



3200 Walnut Street  
Boulder, Colorado  
80301  
Phone: 303-381-6600  
Fax: 303-449-5376

Victor Sandor, MD, CM, FRCPC  
Chief Medical Officer  
Array BioPharma Inc.  
100 Cambridge Park Drive, Suite 505  
Cambridge, MA 02140

Date of request: July 16, 2019

#### **NCCN® Guidelines Panel: Colon and Rectal Cancer**

On behalf of Array BioPharma Inc., I respectfully request the Panel consider the enclosed data supporting the triplet combination therapy of encorafenib (BRAF inhibitor), binimetinib (MEK inhibitor), and cetuximab (EGFR inhibitor) for patients with *BRAF* V600E metastatic colorectal cancer (mCRC) after failure of prior therapy.

**Specific Changes:** I respectfully request the Panel consider updating the triplet combination of encorafenib, binimetinib and cetuximab from a category 2a option to a category 1 option for the following:

- COL-D: subsequent therapy – systemic therapy for advanced or metastatic disease following previous systemic therapy (with or without irinotecan) in patients positive for the *BRAF* V600E mutation
- REC-F: subsequent therapy – systemic therapy for advanced or metastatic disease in patients positive for the *BRAF* V600E mutation

**FDA Clearance:** Currently, encorafenib (BRAFTOVI®) in combination with binimetinib (MEKTOVI®) is FDA-approved for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation as detected by an FDA-approved test (not indicated for wild-type *BRAF* melanoma).<sup>1,2</sup> The FDA has granted Breakthrough Therapy Designation to the triplet combination of encorafenib, binimetinib and cetuximab for the treatment of patients with *BRAF* V600E mCRC after failure of prior therapy. This combination is being studied in a randomized trial (BEACON CRC) and is not currently FDA-approved for this indication.

**Rationale:** *BRAF* V600E-mutant mCRC has a poor prognosis and standard treatment options after initial therapy for mCRC patients have resulted in poor outcomes with expected median overall survival (OS) between 4 to 6 months, median progression-free survival (PFS) of ~2 months and objective response rate (ORR) of 4%, clearly demonstrating a need for new treatment options.<sup>3-10</sup> The BEACON CRC Phase 3 trial evaluated the combination of encorafenib, binimetinib and cetuximab in patients with *BRAF* V600E mCRC who have progressed after 1 or 2 prior regimens. The study is complete relative to its primary and alpha controlled secondary endpoints and met all of these endpoints indicating a clear superiority of the triplet over the control on all endpoints. The results of the safety lead-in (SLI) phase, which included 30 patients, was the basis of the current category 2A recommendation of the triplet combination for subsequent therapy following previous systemic therapy for patients with *BRAF* V600E mutation positive advanced or metastatic colon and rectal cancer.<sup>11-13</sup>

The initial results from the randomized portion of the BEACON CRC trial were presented at the ESMO World Congress on Gastrointestinal (GI) Cancer on July 6, 2019. A total of 665 patients were randomized 1:1:1 to triplet arm (encorafenib, binimetinib and cetuximab; n=224), doublet arm (encorafenib and cetuximab; n=220), and control arm (FOLFIRI and cetuximab or irinotecan and cetuximab; n=221). A pre-planned interim analysis (data cutoff date of February 11, 2019) for the co-primary endpoints of ORR by blinded independent review with the first 331 randomized patients and OS with all 665 randomized patients was conducted. A summary of the efficacy results is shown in Table 1.<sup>14</sup>

**Table 1. Interim Efficacy Results from the Randomized Phase Portion of BEACON CRC Trial<sup>14</sup>**

Outcomes	Triplet Arm	Control Arm	HR (95% CI)	P value
BICR-assessed overall response rate (n=331)	26%	2%	Not reported	<0.0001
Median overall survival (n=615)	9 months	5.4 months	0.52 (0.39-0.70)	<0.0001

Results from the secondary endpoint analysis showed patients treated with the doublet combination demonstrated a statistically significant improvement in ORR (20% vs. 2%,  $p < 0.0001$ , per BICR) and OS (median 8.4 months vs. 5.4 months, [HR 0.60, 95% CI (0.45-0.79),  $p = 0.0003$ ]) compared to control.<sup>14</sup>

