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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.¹⁻⁵ 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. Warschkow et al was focused on localized tumor stages (I-III) and their prognosis without treatment information;⁷ 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;⁸ 3. Chen et al was an observational study of *KRAS* exon 2 wild-type (full *RAS* status unknown) without a comparator arm;⁹ 4. Loupakis 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;¹⁰ 5. Although Brulé 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);¹¹ 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.”¹²

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

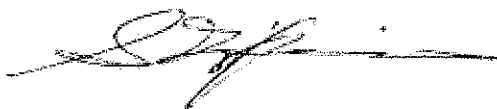
1. Outcome according to left vs. right side in the panitumumab studies. Presented by Peeters M at: the European Society for Medical Oncology 2016 (special session); October 10, 2016; Copenhagen, Denmark. (<https://cslide.ctimeetingtech.com/library/esmo/browse/search/p#2z95y02nA>).
2. Outcome according 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>).
3. Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumour location with metastatic colorectal cancer. A meta-analysis of first-line clinical trials. *Eur J Cancer*. 2016;70:87-98.
4. Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with *RAS* wild-type metastatic colorectal cancer: Retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol*. 2016.

5. Boeckx N, Koukakis R, Op de Beeck K, et al. Primary tumor sidedness has an impact on prognosis and treatment outcomes in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. 2017. *Eur J Cancer*. Submitted for publication.
6. Vectibix® (panitumumab) prescribing information, Amgen Inc. (v23 2015).
7. Warschkow R, Sulz MC, Marti L, et al. Better survival in right-sided versus left-sided stage I – III colon cancer patients. *BMC Cancer*. 2016;16:554.
8. Moretto R, Cremolini C, Rossini D, et al. Location of primary tumor and benefit from anti-epidermal growth factor receptor monoclonal antibodies in patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer. *Oncologist*. 2016;21.
9. Chen K-H, Shao Y-Y, Chen H-M, et al. Primary tumor site is a useful predictor of cetuximab efficacy in the third-line or salvage treatment of *KRAS* wild-type (exon 2 non-mutant) metastatic colorectal cancer: a nationwide cohort study. *BMC Cancer*. 2016;16:327.
10. Loupakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst*. 2015;107(3).
11. Brulé SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. *Eur J Cancer*. 2015;51:1405-1414.
12. Lee MS, Advani SM, Morris J, et al. Association of primary (1°) site and molecular features with progression-free survival (PFS) and overall survival (OS) of metastatic colorectal cancer (mCRC) after anti-epidermal growth factor receptor (α EGFR) therapy. *J Clin Oncol*. 2016;34(suppl). Abstract 3506.

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,



Suzana Giffin, PharmD
Executive Director, Global Scientific Communications
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