Editorial Commentary

Pembrolizumab in metastatic mismatch repair deficient colorectal cancer: the beginning of a journey into the land of immunotherapies for all cancers

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Mismatch repair deficiency (dMMR) defines a biologic cell phenotype characterized by a high frequency of genetic alterations, commonly in form of frameshift mutations, due to absence of the expression of at least one of four mismatch repair proteins, MLH1, PMS2, MSH2, and MSH6 (1). A dMMR status leads to high degree of microsatellite instability (MSI-H) assessed by polymerase chain reaction (PCR) or next-generation sequencing (NGS). It has long been known that MSI-H/dMMR cancers are highly immunogenic and thus candidates for immunotherapies. In colorectal cancer (CRC), the prevalence of MSI-H/dMMR status is stage and location dependent with earlier stages and right-sided primary tumors showing a higher likelihood of exhibiting this phenotype (1). About 4–5% of metastatic CRC are characterized as MSI-H/dMMR, identifying a patient population which has shown remarkable responses to antibodies targeting the programmed cell death receptor-1 (PD-1) or its ligand in a chemotherapy-refractory setting. Based on documented anti-tumor activity in single-arm studies, the US Food and Drug Administration (FDA) granted approval of these therapies in 2017 (2-4), however, other regulatory agencies required randomized controlled trial results to follow the FDA's lead.

KEYNOTE-177 was the first randomized phase 3 trial comparing pembrolizumab, a PD-1 antibody, against standard chemotherapy in a first-line setting in 307 patients with MSI-H/dMMR mCRC (5). The trial was designed with two co-primary endpoints, progression-free survival (PFS) and overall survival (OS). The initial data analysis demonstrated that the PFS endpoint was met with a hazard ratio (HR) of 0.59 (median PFS 16.5 *vs.* 8.2 months, P=0.0002). In addition, the overall response rate with pembrolizumab was higher with a remarkable duration of response suggesting a plateau in Kaplan-Meier analysis beyond 3 years of follow-up. It is conceivable that some patients with excellent response might never have to be exposed to conventional chemotherapy and can enjoy a prolonged period of "no evidence of disease". The toxicity profile and quality of life results also clearly favored pembrolizumab over chemotherapy (6). These results established pembrolizumab as standard first-line therapy in MSI-H/dMMR mCRC, even before definitive OS data became available. The most recent presentation of KEYNOTE-177 now reveals the final OS results which show a statistical trend toward improvement in the pembrolizumab arm with a HR of 0.74 (median OS "not reached" *vs.* 36.7 months, P=0.036) (7). It is of note that the prespecified significance level for superiority was set at P=0.025 and thus the OS data missed the co-primary endpoint of superiority for pembrolizumab (7). Importantly though, 60% of patients crossed over from chemotherapy to immunotherapy either within or outside of the trial in the course of their treatment which clearly impacted the potential difference in OS outcome.

Despite its convincing efficacy results, KEYNOTE-177 still raises several questions. The percentage of patients with upfront progressive disease was higher in the pembrolizumab than the chemotherapy arm (29.4%

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vs. 12.3%). This phenomenon is mirrored in the PFS curves which cross after about 6 months. To date, the patient population which apparently did not benefit from pembrolizumab in spite of the immunogenic MSI-H/dMMR phenotype of their cancers has not been well characterized. It appeared that patients with RAS mutated cancers had attenuated benefit from pembrolizumab, even though this phenomenon has not been seen in other studies with immunotherapy in MSI-H/dMMR CRC (3,4). Differences in tumor mutation burden and expression patterns of specific mismatch repair proteins could be considered as explanation, but these analyses have yet to be performed. It will be important to await the results of ongoing trials investigating combinations of pembrolizumab with conventional cytotoxic chemotherapy and/ or other immune activators [e.g., CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) antibodies] with the goal to increase the upfront response rate and avert the initial detriment in PFS. In this context, non-randomized data of a nivolumab plus ipilimumab combination showed a remarkably high response rate in first line for MSI-H/dMMR mCRC albeit in a small patient population (8).

The future will conceivably see an even earlier use of immunotherapy in MSI-H/dMMR CRC. Recent data showed astounding results of the PD-1 antibody dostarlimab as definitive therapy in mismatch repair deficient stage 2 and 3 rectal cancers (9). Twelve consecutive rectal cancer patients treated with 6 months of dostarlimab all showed complete clinical responses and were subsequently followed in a non-operative management strategy, meaning they did not undergo surgical resection. Of note is that the median follow-up for these patients is still rather short and it remains to be seen how durable these responses will be. Similar results were seen in the NICHE-2 study which used nivolumab plus ipilimumab as short-course neoadjuvant therapy in 107 patients with MSI-H/dMMR early stage colon cancer followed by surgery within 6 weeks from registration (10). A major or complete pathologic response was seen in 92% of patients with 67% pathologic complete responses. At a median follow-up of 13 months none of the patients had experienced disease recurrence which compares very favorably to historic controls. These data suggest that immunotherapy of MSI-H/dMMR CRC can be even more active in earlier stages than in advanced disease, potentially due to less tumor cell heterogeneity and a less immune suppressive microenvironment. In fact, results of the precursor study to NICHE-2 showed pathologic responses to neoadjuvant nivolumab plus ipilimumab even in 4 of 15 colon cancers with proficient mismatch repair status (pMMR) which are not considered immunogenic (11). An analysis of biologic factors which can explain why these cancers respond to combined anti-PD-1/CLTA-4 therapy might open a path toward development of novel, active immunotherapy approaches in metastatic pMMR CRC which represents a high unmet need.

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