January 30, 2017

National Comprehensive Cancer Network  
Joan McClure, MS, Sr. Vice President, Clinical Information & Publications  
275 Commerce Drive, Suite 300  
Fort Washington, PA 19034

Dear Ms. McClure,

We would like to draw your attention to the following issues related to the current Vectibix® (panitumumab) NCCN Drugs & Biologics Compendium® monograph available online (as of 11/29/2016):

Under NCCN Recommended Use for NCCN Disease Indication for Colon Cancer, the current monograph states that panitumumab is supported for use with:

- “therapy for left-sided only tumors expressing KRAS/NRAS wild-type gene in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen or as a single agent in patients not appropriate for intensive therapy…”
- “initial treatment for left-sided only tumors expressing KRAS/NRAS wild-type gene for unresectable synchronous liver and/or lung metastases in combination with…”
- “therapy for left-sided only tumors expressing KRAS/NRAS wild-type gene in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen, or as a single agent in patients not appropriate for intensive therapy…”

Our pivotal trials were designed to establish the efficacy of panitumumab without examining left versus right tumor sidedness.

We recognize the scientific discussion on the biologic importance of anatomic tumor location and the therapeutic impact this may have in choosing a biologic agent in the current NCCN guidelines. A broader body of evidence (ESMO symposium,1,2 two peer reviewed published manuscripts,3,4 and another manuscript currently submitted for peer-review publication5) has become available after the panel meeting in August. The total body of evidence available today — with its limitations of small sample sizes — is inconclusive and therefore should not be used as scientific evidence to exclude mCRC RAS wild-type patients with tumor origination at the right side from treatment with anti-EGFR therapy. Indeed, the FDA has approved Vectibix® (panitumumab) for use in patients with KRAS wild-type mCRC regardless of whether the tumor originates at the left or right side.6
Treatment outcomes of patients with RAS wild-type tumors originating on the left side are supported by adequate sample sizes for meaningful and statistically robust conclusions. All available retrospective analyses - based on peer-reviewed publications and ESMO presentations of prospective trials - suggest a substantial improvement for the anti-EGFR treatment arms in comparison to their controls, whether they are chemotherapy alone or containing anti-VEGF therapy. Given that the NCCN recognizes the importance of tumor origination, and how this could influence treatment choice, we feel strongly that these consistent conclusions should be reflected in the NCCN Drugs & Biologics Compendium.

The body of literature cited to support the current version of the guidelines has significant limitations. 1. Warschows et al was focused on localized tumor stages (I-III) and their prognosis without treatment information. 2. Although Moretto et al reported overall response rates were 41% and 0% in patients receiving anti-EGFR therapy with left- and right-sided primaries, respectively, it is important to carefully consider that there was a limited number of patients with right-sided tumors (n = 14), this study was not evaluating first-line therapy, and, per the author, was limited by the lack of a control arm including untreated patients. 3. Chen et al was an observational study of KRAS exon 2 wild-type (full RAS status unknown) without a comparator arm. 4. Loupaks et al, analyzing three trials with anti-VEGF containing arms (none with anti-EGFR arms) concluded only on the prognostic implication of the tumor location of origin. Although Bruel et al concluded that primary tumor location may be predictive of PFS from use of anti-EGFR therapy, their analyses were limited to wild-type KRAS exon 2 (full RAS mutational status unknown) and with a total of 56 subjects on the right side (only 29 of whom received cetuximab). 6. Lee et al, also limited by small number of samples in KRAS exon 2 wild-type mCRC, reported that tumor side was prognostic only in univariate models, and that perhaps "molecular analyses suggest that BRAF MT, NRAS MT, molecular subtypes, and tumor methylation account for the effect and may provide a biologic explanation for the association with anatomic location.

The following materials provide clinical data to support our recommendations. They are listed for your reference regarding the NCCN Drugs & Biologics Compendium panitumumab monograph:

1. Outcome according to left vs. right side in the panitumumab studies. Presented by Peeters M at: the European Society for Medical Oncology 2016 (special session); October 10, 2016; Copenhagen, Denmark. (https://cslide.ctimeetingtech.com/library/esmo/browse/search/p#2z95y02nA).

2. Outcome according to left vs. right side in the FOLFIRI cetuximab and FIRE 3 study. Presented by Heinemann V at: the European Society for Medical Oncology 2016 (special session); October 10, 2016; Copenhagen, Denmark. (https://cslide.ctimeetingtech.com/library/esmo/browse/search/bcc#2z95y02nB).


6. Vectibix® (panitumumab) prescribing information, Amgen Inc. (v23 2015).


This information was also provided by Phuong Khanh (PK) Morrow, MD, Executive Medical Director (Amgen, Inc.) in submission to the NCCN Guidelines Panels for Colorectal/Anal Cancer on December 20, 2016. Should you have any questions or require additional materials, please feel free to contact me directly at 805-447-8041. Thank you in advance for your prompt attention to this matter.

The Vectibix® (panitumumab) Prescribing Information, Amgen Inc. (v23 03/2015) is enclosed.

Sincerely,

[Signature]

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