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Dear Members of the Colorectal/Anal Cancer NCCN Panel,

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. We appreciate the NCCN is reflecting this in the updated guidelines, and we want to point out that a broader body of evidence (ESMO symposium,[1,2] two peer reviewed published manuscripts,[3,4] and another manuscript currently submitted for peer-review publication[5]) has become available after the panel meeting in August. Reflecting on these new analyses and referring to your recent guideline, we would like to make the following comments:

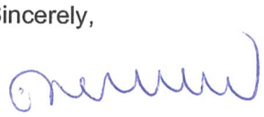
1. The updated NCCN Colon Cancer guidelines state that anti-EGFR therapy is only recommended for left-sided tumors. However, the total body of evidence available today – with its limitations of small sample sizes – is inconclusive and therefore should not be used as scientific evidence to exclude mCRC *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]

2. 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 guidelines.

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]

Previously, the NCCN guidelines adopted new language concerning extended *RAS* biomarker only after a thorough review of data from several large trials with consistent outcomes. While we acknowledge that all the current data are exploratory and retrospective in nature with different definitions of primary tumor origin, in light of both the new additional available data on treatment outcomes based on tumor primary origin and the limitations stated above, we respectfully request that the panel review the current totality of evidence and reconsider the current guideline language.

Sincerely,



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Enclosures

References

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