MSI-I/dMMR Tumor Testing

DNA mismatch repair (MMR) proteins are involved in DNA repair of genetic sequence code. In normal cells, the MMR pathway identifies and corrects genetic mismatch during DNA replication. A deficient MMR (dMMR) system leads to accumulations of mismatches, insertions, and deletions in microsatellite repetitive sequences, resulting in microsatellite instability (MSI). The absence of 1 of the 4 key MMR proteins, MLH1, MSH2, MSH6, or PMS2, can serve an an important prognostic biomarker for several cancer diagnoses. A dMMR pathway can be caused by somatic or inherited pathogenesis.

Recent data show that MSI analysis is effective as a predictive biomarker for the effect of immune checkpoint inhibitors, including anti-PD-1 and anti-PD-L1 antibodies. Keytruda® (pembrolizumab) is approved for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR tumors. Recently, Opdivo (nivolumab) plus low-dose Yervoy (ipilimumab) has been approved for adult and pediatric patients 12-years old and older with previously treated, MSI-H or dMMR metastatic colorectal cancer.

To determine if patients have MSI-H or dMMR, requests are made to the pathology department, and testing can be performed on patients' archived tissue blocks or fresh biopsy tissue. Two molecular biology-based methods can be performed: polymerase chain reaction (PCR) for MSI and immunohistochemistry (IHC) testing for MMR. In PCR, MSI-H will show instability in ≥2 microsatellite markers, whereas MSI low (MSI-L) shows instability in 1 microsatellite marker.

If mutations are not found, the tumor is classified as microsatellite stable (MSS), and the MMR system successfully recognizes and repairs genetic mismatches or typos that can occur during replication. IHC testing will determine if there is a loss of 1 of the 4 MMR proteins. Tumor tissues found to have dMMR proteins by IHC are more than 90% likely to be MSI-H.

Most pathologists are routinely performing IHC testing on their cases with colon and endometrial cancer per recommended guidelines. IHC tends to be less expensive and simpler than the PCR method. With the new treatment indications for MSI-H or dMMR tumors, pathologists are now being asked to perform IHC testing on a variety of extracolonic tumors such as gastric, small bowel, urothelial, central nervous system, pancreatic, and prostate cancers. Most hospital and facility laboratories will accept verbal or written requests from the patients' healthcare provider for testing, with results obtained within 2 weeks.

IHC is a screening technique and not used to diagnose Lynch syndrome. A molecular laboratory test would be used to diagnosis Lynch syndrome, not just IHC.

Thus far, MSI-H tumors have the highest response rates to PD-1 inhibitors for any cancer type.

RESOURCES

- André T, Lonardi S, Wong M, et al: Nivolumab + ipilimumab combination in patients with DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer: First report of the full cohort from CheckMate-142. "https://meetinglibrary.asco.org/record/155742/abstract" 2018 Gastrointestinal Cancers Symposium. Abstract 553. Presented January 20, 2018.
- Garg K, Soslow RA. Lynch syndrome (hereditary non-polyposis colorectal cancer) and endometrial carcinoma. *J Clin Pathol*. 2009;62:679-684.
- Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* 2015;372:2509-2520.
- Lenz H-J, Lonardi S, Zagonel V, et al: Nivolumab plus low-dose ipilimumab as first-line therapy in microsatellite instability-high/DNA mismatch repair deficient metastatic colorectal cancer: Clinical update. "https://meetinglibrary.asco.org/record/181902/abstract" 2020 Gastrointestinal Cancers Symposium. Abstract 11. Presented January 25, 2020."
- Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types. *Lancet Oncol*. 2014;15:e268-e278.
- Ott PA, Bang YJ, Berton-Rigaud D, et al. Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1-positive endometrial cancer: results from the KEYNOTE-028 study. *J Clin Oncol*. 2017;35:2535-2541.
- Stelloo E, Jansen AML, Osse EM, et al. Practical guidance for mismatch repair-deficiency testing in endometrial cancer. *Ann Oncol*. 2017;28:96-102.
- Yamashita H, Nakayama K, Ishikawa M, et al. Microsatellite instability is a biomarker for immune checkpoint inhibitors in endometrial cancer. *Oncotarget*. 2017;9:5652-5664.