and *BRAF* inhibitor regimens with improved response rates (15-17). The combination of vemurafenib, cetuximab and irinotecan demonstrated a response rate (RR) of 16% versus 0% with standard chemotherapy and an improvement in median progression free survival (PFS) of 4.4 versus 2.0 months (HR 0.42, *P*<0.001) in patients with treatment refractory metastatic *BRAF*^{V600} mutant CRC (18). Most recently triplet combinations targeting EGFR, *BRAF*, and MEK have

Table 1 Clinical trials of targeted therapy for BRAF mutant metastatic colorectal cancer

Therapeutic targets	Study	Phase	Inclusion criteria	Therapy	n	RR (%)	PFS (mos)	OS (mos)
Triplet therapy								
BRAF/MEK/EGFR inhibition	BEACON CRC	III	≥1 lines of systemic therapy	Encorafenib, binimetinib, cetuximab	224	26	4.3	9.0
	NCT01750918	I	Any line of therapy	Dabrafenib, trametinib, panitumumab	91	21	4.2	N/A
BRAF/PIK3CA/EGFR inhibition	NCT01719380	Ib/II	≥1 lines of systemic therapy	Encorafenib, alpelisib, cetuximab	52	27	5.4	13.1
BRAF/EGFR Inhibition with chemotherapy	SWOG1406	II	≥1 lines of systemic therapy	Vemurafenib, cetuximab, irinotecan	49	16	4.4	9.6
Doublet therapy								
BRAF/EGFR inhibition	BEACON CRC	III	≥1 lines of systemic therapy	Encorafenib, cetuximab	220	16	4.2	8.4
	NCT01719380	Ib/II	≥1 lines of systemic therapy	Encorafenib, cetuximab	50	22	4.2	12.4
	NCT01524978	II, basket	Any line of therapy	Vemurafenib, cetuximab	27	4	4.5	9.3
	NCT01750918	I	Any line of therapy	Dabrafenib, panitumumab	20	10	3.5	8.4
	NCT01791309	I	Any line of therapy	Vemurafenib, panitumumab	15	13	3.2	7.6
BRAF/MEK inhibition	NCT01072175	I/II	Any line of therapy	Dabrafenib, trametinib	43	12	3.5	N/A
Non-BRAF therapy (control arms)	BEACON CRC	III	≥1 lines of systemic therapy	Irinotecan, cetuximab or FOLFIRI, cetuximab	107	4	1.5	5.4
	SWOG1406	II	≥1 lines of systemic therapy	Irinotecan, cetuximab	50	4	2.0	5.9
	NCT01750918	I	Any line of therapy	Trametinib, panitumumab	31	0	2.6	N/A

been investigated to enhance the efficacy of this treatment strategy (16,19) (*Table 1*).

Phase III BEACON Colorectal Cancer Study

Dr. Van Cutsem, *et al.*, published the results of the safety lead in of the phase III BEACON Colorectal Cancer Study examining the combination of binimetinib, encorafenib and cetuximab (19). This manuscript detailed the results of the first 30 patients enrolled in this clinical trial examining the use of this regimen for patients with *BRAF*^{V600E} mutant metastatic CRC in the treatment refractory setting. The primary endpoint of the safety lead-in was to determine the safety and tolerability of this triplet regimen dosed at encorafenib 300 mg every day, binimetinib 45 mg twice a day and cetuximab 400 mg/m² followed by 250 mg/m² intravenously weekly in 28-day cycles. Dose limiting toxicities were observed in 5 of the 30 patients, including

serous retinopathy, reversible decreased left ventricular ejection fraction, and cetuximab-related infusion reactions. The most common grade 3/4 adverse events included fatigue, anemia, increased creatine phosphokinase, increased AST, and urinary tract infections. Overall, this regimen was deemed tolerable. Interestingly, diarrhea and acneiform rash were less severe than reported prior studies of MEK and EGFR inhibition alone (16,20). Preliminary clinical efficacy was also evaluated in this cohort of patients identifying a RR of 48% and median PFS of 8.0 months.

Most recently, the prespecified interim analysis of the Phase III BEACON Colorectal Cancer Study was reported (21). This trial enrolled 665 patients with *BRAF*^{V600E} evenly across three cohorts, including the triplet regimen of encorafenib, binimetinib and cetuximab; the doublet regimen of encorafenib and cetuximab; and a control cohort where patients could receive either cetuximab and irinotecan or cetuximab with FOLFIRI

