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 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 unless given with a BRAF inhibitor (2)	
		In MMRd tumors with MLH1 loss	Presence of mutation strongly favors sporadic tumor; the presence of BRAF mutations does not exclude the risk of Lynch Syndrome	
NTRK	Fusions	Therapy selection	Predicts response to larotrectinib (2)	NGS, pyrosequencing, FISH, IHC, PCR-base assays
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 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. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Colon Cancer. Version 4.2020 – June 15, 2019; NCCN.org. *accessed 9/8/2020*

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