



Emerging role of immunotherapy in the treatment naïve metastatic colorectal cancer patient

Audrey E. Kam¹, Cathy Eng²

¹Department of Hematology, Oncology and Cell Therapy, Rush University Medical Center, Chicago, IL, USA; ²Vanderbilt-Ingram Cancer Center, Nashville, TN, USA

Correspondence to: Cathy Eng, MD, FACP, FASCO. Professor of Medicine, Hematology and Oncology, Co-Director, GI Oncology, Co-Leader, Gastrointestinal Cancer Research Program, Vanderbilt-Ingram Cancer Center, 2220 Pierce Avenue, 777 Preston, Research Building, Nashville, TN 37232, USA. Email: cathy.eng@vumc.org.

Comment on: Le DT, Kim TW, Van Cutsem E, *et al.* Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. *J Clin Oncol* 2020;38:11-9.

Received: 08 June 2020. Accepted: 29 June 2020; Published: 30 December 2020.

doi: 10.21037/dmr-2020-22

View this article at: <http://dx.doi.org/10.21037/dmr-2020-22>

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide (1). An estimated 147,950 new cases will be diagnosed in the US this year alone, along with an estimated 53,200 deaths (2). Despite significant advances in the treatment of CRC, the prognosis of metastatic CRC (mCRC) remains poor with a 5-year survival rate of 14% (3). Consequently, there is an unmet need to improve therapeutic outcomes in this patient population.

Over the past few years, immune checkpoint inhibitors (ICIs) have shown clinical efficacy across multiple solid tumors with durable responses (4,5). In CRC, response to ICIs has mainly been observed in tumors exhibiting deficient mismatch repair (dMMR). MMR proteins are responsible for correcting DNA base pair mismatches located in repetitive DNA sequences, known as microsatellites (6). Deficiency of the MMR system results in the accumulation of microsatellites of differing lengths, known as microsatellite instability-high (MSI-H), and the epigenetic hypermutated phenotype (7). The presence of high tumor mutational burden (TMB) produces a large number of mutation-associated neo-antigens (MANAs) that may be recognized by the immune system (8). In CRC, dMMR/MSI-H occurs in ~15–20% of cases with decreasing incidence by stage (9). In mCRC, only ~4% of patients exhibit MSI-H/dMMR tumors, whereas proficient mismatch repair (pMMR) or microsatellite stable (MSS) tumors are more common. MSI-H/dMMR mCRC is characterized by

distinct clinicopathologic features including their association with: proximal tumor location; BRAF mutation; poor differentiation with mucinous or signet ring cells; increased tumor infiltrating lymphocytes (TILs); poor response to chemotherapy; and poor prognosis (10–12).

The most extensively studied ICIs in mCRC include pembrolizumab and nivolumab, monoclonal antibodies directed against the immune checkpoint programmed death 1 (PD-1). In a pilot phase II trial, Keynote-016, 41 patients with pMMR CRC (N=21), chemorefractory dMMR CRC (N=11), and dMMR non-CRCs (N=9) were treated with pembrolizumab (13). The initial report revealed an overall response rate (ORR) of 40% in the dMMR mCRC cohort that was durable, compared to 0% in the pMMR mCRC cohort. In an updated analysis, which included 86 patients with dMMR tumors, the ORR was 52% in the CRC cohort. The 2-year progression-free survival (PFS) was 59% and the 2-year overall survival (OS) was 72% (8). To further evaluate the activity of pembrolizumab in dMMR mCRC, two follow-up studies, Keynote-164 (phase II) and Keynote-177 (phase III), were initiated and are discussed below.

Nivolumab was studied in the two-arm phase II Checkmate-142 trial. A total of 74 patients with chemorefractory dMMR mCRC were treated with single agent nivolumab and achieved an ORR of 31%. The 12-month PFS rate and OS rate were 50% and 73%, respectively (14). In a separate parallel cohort, 45 patients received nivolumab in combination with ipilimumab,

an inhibitor of the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). In the most updated analysis, ORR was 69% and the 24-month PFS and OS rates were 74% and 79%, respectively (15). Data from Keynote 016 and Checkmate 142 led to the FDA approval of pembrolizumab and nivolumab (with or without ipilimumab) for the treatment of MSI-H/dMMR mCRC after progression on fluoropyrimidine, oxaliplatin and irinotecan or for patients who are not candidates for cytotoxic chemotherapy (16,17).

In the phase II Keynote-164 trial by *Le et al.* 2020, patients with MSI-H/dMMR mCRC who had previously received ≥ 2 prior lines of therapy, including fluoropyrimidine, oxaliplatin, irinotecan, were enrolled (cohort A) (18). The study was later amended to include patients with disease progression after one or more fluorouracil-based regimens (cohort B). Patients received pembrolizumab for up to 2 years) until progression, unacceptable toxicity, or withdrawal. Of note, patients who attained a confirmed complete response (CR) and who received at least 6 months of therapy had the option of discontinuing pembrolizumab. In addition, patients who stopped pembrolizumab either after 2 years of therapy or after achieving CR could resume pembrolizumab for an additional 1 year. A total of 124 patients with MSI-H/dMMR mCRC were enrolled [cohort A (n=61); cohort B (n=63)]. At the time of data cut off, the median follow-up was 31.3 months (mo) for cohort A and 24.2 mo for cohort B. The ORR was 33% (95% CI, 21% to 46%) in cohort A and 33% (95% CI, 22% to 46%) in cohort B. The median duration of response (DOR) was not reached in either cohort. Median PFS was 2.3 mo (95% CI, 2.1–8.1 mo) and 4.1 mo (95% CI, 2.1–18.9 mo) in cohort A and B, respectively. Median OS was 31.4 mo (95% CI, 21.4 mo–NR) and not reached (95% CI, 19.2 mo–NR) in cohort A and B, respectively. In terms of safety, the incidence of grade 3/4 treatment-related adverse events (TRAE) was 16% (10/61) in cohort A and 13% (8/63) in cohort B. TRAE led to treatment discontinuation in two patients in cohort A and two patients in cohort B. Immune-related AEs or infusion reactions were observed in 21% of patients in cohort A and 37% in cohort B. Grade 3/4 immune-related AE occurred in four patients in cohort A (pancreatitis in two patients and hepatitis, pneumonitis, and severe skin toxicity in one patient each) and in two patients in cohort B (colitis and pneumonitis in one patient each).

A more in depth review of the results from Keynote-164 reveals a few interesting points. The response to pembrolizumab in MSI-H/dMMR mCRC was quite durable. The median DOR was not reached in both cohorts,

with a median OS of 31 mo in cohort A and not reached in cohort B. In addition, responses were observed regardless of the number of prior therapies. In cohort B, 38% of patients had only received 1 prior line of therapy and achieved an ORR 29%, therefore representing response to pembrolizumab earlier in the disease course. Furthermore, analysis of response rate by mutation status demonstrated that durable responses were achieved independent of BRAF and RAS mutational status. However, the small study size limits the interpretation of the subgroup analysis. Another weakness of the study is the non-randomized nature of the trial without a comparator arm. Finally, other potential biomarkers such as, PD-L1 expression and TMB, were not explored as dMMR status was assessed locally (18).