(folinic acid, 5-fluorouracil, and irinotecan). The primary endpoints were overall survival (OS) and RR between the triplet regimen and the control group. The statistical analysis plan was not designed to compare the triplet and doublet regimens. The three cohorts were similar at baseline with the majority of patients being treated in the second-line setting (66%). At the time of interim analysis, the median duration of survival follow-up is 7.8 months. The median OS for the control group was 5.4 months, 8.4 months in the doublet therapy group, and 9.0 months with the triplet therapy (comparing the triplet therapy *vs.* control; HR 0.52; $P < 0.001$). A blinded independent central review assessed RR in this analysis for the first 331 patients who underwent randomization. The RR in the control arm was 2% compared to 20% with the doublet therapy and 26% in the triplet therapy group (comparing control *vs.* triplet therapy; $P < 0.001$). Of note, a substantial portion of the patients were not able to be evaluated for response with the majority of these patients being those with clinical progression or who discontinued therapy due to adverse events (15.4%). Median PFS, by central review, was 1.5 months in the control group, 4.2 months in the doublet therapy group, and 4.3 months with triplet therapy. Interestingly, the percent of patients with a response who had a duration of response ≥ 6 months was greater in the doublet therapy (43%) than with the triplet regimen (24%). Toxicities were similar to that seen in the lead-in phase, however notable improvements in toxicities were seen with the doublet compared to the triplet regimen including diarrhea (62% *vs.* 33%), acneiform dermatitis (49% *vs.* 29%), nausea (45% *vs.* 34%), and vomiting (38% *vs.* 21%).

Discussion

Reduced cost next-generation sequencing has resulted in a dramatically improved understanding of CRC including distinct molecular subtypes. It is now standard of care to test the tumors of patients with metastatic CRC for *KRAS/NRAS/BRAF* mutations, *HER2* amplification, and microsatellite instability/mismatch repair deficiency. These molecular alterations are both prognostic and predictive and aid in defining personalized treatment algorithms at diagnosis or first evidence of metastatic disease.

The phase III BEACON Colorectal Cancer Study provides a significant advance for those patients with *BRAF*^{V600} mutant metastatic CRC. It is now standard of care to treat patients with *BRAF*^{V600} mutant metastatic

CRC with the triplet regimen of encorafenib, binimetinib and cetuximab in the treatment refractory setting. It should also be considered reasonable to replace cetuximab with panitumumab if desired by the treating physician. This regimen should replace the use of an anti-EGFR therapy with chemotherapy or as part of the vemurafenib, irinotecan, and cetuximab regimen. It is notable how poorly the control group did with this prior standard therapy.

Of note, not all *BRAF* mutations have the same clinical impact with *BRAF*^{non-V600} mutations (2% of CRCs) largely having a more indolent clinical course (22,23). These mutations can result in different changes in the *BRAF* protein other than activating the kinase domain. For now, these regimens presented here should be restricted to those cancers with *BRAF*^{V600} mutations or at least alterations that are thought to result in a similar activation of the kinase domain.

Further follow-up is needed to assess the differences between the doublet and triplet regimens. The triplet regimen may result in greater treatment response, however this study was not powered to detect this difference and comes at the expense of greater toxicities. For now, the triplet regimen is preferred due to the response benefit. However, should a patient develop treatment related toxicities requiring dose modification, if these toxicities could in any way be attributable to the MEK inhibitor than would favor discontinuation of binimetinib, over dose reduction or delay of encorafenib or cetuximab. Additionally, for some patients with worse performance status or co-morbidities it would be reasonable to initiate therapy doublet regimen with the doublet regimen.

BRAF^{V600} mutations also occur in cancers with mismatch repair deficiency (dMMR). *BRAF* mutations can occur in tumors that develop through the serrated/methylated pathway, which are characterized by the CpG island methylator phenotype (CIMP) (24). CIMP-high tumors commonly possess epigenetic silencing of *mutL* homolog 1 (*MLH1*) resulting in dMMR. Those cancers with a *BRAF*^{V600} mutation and dMMR have an intermediate prognosis between *BRAF*^{V600} mutant cancers without dMMR and *BRAF* wild-type cancers (24). The Checkmate-142 study recently demonstrated benefit for dMMR CRCs with single agent nivolumab and the combination of nivolumab and ipilimumab. Specifically for those dMMR cancers with *BRAF* mutations a RR of 25% was observed with nivolumab alone and a RR of 55% was observed with the combination of nivolumab and ipilimumab (25). Anti-PD1 therapies also provide the potential for a much longer duration

of response, thus would prefer immunotherapy prior to targeted therapy for patients with *BRAF*^{V600} mutant dMMR cancers.

In summary, *BRAF*^{V600} mutant metastatic CRC is a distinct biological subtype with a poor prognosis and evolving treatment considerations. Cytotoxic chemotherapy in combination with anti-angiogenic therapy remains the standard of care first-line option. Future clinical studies are needed to assess the benefit of targeted therapies in the first-line setting to better understand which patients with *BRAF*^{V600} mutant CRC are most likely to benefit.

