Editorial Commentary

What are the optimal first-line therapies for patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer?

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Colorectal cancer (CRC) is the third most common type of cancer and the second leading cause of cancer death worldwide (1). Among people diagnosed with CRC, 20% have metastatic CRC (mCRC) (2). The prognosis of mCRC is poor with a 5-year survival rate of less than 15% (3).

However, the number of chemotherapies available to clinicians is gradually increasing. We can use standard chemotherapies as first-line treatment, including fluoropyrimidines, oxaliplatin, irinotecan, anti-vascular endothelial growth factor (VEGF) agents (bevacizumab), and anti-epidermal growth factor receptor (EGFR) agents (cetuximab and panitumumab), alone or in combination (4). Currently, the median overall survival (OS) in mCRC is about to reach approximately 30 months (5,6).

Microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR)/colorectal tumors are identified in approximately 15% of stage I–III CRC patients (7). They show a favorable prognosis compared with that of microsatellite stable/mismatch repair proficient (MSS/pMMR) CRC. In contrast, patients with dMMR/MSI-H mCRC in stage IV account for approximately 5% of all patients with CRC and have poor outcomes with a median OS of only 13.6–16.8 months to benefit from standard chemotherapy (8). Recently, immune-checkpoint inhibitors (ICIs) have been widely used for many cancers and shown to be effective (9-11). For mCRC, various clinical trials are underway, and ICIs have already shown a clinical benefit (12,13). ICIs consist of antagonists of programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) (2).

Recently, two pivotal trials (CheckMate-142 and KEYNOTE-177) have been conducted to investigate first-line therapy for patients with MSI-H/dMMR mCRC (14-19).

CheckMate-142 is a phase II, multicohort, non-randomized study of nivolumab (the fully human immunoglobulin G4 monoclonal antibody inhibitor of PD-1)-based therapies in patients with MSI-H (previously treated and untreated) and non-MSI-H mCRC (14,15). One study has reported on a previously treated cohort that underwent nivolumab monotherapy and nivolumab plus ipilimumab (the fully human immunoglobulin G1 monoclonal antibody that targets the CTLA-4 checkpoint receptor) therapy (14). The previously treated cohort showed a durable response and manageable safety profile. The primary endpoint was the investigator-assessed objective response rate (ORR). In the nivolumab monotherapy cohort of CheckMate-142, at a median follow-up of 12 months, the investigator-assessed ORR

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was 31.1% [95% confidence interval (CI), 20.8–42.9%], and the disease control rate for ≥12 weeks was 69% (95% CI, 57–79%). Median progression-free survival (PFS) was 14.3 months [95% CI, 4.30–not estimable (NE)], and the 12-month PFS was 50% (95% CI, 38–61%). The 12-month OS was 73% (95% CI, 62–82%). The rates of any-grade and grade 3 to 4 treatment-related adverse events (TRAEs) were 70% and 20%, respectively. In the nivolumab plus ipilimumab cohort, at a median follow-up of 13.4 months, the investigator-assessed ORR was 55% (95% CI, 45.2–63.8%), and the disease control rate for ≥12 weeks was 79% (95% CI, 70.6–85.9%). The 9- and 12-month PFS rates were 76% (95% CI, 67.0– 82.7%) and 71% (95% CI, 61.4–78.7%), respectively (15). The 9- and 12-month OS rates were 87% (95% CI, 80.0–92.2%) and 85% (95% CI, 77.0–90.2%), respectively. The rates of any-grade and grade 3 to 4 TRAEs were 73% and 32%, respectively. The any-grade TRAEs were comparable to those in the nivolumab monotherapy cohort. In general, nivolumab plus ipilimumab therapy was reported to result in more adverse events than nivolumab monotherapy. Nivolumab plus ipilimumab therapy has been investigated using different doses and intervals to solve these problems. The CheckMate-142 previously treated cohort underwent nivolumab therapy (3 mg/kg) plus low-dose (1 mg/kg) ipilimumab every 3 weeks. This low-dose ipilimumab led to decreased adverse events.

Recently, the results of nivolumab plus low-dose ipilimumab as first-line therapy for patients with MSI-H/dMMR mCRC have been reported in another CheckMate-142 cohort (17). This is the first report of dual immune-oncology (I-O) combination first-line therapy for MSI-H/dMMR mCRC. The primary endpoint was investigator-assessed ORR. After a median follow-up of 29 months, the investigator-assessed ORR, complete response (CR), and disease control rate were 69% (95% CI, 53–82%), 13%, and 84%, respectively. The ORR benefit was observed in all evaluated subgroups, including those with BRAF or KRAS mutation status. Median PFS and OS were not reached. The 24-month PFS and OS rates were 73.6% (95% CI, 57.2–84.5%) and 79.4% (95% CI, 64.1–88.7%), respectively, and the progressive disease (PD) rate was 13%. The rates of any-grade and grade 3 to 4 TRAEs were 80% and 22%, respectively. The rates of grade 3 to 4 TRAEs were comparable to those of the nivolumab monotherapy cohort in previously treated MSI-H/dMMR mCRC. This cohort used nivolumab (3 mg/kg) every 2 weeks plus low-dose ipilimumab (1 mg/kg) every 6 weeks. The less frequent and low-dose ipilimumab was manageable and resulted in to fewer serious TRAEs.

