EDITORIALS

Pembrolizumab in MSI-H–dMMR Advanced Colorectal Cancer — A New Standard of Care

Axel Grothey, M.D.

Nothing has changed cancer therapy more in the past 5 to 10 years than the introduction of immune checkpoint inhibitors. In solid tumors, the activity of these agents is commonly linked to the presence of a hypermutated phenotype with the expression of tumor-specific neoantigens at the surface of cancer cells that can serve as targets for T cells. A higher tumor mutation burden can be the result of exogenous, DNA-damaging carcinogens, such as ultraviolet light and smoking, or linked to cell-intrinsic deficiencies in DNA repair mechanisms. Germline mutations in genes encoding mismatch repair proteins are the hallmarks of the Lynch syndrome, but the deficient mismatch repair (dMMR) phenotype, identified by immunohistochemical analysis, is more commonly found in sporadic, nonfamilial cancers. The phenotype itself leads to a high degree of microsatellite instability (MSI-H), which is assessed with the use of polymerase chain reaction or next-generation sequencing.

MSI-H–dMMR cancers have been recognized to be sensitive to treatment with immune checkpoint inhibitors such as programmed death 1 (PD-1) antibodies, with or without the addition of cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) antibodies.[1-3] In fact, in 2017, the PD-1 antibody pembrolizumab received the first tumor-type–agnostic approval from the Food and Drug Administration (FDA) for use as salvage therapy in patients with any MSI-H–dMMR cancer independent of the site of tumor origin.

In colorectal cancer, only 4 to 5% of metastatic cancers show the MSI–dMMR phenotype; the prevalence is greater in *BRAF*^{V600E}-mutated cancers, in cancers originating on the right side, and in female patients. The activity of immune checkpoint inhibitors in MSI-H–dMMR colorectal cancers in later lines of treatment was convincingly documented in nonrandomized studies, with response rates of 30 to 40% for single-agent anti–PD-1 antibodies (pembrolizumab or nivolumab) and 40 to 50% for the combination of nivolumab and the anti–CTLA-4 antibody ipilimumab.[1-3] The achieved responses showed remarkable durability, which convinced the FDA to grant approval for pembrolizumab and nivolumab (with or without ipilimumab) in 2017 and 2018, respectively, for use as salvage therapy in colorectal cancer. Conversely, no convincing activity of immune checkpoint inhibitors has been shown to date in patients with microsatellite-stable, mismatch repair–proficient (MSS–pMMR) metastatic colorectal cancers.

In this issue of the *Journal*, André et al. present the long-awaited data from the KEYNOTE-177 trial, in which single-agent pembrolizumab was compared with the investigator's choice of doublet chemotherapy, with or without the addition of a biologic agent, as first-line therapy for MSI-H–dMMR colorectal cancer.[4] The trial showed that median progression-free survival, one of the two primary end points, was more than twice as long with pembrolizumab as with chemotherapy. The trial allowed patients to cross over from the chemotherapy group to receive pembrolizumab, and, in fact, 59% of patients randomly assigned to the chemotherapy group received pembrolizumab at some point during the course of their therapy. It is conceivable that this high rate of crossover will make it difficult to ever achieve a significant difference in the second primary end

point, overall survival. Pembrolizumab also led to a higher overall response (complete or partial response) than chemotherapy (in 43.8% vs. 33.1% of patients) and showed a remarkable durability of response, a phenomenon well documented with immune checkpoint inhibitors in highly immunogenic cancers. The percentage of patients with a complete response was likewise higher in the pembrolizumab group than in the chemotherapy group (11.1% vs. 3.9%), and evidence is emerging that the number of actual complete responses is probably underestimated by conventional imaging, since resection of persistent residual lesions after treatment with immune checkpoint inhibitors commonly does not identify any viable tumor cells.[5]

In conjunction with the durability of response observed in many patients, the idea of a potential curative approach with immune checkpoint inhibitors in advanced MSI-H–dMMR colorectal cancers has emerged. In addition to higher efficacy, pembrolizumab was also associated with fewer toxic effects and better long-term quality of life than chemotherapy.[6] These results have established pembrolizumab as a new standard for first-line therapy in patients with MSI-H–dMMR colorectal cancer and have led to subsequent FDA approval of pembrolizumab for first-line therapy. The data also have clinically relevant implications for countries in which regulatory agencies considering immune checkpoint inhibitors for drug approval have not accepted the results of single-group studies.

The results of the KEYNOTE-177 trial, however, deserve some scrutiny. More patients in the pembrolizumab group than in the first-line chemotherapy group had progression of disease as the best response (29.4% vs. 12.3%). This is mirrored by an early poorer performance, as shown in the Kaplan–Meier curves, among patients treated with pembrolizumab than among those who received chemotherapy until about 6.5 months after onset of therapy, beyond which the pembrolizumab group showed protracted improvement — a phenomenon seen in various other trials with PD-1 antibodies in gastrointestinal cancers. It appears that a subgroup not yet clearly defined within the MSI-H–dMMR population does not have a response to immune checkpoint inhibitors. Previous studies have indicated that in MSI-H–dMMR cancers, tumor mutational burden can be used as a predictive marker, with higher tumor mutational burden associated with a very high likelihood of response to immune therapy.[7] The pattern of MMR protein expression should also be investigated, since the effect on tumor mutational burden was found to vary with the loss of different individual mismatch repair proteins.[8] Recent data suggest that longitudinal circulating tumor DNA levels can identify patients with primary resistance to immune checkpoint inhibitors.[9] In addition, to decrease the number of patients with progression of disease as the best response, combination strategies with pembrolizumab plus either chemotherapy or other checkpoint inhibitors such as CTLA-4 antibodies can be considered. In this context, preliminary data regarding immune checkpoint inhibitor combination therapies are encouraging.[2] One of the surprise findings of the KEYNOTE-177 trial is that patients with *RAS*-mutated cancers did not appear to benefit from pembrolizumab more than from chemotherapy, even though in previous, nonrandomized studies, *RAS* mutations had not been associated with decreased activity of immune checkpoint inhibitors.[2,3]