Acknowledgments

Funding: The authors thank the University of Wisconsin Biology of Aging and Age-Related Diseases T32 Training Grant #5T32AG000213-28 for providing salary support for Dr. Kratz.

Footnote

Conflicts of Interest: Dr. Kratz has no conflicts of interest to declare. Dr. Deming has served on an advisory board for Array BioPharma.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012;487:330-7.
2. Loupakis F, Moretto R, Aprile G, et al. Clinico-pathological nomogram for predicting BRAF mutational status of metastatic colorectal cancer. *Br J Cancer* 2016;114:30-6.
3. Innocenti F, Ou FS, Zemla T, et al. Somatic DNA mutations, MSI status, mutational load (ML): Association with overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC) of CALGB/SWOG 80405 (Alliance). American Society of Clinical Oncology, 2017.
4. 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* 2015;16:1306-15.
5. Bokemeyer C, Van Cutsem E, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. *Eur J Cancer* 2012;48:1466-75.
6. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN guidelines insights: colon cancer, version 2.2018. *J Natl Compr Canc Netw* 2018;16:359-69.
7. Pietrantonio F, Petrelli F, Coinu A, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. *Eur J Cancer* 2015;51:587-94.
8. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 2013;369:1023-34.
9. Rowland A, Dias M, Wiese M, et al. Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer. *Br J Cancer* 2015;112:1888-94.
10. Nakayama I, Shinozaki E, Matsushima T, et al. Retrospective study of RAS/PIK3CA/BRAF tumor mutations as predictors of response to first-line chemotherapy with bevacizumab in metastatic colorectal cancer patients. *BMC Cancer* 2017;17:38.
11. Kopetz S, Desai J, Chan E, et al. Phase II pilot study of vemurafenib in patients with metastatic BRAF-mutated colorectal cancer. *J Clin Oncol* 2015;33:4032-8.
12. Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet* 2012;379:1893-901.
13. Gomez-Roca C, Delord J, Robert C, et al. 535P Encorafenib (LGX818), an oral BRAF inhibitor, in patients (pts) with BRAF V600E metastatic colorectal cancer (mCRC): results of dose expansion in an open-label, phase 1 study. *Ann Oncol* 2014;25:iv182-iv3.
14. Corcoran RB, Ebi H, Turke AB, et al. EGFR-mediated reactivation of MAPK signaling contributes to insensitivity of BRAF-mutant colorectal cancers to RAF inhibition with vemurafenib. *Cancer Discov* 2012;2:227-35.
15. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N Engl J Med* 2015;373:726-36.
16. Corcoran RB, Andre T, Atreya CE, et al. Combined BRAF, EGFR, and MEK Inhibition in Patients with

- BRAF(V600E)-Mutant Colorectal Cancer. *Cancer Discov* 2018;8:428-43.
17. van Geel RM, Tabernero J, Elez E, et al. A phase Ib dose-escalation study of encorafenib and cetuximab with or without alpelisib in metastatic BRAF-mutant colorectal cancer. *Cancer Discov* 2017;7:610-9.
 18. Kopetz S, McDonough SL, Morris VK, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG 1406). *American Society of Clinical Oncology*, 2017.
 19. Van Cutsem E, Cuyle PJ, Huijberts S, et al. BEACON CRC study safety lead-in (SLI) in patients with BRAF V600E metastatic colorectal cancer (mCRC): Efficacy and tumor markers. *American Society of Clinical Oncology*, 2018.
 20. Deming DA, Cavalcante LL, Lubner SJ, et al. A phase I study of selumetinib (AZD6244/ARRY-142866), a MEK1/2 inhibitor, in combination with cetuximab in refractory solid tumors and KRAS mutant colorectal cancer. *Investigational new drugs* 2016;34:168-75.
 21. 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.
 22. Jones JC, Renfro LA, Al-Shamsi HO, et al. Non-V600BRAF mutations define a clinically distinct molecular subtype of metastatic colorectal cancer. *J Clin Oncol* 2017;35:2624-30.
 23. Johnson B, Loree JM, Jacome AA, et al. Atypical, Non-V600 BRAF Mutations as a Potential Mechanism of Resistance to EGFR Inhibition in Metastatic Colorectal Cancer. *JCO Precision Oncology* 2019:1-10.
 24. English DR, Young JP, Simpson JA, et al. Ethnicity and risk for colorectal cancers showing somatic BRAF V600E mutation or CpG island methylator phenotype. *Cancer Epidemiol Biomarkers Prev* 2008;17:1774-80.
 25. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. *J Clin Oncol* 2018;36:773-9.

Cite this article as: Kratz JD, Deming DA. The evolving treatment paradigm for BRAF V600 mutant colorectal cancer. *Ann Transl Med* 2019;7(Suppl 8):S257. doi: 10.21037/atm.2019.12.61