The BEACON CRC trial was not powered to formally compare the results of the triplet combination to the doublet combination. Results of descriptive analyses favored the triplet over the doublet. Best percentage change in the sum of diameters indicated a greater depth of response with the triplet combination. In addition, an exploratory analysis of OS for triplet versus doublet showed an estimated 21% reduction in the risk of death in favor of the triplet combination [HR 0.79, 95% CI (0.59, 1.06)].<sup>14</sup>

Grade 3 or greater adverse events (AE) occurred in 58% and 50% of patients treated with the triplet and doublet regimens, respectively. The most common ( $\geq 5\%$ ) grade  $\geq 3$  AEs for encorafenib, binimetinib and cetuximab were diarrhea, decreased hemoglobin, abdominal pain, and nausea. Discontinuation of therapy due to an AE was seen in 7% of patients in the triplet and 8% of patients in the doublet. Discontinuation of any one drug in the combination was seen in 15% and 12%, respectively. The safety and tolerability of both combinations allow maintenance of high dose intensity for the majority of patients.<sup>14</sup>

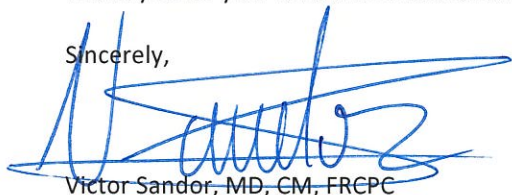
In conclusion, this initial analysis of the triplet combination of encorafenib, binimetinib, and cetuximab and the doublet combination of encorafenib and cetuximab, as compared to a current standard of care, shows significant and clinically relevant improvement in OS and ORR for both combinations in patients with *BRAF* V600E-mutant metastatic CRC whose disease had progressed after 1 or 2 prior regimens. The data suggest that the triplet combination offers improved efficacy with the addition of some manageable toxicity and that it may also mitigate some toxicities seen with the doublet combination.<sup>14</sup>

Please find enclosed the full presentation in support of this request.

- Kopetz S, et al. A randomized, 3-arm, phase 3 study of encorafenib and cetuximab with or without binimetinib vs. choice of either irinotecan or FOLFIRI plus cetuximab in *BRAF* V600E-mutant metastatic colorectal cancer. Presented at the ESMO 21<sup>st</sup> World Congress on Gastrointestinal Cancer 2019. July 3-6, 2019. Barcelona, Spain.

Thank you for your review and consideration of this request.

Sincerely,



Victor Sandor, MD, CM, FRCPC

#### References

1. [BRAFTOVI® \(encorafenib\) prescribing information](#). Boulder, CO: Array BioPharma; 2019.
2. [MEKTOVI® \(binimetinib\) prescribing information](#). Boulder, CO: Array BioPharma; 2019.
3. Loupakis F, et al. *Br J Cancer*. 2009;101:715-21.
4. Ulivi P, et al. *J Transl Med*. 2012;10:87.
5. Saridaki Z, et al. *PLoS One*. 2013 Dec 18;8(12):e84604.
6. Seymour MT, et al. *Lancet Oncol*. 2013;14:749-759.
7. Morris V, et al. *Clin Col Cancer Res*. 2014;13:164-71.
8. Peeters M, et al. *J Clin Oncol*. 2014;32:5s, (suppl; abstr 3568).
9. Mitani S, et al. *Ann Oncol*. 2017;28:Abstr. 532.
10. Kopetz S, et al. *J Clin Oncol*. 2017 ;35:(suppl; abstr 3505).
11. Van Cutsem E, et al. *J Clin Oncol* 2019 June 10;37(17):1460-1469. Doi: 10.1200/JCO.18.02459. Epub 2019 Mar 20.
12. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V2.2019. [https://www.nccn.org/professionals/physician\\_gls/pdf/colon.pdf](https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf). Accessed July 2, 2019.
13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer V2.2019. [https://www.nccn.org/professionals/physician\\_gls/pdf/rectal.pdf](https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf). Accessed July 2, 2019.
14. Kopetz S, et al. A randomized, 3-arm, phase 3 study of encorafenib and cetuximab with or without binimetinib vs. choice of either irinotecan or FOLFIRI plus cetuximab in *BRAF* V600E-mutant metastatic colorectal cancer. Presented at the ESMO 21<sup>st</sup> World Congress on Gastrointestinal Cancer 2019. July 3-6, 2019. Barcelona, Spain.