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PRO/CON DEBATES

Systemic treatment of mismatch repair deficient/microsatellite instability-high metastatic colorectal cancer—single versus double checkpoint inhibition

THE CASE FOR FIRST-LINE NIVOLUMAB + IPILIMUMAB FOR PATIENTS WITH MICROSATELLITE INSTABILITY-HIGH/ MISMATCH REPAIR DEFICIENT METASTATIC COLORECTAL CANCER TODAY

(Sabatini, Bengala, Ciurluini, Picone, Santini, Marinelli)

Microsatellite instability (MSI) is found in ∼5% of all patients with metastatic colorectal cancer (mCRC). Solid evidence has shown that MSI-high/mismatch repair deficient (MSI-H/dMMR) tumors are less responsive to chemotherapy and sensitive to immunotherapy due to a higher tumor neoantigen load and immune cell infiltration.[1,2]

The KEYNOTE-177 phase III trial recently showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) with the anti-programmed cell death protein 1 (anti-PD-1) agent pembrolizumab when compared with chemotherapy in the first-line setting of MSI-H/dMMR mCRC.[3] Although most responses were durable, about one-third of patients treated with pembrolizumab monotherapy experienced primary resistance to immunotherapy as a result of disease progression or death during the first 3 months of treatment, leading to 12- and 24-month PFS of 55% and 47%, respectively. Indeed, an early crossing of survival curves in KEYNOTE-177 suggested that a significant fraction of patients were harmed by the experimental treatment as a result of a transiently lower efficacy of immunotherapy when compared with chemotherapy. Multiple clinical trials are currently assessing anti-programmed death-ligand 1 (anti-PD-L1)-based combinations to address treatment failures associated with anti-PD-1 monotherapy because a significant fraction of patients with MSI-H/dMMR mCRC still fail to obtain durable disease remission with anti-PD-1 monotherapy.

In MSI-H/dMMR CRC, the interplay between an extensive antitumor immune infiltration and the upregulation of multiple immune checkpoints is crucial during cancer evolution.[2,4] The synergistic effects of combining anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) therapies underscore the importance of combination immunotherapy. CTLA-4 blockade facilitates priming of effector T cells, while PD-1 inhibition enhances T-cell activity within the tumor microenvironment. This dual mechanism potentiates antitumor immune responses and mitigates immune evasion. Thus we envision that the combined blockade of immune inhibitory signals at both the PD-1 and CTLA-4 pathways might improve clinical outcomes. Accordingly, patients with MSI-H/dMMR mCRC treated in first line with nivolumab + ipilimumab in CheckMate-142, a nonrandomized, multicohort phase II study, had a promising 12- and 24-month PFS of 76% and 74%, respectively, with only 13% of cases showing primary resistance to immunotherapy.[5]

Results from the CheckMate-8HW phase III trial were recently presented during the 2024 ASCO Gastrointestinal (GI) Cancers Symposium.[6] The latter compared either the combination of nivolumab and ipilimumab or nivolumab monotherapy with chemotherapy in patients with MSI-H/dMMR mCRC. With a median follow-up of 24.3 months, among 255 patients treated with first-line therapy, the experimental treatment with nivolumab + ipilimumab showed a 79% reduction in the risk of progression or death when compared with chemotherapy (HR 0.21, 95% confidence interval 0.14-0.32). The median PFS had not yet been reached in the experimental arm, indicating a sustained benefit over time, with PFS rates of 79% and 72% at 12 and 24 months compared with 21% and 14% PFS in the chemotherapy arm, respectively.

To tentatively compare the efficacy of nivolumab + ipilimumab with pembrolizumab, the current standard of care, we reconstructed individual patient data (IPD) from published Kaplan—Meier curves of the CheckMate-8HW and KEYNOTE-177 trials using the IPDfromKM method.[7] As shown in Figure 1, our analysis highlights that the percentage of patients with early progression or death seems to be halved with the combination of nivolumab and ipilimumab, as only ∼15% of patients had a PFS event at the 3-month landmark. Furthermore, in the reconstructed data, only 55% and 48% of patients treated with pembrolizumab were progression free at 12 and 24 months compared with 79% and 73%, respectively, with nivolumab + ipilimumab, leading to a 56% PFS risk reduction.

