Date of request: 26 February 2019

NCCN Guidelines® Panel: Colon and Rectal Cancer

On behalf of Array BioPharma Inc., I respectfully request that 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 adding the triplet combination of encorafenib, binimetinib and cetuximab to the following guidelines and sections:

- 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). 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: The presence of BRAF mutations signifies poor prognosis in colon and rectal malignancies and as such, BRAF testing is currently recommended by the NCCN Guidelines®. After the first-line setting, multiple retrospective studies of BRAF mCRC patients have shown limited activity demonstrated by overall response rates (ORRs) that are <10%, median progression-free survival (PFS) of ~2 months and median overall survival (OS) between 4 to 6 months. SWOG S1406, a prospective, phase 2 study, evaluated irinotecan and cetuximab with or without vemurafenib in patients with BRAF mCRC who had received 1 or 2 prior regimens demonstrated an ORR of 4% and a median PFS of 2.0 months in the irinotecan plus cetuximab arm (N = 50). In the same study, the vemurafenib, irinotecan and cetuximab (VIC) regimen (N = 49) showed an ORR of 16% (confirmed and unconfirmed), median PFS of 4.3 months, and median OS of 9.6 months after a median follow-up of 7.3 months. Based on the results from SWOG S1406, the combination of VIC was included as a category 2A recommendation. These data still underscore a significant unmet medical need in this population.

The BEACON CRC phase 3 trial was initiated with a safety lead-in phase of 30 patients with BRAF V600E mCRC who have progressed after 1 or 2 prior regimens and received the combination of encorafenib, binimetinib and cetuximab. After a median duration of follow-up for survival of 18.2 months, the results of the safety lead-in showed median OS of 15.3 months (95% CI, 9.6–not reached), median PFS of 8.0 months (95% CI, 5.6–9.3) and confirmed ORR by local review of 48% (95% CI, 29.4–67.5), with 10% of patients achieving a complete response.
Among responders, median duration of response per local review was 5.5 months (95% CI, 4.1–not reached) with 43% of patients achieving a response duration of ≥ 6 months. Consistent with local review, the confirmed ORR by central review was 41% (95% CI, 23.5–61.1). Median duration of response among responders confirmed by central assessment was 8.1 months (95% CI, 2.8–not reached) with 73% of patients achieving a response duration of ≥ 6 months. The most common (≥10%) grade 3/4 adverse events were fatigue (13%), anemia, increased aspartate aminotransferase, increased creatinine phosphokinase, and urinary tract infections (10% each).\textsuperscript{13}

Additional Supporting Data: A phase 1b/2 study was conducted to evaluate the dual combination of encorafenib and cetuximab in BRAF V600E mutant mCRC after 1 or more prior treatments. The phase 1b portion established the pharmacokinetics, safety, and preliminary efficacy; the phase 2 portion assessed safety and efficacy.


Thank you for your review and consideration of this request.

Sincerely,

\[Signature\]

Victor Sandor, MD, CM, FRCPC
Chief Medical Officer

References: