Editorial Commentary

Is dual immunotherapy needed in first-line treatment of microsatellite instability (MSI)-high metastatic colorectal cancer?

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In microsatellite instability (MSI)-high or mismatch repair (MMR)-deficient metastatic colorectal cancer (CRC), first-line treatment with immunotherapy with pembrolizumab is now the standard of care (1). Pembrolizumab, a programmed death 1 (PD-1) inhibitor, versus chemotherapy demonstrated a median progression-free survival (PFS) of 16.5 months versus 8.2 months, respectively (P=0.0002), and the median overall survival (OS) with pembrolizumab was not reached (1). Despite improved survival, more patients had progressive disease as best response with pembrolizumab (29.4%) than with chemotherapy (12.3%), suggesting resistance in a subset of patients (1). The mechanism of resistance in the cohort of patients who did not have a response to single-agent PD-1 blockade is not clear, however, it is possible that combinations with chemotherapy or anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors to PD-1 blockade may result in improved responses by overcoming resistance, and thus, survival. There is promise that dual checkpoint blockade with the addition of CTLA-4 inhibitor to anti-programmed death ligand-1 (PD-L1)/PD-1 inhibitor may result in improved survival, however, at what cost to toxicity and quality of life?

In CheckMate 142 Study, Lenz *et al.* present the efficacy and safety of first-line dual immunotherapy with nivolumab (PD-1 inhibitor) plus low-dose ipilimumab (CTLA-4 inhibitor) in MSI-high/MMR-deficient metastatic CRC (2). This phase 2, multi-cohort study included patients who were untreated and previously treated (2). In this study, those enrolled onto the first-line cohort received nivolumab 3 mg/kg once every 2 weeks and low-dose ipilimumab 1 mg/kg once every 6 weeks (2). Of the 45 patients, median age was 66 (range, 21–85) years (2). BRAF mutations were in 38%, and KRAS mutations were in 22% of patients (2). Thirty patients discontinued treatments (2). Disease progression (18%) was the most common cause of discontinuation, followed by maximum clinical benefit (13%), adverse events (AEs) related to study drug (11%), patient request to discontinuation (9%), and lost to follow-up (2%) (2). Eleven patients went on to receive subsequent therapies, whereas 19 patients did not receive subsequent therapies (2).

The primary endpoint was objective response rate (ORR). ORR was 69% (75% in patients with BRAF mutations and 80% in patients with KRAS mutations) (2). Other RAS mutations or HER2 aberrations were not reported. Complete response (CR) rate was 13% (2). Median time to response was 2.7 months; median duration of response (DOR) was not reached (2). Median OS was not reached, and the 12-month OS rate was 84.1% [95% confidence

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Table 1 Summary of key findings from CheckMate 142 and Keynote-177 for first-line treatment of metastatic MSI-high CRC

Treatment	Phase	n	Median OS	Median PFS	12-month PFS	24-month PFS	ORR	Duration of response	% AE	% Grade 3/4 AE	QOL
Nivolumab plus Ipilimumab (2)	II	45	NR	NR	76.4%	73.6%	69%	NR (range, 1.4+ to 29.0+ months)	80%	22%	Stable over the treatment period based on EORTC QLQ-C30 and EQ-5D
Pembrolizumab *vs.* chemotherapy (1,3)	III	153 *vs.* 154 (60% crossed from chemotherapy to pembrolizumab)	NR (95% CI: 49.2–NR) *vs.* 36.7 months (27.6–NR); HR 0.74; 95% CI: 0.53–1.03; P=0.036	16.5 months (95% CI: 5.4 to 38.1) *vs.* 8.2 months (95% CI: 6.1 to 10.2)	55.3% *vs.* 37.3%	48.3% *vs.* 18.6%	43.8% *vs.* 33.1%	NR (range, 2.3+ to 41.4+) *vs.* 10.6 months (range, 2.8 to 37.5+)	97% *vs.* 99%	56% *vs.* 78% (TRAE: 22% *vs.* 66%)	Baseline to prespecified week 18 showed a clinically meaningful improvement in EORTC QLQ-C30 GHS/QOL scores with pembrolizumab versus chemotherapy [between-group LSM difference 8.96 (95% CI: 4.24–13.69); two-sided nominal P=0.0002]

MSI, microsatellite instability; CRC, colorectal cancer; n, number; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; AE, adverse events; QOL, quality of life; NR, not reached; CI, confidence interval; TRAE, treatment-related AE; GHS, global health status; LSM, least squares mean.

interval (CI): 69.5 to 92.1], 18-month OS rate was 81.7% (95% CI: 66.8 to 90.4), and 24-month was OS rate: 79.4% (95% CI: 64.1 to 88.7) (2). Eighty percent patients had AEs, of which 22% were grade 3 or higher AEs (2). Additionally, quality of life remained stable over the treatment period based on EORTC QLQ-C30 and EQ-5D questionnaires (2). Although this study enrolled a smaller cohort of patients compared to the pivotal KEYNOTE-177 trial, which led to FDA-approval of front-line pembrolizumab in MSI-high metastatic CRC, similar toxicity outcomes, percentage of total AEs and grade 3 or higher AEs, were reported with pembrolizumab monotherapy (1).