The results of the KEYNOTE-177 trial support ongoing trials investigating immune checkpoint inhibitors in earlier treatment lines, such as the ongoing ATOMIC trial (ClinicalTrials.gov number, NCT02912559) involving patients with MSI-H–dMMR stage 3 colon cancer, in which the anti–PD-L1 antibody atezolizumab is added to adjuvant FOLFOX (fluorouracil, leucovorin [folinic acid], and oxaliplatin) chemotherapy. Neoadjuvant approaches are also being investigated in rectal cancer, and the preliminary data are intriguing. The ultimate goal of immunotherapy in colorectal cancer, however, is to find active treatment approaches for MSS–pMMR cancers, which constitute the vast majority of advanced colorectal cancers. For MSI-H–dMMR colorectal cancer, the durability of response, better safety profile, and improved quality of life associated with immunotherapy as compared with chemotherapy make pembrolizumab the preferred choice.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From GI Cancer Research, West Cancer Center and Research Institute, Germantown, TN.

1. 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.
2. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch re-

pair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 2018;36:773-9.
3. 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.
4. André T, Shiu K-K, Kim TW, et al. Pembrolizumab in microsatellite-instability–high advanced colorectal cancer. N Engl J Med 2020;383:2207-18.
5. Ludford K, Cohen R, Svrcek M, et al. Pathological tumor response following immune checkpoint blockade for deficient mismatch repair advanced colorectal cancer. J Natl Cancer Inst 2020 April 15 (Epub ahead of print).
6. André T, Amonkar M, Norquist J, et al. 396O Health-related quality of life (HRQoL) in patients (pts) treated with pembrolizumab (pembro) vs chemotherapy as first-line treatment in microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR) metastatic colorectal cancer (mCRC): Phase III KEYNOTE-177 study. Ann Oncol 2020;31:Suppl 4S409. abstract.
7. Schrock AB, Ouyang C, Sandhu J, et al. Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer. Ann Oncol 2019;30:1096-103.
8. Salem ME, Bodor JN, Puccini A, et al. Relationship between MLH1, PMS2, MSH2 and MSH6 gene-specific alterations and tumor mutational burden in 1057 microsatellite instability-high solid tumors. Int J Cancer 2020;147:2948-56.
9. Zhang Q, Luo J, Wu S, et al. Prognostic and predictive impact of circulating tumor DNA in patients with advanced cancers treated with immune checkpoint blockade. Cancer Discov 2020 August 14 (Epub ahead of print).

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Finerenone — Halting Relative Hyperaldosteronism in Chronic Kidney Disease

Julie R. Ingelfinger, M.D., and Clifford J. Rosen, M.D.

Type 2 diabetes is the most common cause of chronic kidney disease (CKD) and end-stage renal disease. Cardiovascular risk and the risk of progression of kidney disease are very high among patients with diabetes mellitus, particularly among those with CKD. Clinical strategies to prevent cardiovascular disease and the development of new diabetic kidney disease or to slow the progression of CKD that is already present have been incorporated into clinical practice for the past three decades and include angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers and, more recently, sodium–glucose cotransporter 2 (SGLT2) inhibitors (gliflozins), such as dapagliflozin and empagliflozin. However, few of the other drug classes studied have ultimately proved renoprotective — witness, for example, the ultimately disappointing clinical trial experience with bardoxolone,[1] aliskiren,[2] and the erythrocyte stimulatory agent darbepoetin.[3]

Aldosterone, a mineralocorticoid hormone, is a downstream target of activation of the renin–angiotensin system (RAS) (reviewed in Barrera-Chimal et al.[4] with respect to CKD). Angiotensin II, corticotropin, and potassium are considered the main drivers of aldosterone release from the adrenal zona glomerulosa. However, other factors such as nitric oxide, endothelin, and a variety of pituitary and adipose-tissue factors can stimulate aldosterone synthesis. Once released, aldosterone binds to the mineralocorticoid receptor, leading to sodium retention and potassium loss, thereby controlling fluid and electrolyte status as well as blood pressure. Furthermore, the mineralocorticoid receptor also functions as a transcription factor that can increase the levels of inflammatory cytokines as well as genes targeting water resorption.[4] The mineralocorticoid receptor is present in the distal tubule of the kidney and also within glomeruli on podocytes and mesangial cells. Mild hyperaldosteronism, which occurs in patients with CKD, can also mediate inflammation through the mineralocorticoid receptor, increasing local levels of reactive oxygen species and profibrotic factors. Thus, high levels of aldosterone and its receptor may affect multiple kidney compartments.

Strategies to decrease aldosterone activation make sense, and drugs that interfere with the binding of aldosterone to its receptor have been used in a number of clinical conditions, particularly cardiovascular disease, for several decades. Spironolactone, first synthesized in 1957, is a steroidal, nonselective inhibitor of the mineralocorticoid receptor that is still widely used. The steroidal, selective inhibitor eplerenone has been available since the 1980s. Both of these steroidal mineralocorticoid receptor antagonists may lead to hyperkalemia in a high proportion of patients and have other unwelcome side effects, such as