Increased Somatic Mutations with Large Panel Next Generation Sequencing (NGS) in Deficient MMR (dMMR) Tumors: An Illustrative Case Report

Case Report

GG is a 37 y/o man who underwent a right hemicolectomy for a pT3N1b colonic adenocarcinoma in 9-2010. His mother, maternal grandfather, a maternal uncle and a maternal cousin had each been diagnosed previously with colon cancer. Germline testing identified a deleterious MSH2 mutation (1303delA MSH2) (Myriad Genetics, Salt Lake City, Utah, 84108). He completed adjuvant FOLFOX chemotherapy in 3-2011. In 9-2014 he underwent removal of recurrent disease in four mesenteric lymph nodes. In 11-2014 biopsy of one of numerous liver lesions confirmed progressive metastatic disease and treatment with FOLFOXIRI/bevacizumab resulted in radiographic improvement [1,2]. Although there was no progression on FOLFOXIRI/bevacizumab,
he requested NGS of his primary tumor that had been removed in 2010. A single somatic alteration or multiple somatic alterations in a single gene was seen in 70 genes (Memorial Hospital for Cancer and Allied Diseases, MSKCC, Department of Pathology, 1275 York Ave, NewYork/NY 10065).

He received immunotherapy with the checkpoint inhibitor Durvalumab. After an initial response there was radiographic progression in 7-2016. In 10-2016 he started therapy with carinoembryonic T cell biospecific antibody (TCB)/Atezolizumab, but in 1-2017 scanning again demonstrated progression and he then started therapy with FOLFOX/bevacizumab. With further progression in 3-2017, the checkpoint inhibitor Pembrolizumab was added. In 9-2017 he was admitted with peritonitis and he requested NGS of his primary tumor that had been removed in 2010. A single somatic alteration or multiple somatic alterations in a single gene was seen in 70 genes (Memorial Hospital for Cancer and Allied Diseases, MSKCC, Department of Pathology, 1275 York Ave, NewYork/NY 10065).

In 8-2017 Liquid biopsy circulating cf DNA demonstrated a somatic alteration in a single gene or multiple somatic alterations in a single gene in 42 genes. Among these, there was a BRCA2 T3033fs alteration in a single gene or multiple somatic alterations in a single gene was seen in 70 genes (Memorial Hospital for Cancer and Allied Diseases, MSKCC, Department of Pathology, 1275 York Ave, NewYork/NY 10065).

In 8-2017 Liquid biopsy circulating cf DNA demonstrated a somatic alteration in a single gene or multiple somatic alterations in a single gene in 42 genes. Among these, there was a BRCA2 T3033fs alteration identified in roughly 83.2% of the tumor circulating cf DNA. The PARP inhibitor Olaparib was recommended (Guardant Health, Redwood City, CA 94063).

**Discussion**

On May 23, 2017 the FDA granted accelerated approval for the treatment of all patients with unresectable or metastatic solid tumors demonstrating MSI-H or dMMR. For treatment of solid tumors, the FDA approval represented the first time that a drug’s approval was based on a biomarker rather than a tissue of origin. The approval was based on the results of five clinical trials that involved 149 patients with a total of 15 cancer types. The complete or partial response rate was 39.6%. Among 78% of the responding patients, the response lasted for 6 months or longer [3].

Even before the FDA approval, testing CRCs for dMMR (or MSI-H) was recommended for nearly all patients with CRC [2]. Such testing for dMMR is typically done using IHC. With the FDA approval, it would seem reasonable that all patients with nearly all metastatic solid tumors be tested for dMMR (or MSI-H), regardless of the tissue of origin, particularly once progression had occurred on standard therapies.

**References**

1. Schram AM, Reales D, Cambria J (2017) Oncologist use and perception of large panel next-generation tumor sequencing. Ann Oncol 28: 2298-2304.

2. Benson AB, Venook AP, Cederquist L (2017) Clinical practice guidelines in oncology (NCCN guidelines). Colon Cancer.

3. FDA News Release (2017) FDA approves first cancer treatment for any solid tumor with a specific genetic feature.

4. Chalmers ZR, Connelly CF, Fabrizio D (2017) Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Medicine 9: 1-14.

5. Kaufman B, Shapira-Frommer R, Schmutzler RK (2015) Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 33: 244-250.