The outcomes of the study demonstrate that dual immunotherapy shows promise, especially in regard to the CR, survival, and disease control rates (*Table 1*). Further, in subgroups of BRAF and KRAS mutations, which have traditionally poor outcomes to chemotherapy, the median PFS was not reached. ORR (69%) were higher with ipilimumab/nivolumab than those reported with pembrolizumab (11.1%) and chemotherapy (3.9%), which may be attributable to the resistance to anti-PD-1 monotherapy that is overcome by CTLA-4 inhibition (1,2). However, the limitations of this study include that it was a single cohort study without a comparator arm with a small sample size, which may have less impressive outcomes in a larger, randomized controlled study. In the previously treated cohort, patients who had received prior treatment with a PD-1 inhibitor, a PD-L1/PD-L2 inhibitor, a CTLA-4 inhibitor, or any other agents targeting the T-cell co-stimulation or immune checkpoint pathways were excluded (4). This cohort had ORR was 65%, and 48-month rates of PFS and OS were 53% and 71%, respectively, suggesting that dual checkpoint blockade has efficacy in later lines after chemotherapy, but the efficacy of dual checkpoint inhibition after progression on first-line PD-1 inhibitors is not clear (4).

Historically, there has been clinical concern about increased toxicity with the addition of anti-CTLA-4 inhibitors. Therefore, the investigators chose to study less frequent, lower dose of ipilimumab, which showed better tolerability. The combination was tolerated in the first-line setting versus the second-line setting (grade 3/4 treatment-related AEs were 22% versus 32%, respectively) (2). Further, the grade 3/4 AEs appear to be similar to that seen with single agent immunotherapy in Keynote-177 (pembrolizumab 22% versus chemotherapy 66%) (1). Additionally, nivolumab with low-dose ipilimumab show stability of quality of life during treatment, which

Table 2 Ongoing phase II and III clinical trials for first-line treatment of metastatic MSI-high CRC

Phase	Title	Clinical Trials.gov number	Status
III	A Study of Nivolumab, Nivolumab Plus Ipilimumab, or Investigator's Choice Chemotherapy for the Treatment of Participants With Deficient Mismatch Repair (dMMR)/Microsatellite Instability High (MSI-H) Metastatic Colorectal Cancer (mCRC)	NCT04008030	Recruiting
III	Combination Chemotherapy, Bevacizumab, and/or Atezolizumab in Treating Patients With Deficient DNA Mismatch Repair Metastatic Colorectal Cancer, the COMMIT Study	NCT02997228	Recruiting
III	IBI310 in Combination With Sintilimab in Patients With DNA Mismatch Repair Deficient (dMMR)/Microsatellite Instability High (MSI-H) Locally-advanced or Metastatic Colorectal Cancer	NCT04258111	Active, not recruiting
III	Efficacy and Safety of Two Combination Treatment Regimens of Nivolumab and Ipilimumab in Patients With dMMR and/or MSI Metastatic Colorectal Cancer	NCT04730544	Recruiting
Ib/II	M7824 in Patients With Metastatic Colorectal Cancer or With Advanced Solid Tumors With Microsatellite Instability	NCT03436563	Active, not recruiting

MSI, microsatellite instability; CRC, colorectal cancer.

is challenging to interpret in a single-arm study (2). Pembrolizumab resulted in a clinically meaningful improvement in EORTC QLQ-C30 global health status/quality of life versus chemotherapy (3).

In summary, dual immunotherapy with nivolumab and low-dose ipilimumab showed clinical benefit with a manageable safety profile and sustained quality of life in the first-line setting to treat MSI-high metastatic CRC. We still need long-term survival data and confirming efficacy of dual checkpoint blockade in a randomized controlled trial, which is underway (NCT04008030). There are numerous studies evaluating novel immunotherapeutic agents in mCRC (5), including several phase 2 and 3 studies currently enrolling (*Table 2*). Further, the future landscape of dual checkpoint inhibition especially in the neoadjuvant setting of locally advanced CRC and metastatic CRC is exciting given the ORR, the tolerability, and the ability to downstage metastatic CRC or convert metastatic CRC to resectability, and therefore, ultimately cure.

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