In follow-up to Keynote-164, pembrolizumab was studied in the first-line setting for MSI-H/dMMR mCRC in the randomized, phase III, Keynote-177 trial. Data from the interim PFS analysis was presented at the ASCO 2020 Virtual Scientific Program. A total of 307 patients with MSI-H/dMMR mCRC were randomized to receive either first-line pembrolizumab or investigator's choice of chemotherapy with/without bevacizumab or cetuximab (19). Pembrolizumab was shown to be superior to chemotherapy with a median PFS of 16.5 *vs.* 8.2 mo with chemotherapy (HR 0.60; 95% CI, 0.45–0.80; $P=0.0002$). The 12- and 24-month PFS rates were 55.3% and 48.3% with pembrolizumab *vs.* 37.3% and 18.6% with chemotherapy. Confirmed ORR were 43.8% and 33.1%, respectively. The median DOR not reached with pembrolizumab (2.3–41.4 mo) *vs.* 10.6 mo for chemotherapy (2.8–37.5 mo). The incidence of grade 3–5 TRAE was 22% with pembrolizumab *vs.* 66% with chemotherapy. Despite these encouraging results, a few nuances should be noted. The rate of progressive disease was 29.4% for pembrolizumab *vs.* 12.3% for chemotherapy. In addition, during the first 6 months of treatment, the chemotherapy arm was favored with the PFS curves diverging thereafter in favor of pembrolizumab. Thus, it appears that a subgroup of MSI-H/dMMR mCRC patients may not respond to pembrolizumab. In the subgroup analysis, pembrolizumab was favored in most subgroups, with the exception of patients with RAS-mutant tumors. Aside from RAS mutational status, other biomarkers of resistance need to be elucidated. Immunoscore, a robust and validated test of the host immune reaction, measuring CD3+ and CD8+ T-cell densities within the tumor (20), may provide further insight on resistance mechanisms. A high immunoscore is typically observed in MSI-H/dMMR tumors and to a lesser degree

in MSS/pMMR tumors, and has been associated with improved survival outcomes in stage I-III CRC (20). Future studies will need to address whether a low immunoscore correlates with poor response to ICI despite MSI-H/dMMR status. Perhaps, combination therapy with chemotherapy plus ICI may be effective in this subgroup. The COMMIT trial, which is comparing atezolizumab (anti-PD-L1) against chemotherapy with or without atezolizumab, may provide further insight on this matter (NCT02997228). Lastly, it is important to remember that dual ICI as first-line therapy in MSI-H/dMMR mCRC has also demonstrated impressive outcomes. As mentioned previously, in the most updated analysis of Checkmate-142, patients in the nivolumab plus ipilimumab cohort achieved an ORR of 69% with a CR of 13% (15). The median PFS and OS were not reached, and 24-month rates were 74% and 79%, respectively. Grade 3–4 TRAE occurred in 22% of patients with 7% leading to treatment discontinuation. Thus, the clinical question of single agent ICI *vs.* dual ICI as first-line therapy in MSI-H/dMMR mCRC will need to be answered by future studies.

In conclusion, the role of ICI in the treatment of MSI-H/dMMR mCRC has rapidly evolved. The phase II Keynote-164 trial provided evidence supporting the use of pembrolizumab following disease progression on first- or second-line chemotherapy. Interim results from the larger, randomized, phase III Keynote-177 demonstrated a doubling of PFS and a one-third less TRAE with first-line pembrolizumab compared to chemotherapy in MSI-H/dMMR mCRC. Updated results with final OS data are eagerly awaited. For the subset of MSI-H/dMMR mCRC patients who did not respond to pembrolizumab, RAS mutational status appeared to be a biomarker of resistance. It will be important for future studies to confirm this finding and to identify other biomarkers of resistance (e.g., immunoscore). Perhaps combination therapy with chemotherapy plus ICI may overcome such resistance. In addition, whether single agent ICI or dual ICI should be employed as first-line therapy in MSI-H/dMMR mCRC remains to be clarified. Regardless, the impressive promising results in the treatment-naïve metastatic setting suggest that organ preservation and possible omission of surgery may be a possibility in the future. Finally, while strong evidence for ICI in MSI-H/dMMR mCRC exists, the challenge of increasing the immunogenicity of pMSS/pMMR tumors remains. Several combination therapies, either dual ICI, chemotherapy plus ICI, or ICI plus targeted therapy, have been evaluated in a number of clinical trials. In a randomized phase II trial, durvalumab

(anti-PDL1) plus tremelimumab (anti-CTLA4) was compared to best supportive care (BSC) in patients with chemorefractory mCRC. Unfortunately, no difference in OS was demonstrated ($P=0.07$) (21). In the randomized, phase III IMblaze 370 trial, atezolizumab with or without cobimetinib (MEK inhibitor) was compared with regorafenib in chemo-refractory mCRC patients (22). Again, there was no difference in PFS or OS between the three treatment arms. Other early phase trials have combined ICIs with regorafenib with promising results (23,24). As more high-quality evidence becomes available, it is hoped that the benefit of ICIs will be extended to include patients with MSS/pMMR tumors as well.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Digestive Medicine Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/dmr-2020-22>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention

- strategies. *Nat Rev Gastroenterol Hepatol* 2019;16:713-32.
2. American Cancer Society. Key Statistics for Colorectal Cancer. Accessed May 3, 2020. Available online: <https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html>
 3. American Cancer Society. Survival Rates for Colorectal Cancer. Accessed May 3, 2020. Available online: <https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html>
 4. Albertini MR. The age of enlightenment in melanoma immunotherapy. *J Immunother Cancer* 2018;6:80.
 5. Karachaliou N, Fernandez-Bruno M, Rosell R. Strategies for first-line immunotherapy in squamous cell lung cancer: Are combinations a game changer? *Transl Lung Cancer Res* 2018;7:S198-201.
 6. Lynch HT, Snyder C, Shaw TG, et al. Milestones of Lynch syndrome: 1895-2015. *Nat Rev Cancer* 2015;15:181-94.
 7. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012;487:330-7.
 8. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;357:409-13.
 9. Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology* 2010;138:2073-87.e3.
 10. Overman MJ, Ernstoff MS, Morse MA. Where we stand with immunotherapy in colorectal cancer: deficient mismatch repair, proficient mismatch repair, and toxicity management. *Am Soc Clin Oncol Educ Book* 2018;38:239-47.
 11. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: A pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. *Clin Cancer Res* 2014;20:5322-30.
 12. Greenson JK, Bonner JD, Ben-Yzhak O, et al. Phenotype of microsatellite unstable colorectal carcinomas: Well-differentiated and focally mucinous tumors and the absence of dirty necrosis correlate with microsatellite instability. *Am J Surg Pathol* 2003;27:563-70.
 13. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;372:2509-20.
 14. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol* 2017;18:1182-91.
 15. Lenz HJ, Lonardi S, Zagonel V, et al. Nivolumab (NIVO) + low-dose ipilimumab (IPI) as first-line (1L) therapy in microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Two-year clinical update. *J Clin Oncol* 2020;37:3521.
 16. Lemery S, Keegan P and Pazdur R. First FDA approval agnostic of cancer site - when a biomarker defines the indication. *N Engl J Med* 2017;377:1409-12.
 17. Bristol-Myers Squibb, Princeton, NJ, USA: OPDIVO (nivolumab): US prescribing information, 2018.
 18. Le DT, Kim TW, Van Cutsem E, et al. Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. *J Clin Oncol* 2020;38:11-9.
 19. Andre T, Shiu K, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: The phase 3 KEYNOTE-177 study. *J Clin Oncol* 2020;38:LBA4.
 20. Ciardiello D, Vitiello PP, Cardone C, et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat Rev* 2019;76:22-32.
 21. Chen EX, Jonker DJ, Loree JM, et al. CCTG CO.26: Updated analysis and impact of plasma-detected microsatellite stability (MSS) and tumor mutation burden (TMB) in a phase II trial of durvalumab (D) plus tremelimumab (T) and best supportive care (BSC) versus BSC alone in patients (pts) with refractory metastatic colorectal carcinoma (rmCRC). *J Clinical Oncol* 2019;37:3512.
 22. Eng C, Kim TW, Bendell J, et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 2019;20:849-61.
 23. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603). *J Clin Oncol* 2020;38:2053-61.
 24. Cousin S, Bellera CA, Guégan JP, et al. REGOMUNE: A phase II study of regorafenib plus avelumab in solid tumors—Results of the non-MSI-H metastatic colorectal cancer (mCRC) cohort. *J Clin Oncol* 2020;38:4019.

doi: 10.21037/dmr-2020-22

Cite this article as: Kam AE, Eng C. Emerging role of immunotherapy in the treatment naïve metastatic colorectal cancer patient. *Dig Med Res* 2020;3:87.