The two main limitations of this study are its nonrandomized design and its small sample size. However, the therapy investigated in this study showed robust and durable clinical benefits and was well tolerated. Based on these results, the National Comprehensive Cancer Network guidelines recommend nivolumab plus low-dose ipilimumab as a preferred regimen for first-line therapy in patients with MSI-H/dMMR mCRC.

There is also a report on first-line therapy using other ICIs for patients with MSI-H/dMMR mCRC. KEYNOTE-177 was a multicenter open-label phase III study of pembrolizumab, another PD-1 inhibitor, versus 5-fluorouracil-based chemotherapy alone or in combination with bevacizumab or cetuximab as first-line chemotherapy in MSI-H/dMMR mCRC (18,19). Patients receiving chemotherapy were able to cross over to pembrolizumab therapy after disease progression. The two primary endpoints were PFS and OS. The initial report showed that the median PFS was 16.5 months (95% CI, 5.4–32.4 months) in the pembrolizumab group and 8.2 months (95% CI, 6.1–10.2 months) in the chemotherapy group [hazard ratio (HR), 0.60; 95% CI, 0.45–0.80; P=0.0002), after a median follow-up of 32.4 months. The ORR was observed in 43.8% (95% CI, 35.8–52.0%) of the patients in the pembrolizumab group as compared with 33.1% (95% CI, 25.8–41.1%) in the chemotherapy group, with CR in 11% and 4%, respectively. TRAEs of grade 3 or higher occurred in 22% of the patients in the pembrolizumab group, as compared with 66% in the chemotherapy group. The final analysis showed that the median OS was not reached (NR) (95% CI, 49.2–NR) in the pembrolizumab group vs 36.7 months (27.6–NR) in the chemotherapy group (HR, 0.4; 95% CI, 0.53–1.03; P=0.036), after a median follow-up of 44.5 months (19). However, the pembrolizumab group did not meet the initially set one-sided α boundary of 0.025 required for significance. This lack of OS benefit may have been attributed to the use of subsequent therapy in the chemotherapy group. Most patients (60%) received pembrolizumab or other ICIs after progression with first-line chemotherapy. The PD rate was 29%, which was higher than that with nivolumab plus low-dose ipilimumab as first-line therapy in CheckMate-142 (13%), due to primary resistance, misdiagnosed mismatch repair proficient or microsatellite stable disease, and pseudoprogression. The limitations of this study include the lack of a central confirmation of MSI-H/dMMR status and the heterogeneity of treatment regimens

in the chemotherapy group. Based on these results, pembrolizumab was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) as first-line therapy in patients with MSI-H/dMMR mCRC.

In conclusion, the CheckMate-142 trial supports nivolumab plus low-dose ipilimumab as standard first-line therapy in patients with MSI-H/dMMR mCRC. The CheckMate-142 and KEYNOTE-177 have shown that ICI monotherapy and dual I-O combination treatment provided great effectiveness. However, these two trials cannot be compared because of their different sample characteristics. In CheckMate-142, the patients were mostly Caucasian and only 38% were stage 4. On the other hand, in KEYNOTE-177, the all patients were stage 4. Further trials should be conducted to clarify which therapies are best as first-line therapy for patients with MSI-H/dMMR mCRC: ICI monotherapy, dual I-O combination, or ICI plus chemotherapy with or without targeted therapy. Furthermore, a high rate of PD is observed, with 29% in ICI monotherapy and 13% in dual I-O combination treatment. Therefore, to develop a treatment with a lower PD rate and manageable safety, it is necessary to reduce misdiagnosed MSI-H/dMMR status to unify inspection methods and improve their accuracy. Moreover, it is crucial to identify the low responsiveness to ICIs in advance. Reportedly, low tumor mutational burdens, a phosphatase and tensin homolog (PTEN) mutation, and a high neutrophil-to-lymphocyte ratio might be associated with early disease progression (20,21). The confirmation of these findings necessitates the conduction of larger studies taking into consideration the treatment strategies. Additionally, the intervals between CT scans for the CheckMate-142 and KEYNOTE-177 trials were 6 and 9 weeks, respectively. However, the detection of early disease progression requires a shorter interval of about 4 weeks.

Ongoing clinical trials in MSI-H/dMMR mCRC are evaluating different treatment combinations. For example, randomized phase III studies COMMIT (NCT02997228) and CheckMate 8HW (NCT04008030) are currently ongoing. COMMIT evaluates the activity of the combination between standard chemotherapy and bevacizumab with or without PD-L1, and CheckMate 8HW evaluates nivolumab monotherapy, nivolumab plus ipilimumab, or investigator's choice. The results are expected in the near future.

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Footnote

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