Molecular In My Pocket™…

# ONCOLOGY: *Molecular Biomarkers of Colorectal Cancer*

**Samples to Test:** Metastatic or recurrent tumor is preferable if available and adequate*; primary tumor is an acceptable alternative. **Sample Types to Test:** Formalin fixed paraffin embedded tissue (FFPE) or other type of specimens (*e.g.,* cytology). ** Lynch syndrome screening is recommended for all primary colorectal cancers.*

| Biomarker | Specific Alterations/ Alternative Names | Indications | Result Interpretation/ Significance | Assay Techniques |
|---|---|---|---|---|
| ***KRAS*** | Mutations in codons 12, 13 of exon 2; codons 59, 61 of exon 3; codons 117, 146 of exon 4 | Consideration of anti-EGFR therapy Should be performed in all patients with metastatic CRC | Patients with these mutations should not be treated with panitumumab and cetuximab<br>Significant PFS advantage for adding anti-EGFR therapy for *KRAS* WT tumors compared to chemotherapy alone | NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays |
| ***NRAS*** | Mutations in codons 12, 13 of exon 2; codons 59, 61 of exon 3; codons 117, 146 of exon 4 | Consideration of anti-EGFR therapy Should be performed in all patients with metastatic CRC | Patients with these mutations should not be treated with panitumumab and cetuximab | NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays |
| ***BRAF*** | *BRAF* V600; V600E, V600K | Prognostic stratification | Poorer PFS and OS compared to *BRAF* WT patients | NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays |
| | | Consideration of anti-EGFR therapy | Unlikely response to panitumumab and cetuximab (2)<br>Insufficient evidence (1) | |
| | | In MMRd tumors with MLH1 loss | Presence of mutation strongly favors sporadic tumor; absence of BRAF mutation does not exclude risk of Lynch syndrome | |
| **MSI/ MMR** | Loss of *MLH1, PMS2, MSH2, MSH6* expression and/or MSI-high status | Lynch syndrome screening | Consideration of genetic counseling and germline testing (in the absence of *BRAF* mutation or *MLH1* promoter methylation) | IHC, PCR-based assays |
| | MSI-high | Therapy selection (stage II patients) | Improved prognosis and no benefit from 5-FU adjuvant therapy<br>Consideration of immune checkpoint inhibitor therapy | |
| ***MLH1* promoter methylation** | Methylation of *MLH1* promoter | MLH1 loss by IHC | Presence of *MLH1* promoter methylation in a setting of *MLH1* loss suggests sporadic origin | Methylation assays |

**Abbreviations:** CRC - colorectal cancer; NGS - next generation sequencing; PFS - progression free survival; OS - overall survival; WT - wild type (non-mutant); MMRd - mismatch repair deficient; MSI - microsatellite instability; IHC - immunohistochemistry

**Note:** Insufficient evidence to recommend *PIK3CA* mutational analysis for therapy selection outside of clinical trial. Insufficient evidence to recommend *PTEN testing (IHC or FISH)* for therapy selection outside of clinical trial.

**Where to Test:** Testing should be performed in the laboratories that are certified under Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity (molecular pathology) testing.

***References*:**

**1.** Sepulveda AR et al., Molecular Biomarkers for the Evaluation of Colorectal Cancer. *Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology*. The Journal of Molecular Diagnostics, Vol. 19, No. 2, March 2017.

**2.** National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Colon Cancer. Version 2.2017 – March 13, 2017; NCCN.org. *accessed 9/4/2017*

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