

Submitted by: Brian Alexander, MD
Company: Foundation Medicine, Inc.
Address: 150 Second Street, Cambridge, MA 02141
Phone: 617-418-2200 Ext. 2256
Email: baalexander@foundationmedicine.com
Date of request: July 24, 2019
NCCN Guidelines Panel: Rectal Cancer

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Rectal Cancer Guidelines Panel consider the requested updates below and enclosed references, pertaining to the evaluation and management of patients with advanced rectal cancer.

Requested Update 1 and Rationale: Add the evaluation of additional biomarkers, including tumor mutational burden (TMB), as a recommendation to identify additional patients who are likely to benefit from targeted therapies, immunotherapies, or define/refine clinical trial options to the *Principles of Pathologic Review* section (REC-B 5 of 7).

TMB:

Data in multiple solid tumor types suggest that TMB is an important predictive biomarker of response to immunotherapies, and responses to checkpoint inhibitors have been reported in both MSI-high/TMB-high and MS-stable/TMB-high colorectal cancers^{3-5, 23}.

- In one study the evaluation of TMB identified >99% of CRC patients with MSI-high tumors. However, assessing TMB simultaneously with MSI status can identify an additional population of patients with MS-stable but TMB-high tumors who are also likely to benefit from checkpoint inhibitors. This is predicted to lead to a 54% increase in the target population of metastatic CRC patients who may respond to immune checkpoint inhibitors⁶. Other studies have shown that genomic profiling to determine the amount and types of mutations present in a tumor can further refine the MSI-H CRC population to identify responders to checkpoint inhibitors^{25,26}.
- In a recent retrospective analysis of 22 patients with MSI-H metastatic colorectal cancer who were treated with a PD-1 or PD-L1 inhibitor, TMB was the only variable identified as a significant predictor of response, PFS and OS, both as a continuous and categorical variable. 100% (13/13) of patients with MSI-H CRC and TMB >37 mutations/Mb responded compared to only 2/9 patients with MSI-H CRC and TMB <37 mutations/Mb, suggesting that TMB can further stratify the MSI-H CRC population to guide the sequencing and/or combinations of checkpoint inhibitor therapy²⁶.

Other biomarkers:

Comprehensive genomic profiling (CGP) may identify targets for either therapies approved for other indications (eg. testing for *HER2* amplification and non-amplification mutations), as well as additional rare driver alterations that may inform the patient's treatment, including predicted lack of response to anti-EGFR therapies, or the option to enroll in a genomically-matched clinical trial.

- *HER2 (ERBB2)* amplification has been reported in 3% and 7% of all CRC and RAS/RAF wild-type CRC, respectively¹². In the Phase 2 HERACLES trial of patients with *HER2*-positive *KRAS* WT CRC, 30% (8/27) had an overall response, 44% (12/27) had stable disease, and median PFS was 21 months following treatment with a combination of the *HER2* inhibitors lapatinib and trastuzumab¹³. In the ongoing MyPathway trial of patients with *HER2* amplified/overexpressed CRC treated with pertuzumab and trastuzumab 12/32 patients assessed had a partial response and 3/32 had stable disease >4 months¹⁴. *HER2* short variant mutations are also found in 2% of CRC, and these patients are also predicted to respond to *HER2*-targeted therapies¹⁵; these alterations are detectable by CGP but would not be detected using FISH or IHC testing¹².

- One in 3 CRC patients with tumors that are *RAS/RAF* wild-type (WT) harbor a genomic alteration (*EGFR* extracellular domain mutations, *HER2*, *MET*, and *FLT3* amplification, *PIK3CA* and *MEK1* mutations, and *PTEN* inactivating alterations) that could mediate resistance to EGFR therapeutic antibodies⁷⁻¹². Detection of one or more of these alterations may lead to the identification of an appropriate genomically-matched clinical trial, as several prospective trials in solid tumors, including CRC, are currently utilizing CGP for enrollment.
- Kinase fusions of *ALK*, *RET*, *FGFRs*, and *BRAF*, which have been identified as clinically relevant predictors of response to matched targeted therapies in other tumor types including NSCLC, have been identified in a rare subset of CRCs using CGP¹². CRC patients with tumors harboring these alterations have reported lack of response to anti-EGFR therapies, but durable responses to matched therapies targeting *ALK* or *NTRK1*^{16-20,27-29}.
- *BRAF* V600E mutations predict lack of response to EGFR antibodies and confer poor prognosis in CRC. However, 22% of *BRAF* mutations in CRC are non-V600, and are not typically covered by hotspot tests. These mutations predict excellent prognosis relative to cases with *BRAF* V600E or WT *BRAF*, suggesting that patients with tumors harboring non-V600 mutations may achieve benefit from less intensive therapies²¹. Clinical trials exploring effective combination therapies to effectively target *BRAF* V600E in CRC are also ongoing²².
- An inherited genetic mutation may be the driving factor in the development of approximately 5% of CRCs²⁴. Evaluation for MMR protein expression and MSI status may be suggestive of inheritance of Lynch Syndrome or a variant, but will not identify other potential inherited drivers, such as APC alterations. CGP testing of somatic tumor specimens may identify potential germline mutations including those in the MMR pathway, APC or *MUTYH*, for example, and these patients and their families could then potentially be referred for germline testing.

Requested Update 2 and Rationale: Amend the Principles of Pathologic Review (REC-B 5 of 7) section to indicate that genomic testing via a validated, blood-based liquid biopsy test, such as FoundationOne® Liquid, is an acceptable testing method.

Multiple studies have shown a high concordance rate between tissue-based CGP and liquid biopsy for the detection of actionable alterations in numerous tumor types, including colorectal cancer^{26,30-32}. Paired tissue and blood specimens from a subset of 96 patients with colorectal cancer (CRC) from a multi-center prospective clinical study of multiple tumor types were analyzed with tissue-based testing and liquid biopsy respectively, and results were compared. For all cases with MSAF>0, 171 base substitutions and insertions/deletions (indels) were identified in the tumor, and 79% (PPA) of these identical alterations were also identified in the matched ctDNA samples. PPA increased to 87% for cases <270 days between the tissue and the liquid biopsy sample, 95% for <90 days, and 100% PPA for <30 days. For NCCN®-recommended genes (*KRAS*, *NRAS*, *BRAF*), PPA was 80% for all time points for short variants; PPA increased to 90% for cases <270 days between the tissue and liquid biopsy³². Liquid biopsy has been reported to detect evidence of ctDNA in 82% of blood-based circulating tumor DNA (ctDNA) samples from patients with metastatic gastrointestinal tumors (72% colorectal carcinoma [CRC]), and reportable genomic alterations in 89% of these samples. Among 25 temporally-matched blood and tissue samples included in this study, 86% of alterations detected in tissue were also detected in ctDNA².

Thank you for your review of this submission.

Sincerely,



Brian Alexander, M.D.
Chief Medical Officer
Foundation Medicine

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