Despite patients in both control arms receiving the investigator's choice of mFOLFOX6 or FOLFIRI combined with either bevacizumab or cetuximab, a comparison of control arms showed that patients in KEYNOTE-177 had numerically longer PFS. Therefore it is unlikely that the improved results seen with nivolumab + ipilimumab when compared with pembrolizumab are merely a result of selection bias favoring the former. We acknowledge that these suggestions

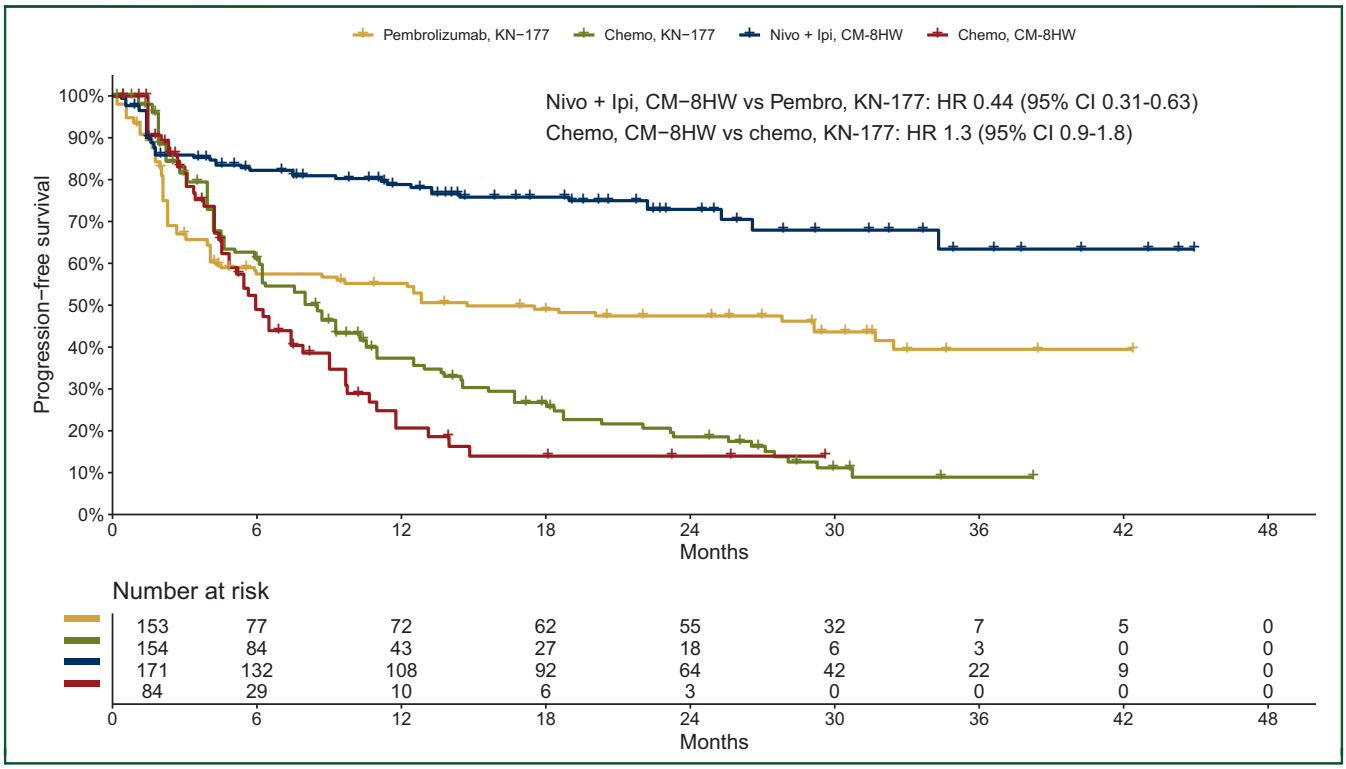

Figure 1. Progression-free survival (PFS) in patients with microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) treated with first-line immunotherapy or chemotherapy in the KEYNOTE-177 and CheckMate-8HW clinical trials.
Chemo, chemotherapy; CI, confidence interval; CM, CheckMate; HR, hazard ratio; Ipi, ipilimumab; KN-177, KEYNOTE-177; Nivo, nivolumab.

need to be confirmed after the disclosure of the nivolumab arm and after careful assessment of overall survival results from CheckMate-8HW, which are not yet available.

In conclusion, despite multiple limitations, cross-trial comparisons suggest that combined anti-PD-1 and anti-CTLA-4 offers notable advantages over anti-PD-1 monotherapy in MSI-H/dMMR mCRC. While KEYNOTE-177 established pembrolizumab monotherapy as the standard of care in the first-line setting, the addition of CTLA-4 blockade to PD-1 inhibition in the CheckMate-142 and CheckMate-8HW trials demonstrated improved outcomes with combination immunotherapy through the enhancement of antitumor immune responses. More data are needed to elucidate optimal treatment sequencing and patient selection criteria to maximize the therapeutic potential of immunotherapy in MSI-H/dMMR mCRC.

THE CASE AGAINST FIRST-LINE NIVOLUMAB + IPILIMUMAB FOR PATIENTS WITH MSI-H/dMMR mCRC TODAY

(Rossini, Pietrantonio, Cremolini)

The first long-awaited results of the phase III CheckMate-8HW trial showed that nivolumab + ipilimumab significantly prolongs PFS when compared with standard chemotherapy with or without targeted agents as initial treatment in patients with unresectable or metastatic MSI-H/dMMR CRC, thus meeting one of its dual primary endpoints. A consistent benefit is demonstrated across all investigated subgroups.[6]

These results clearly and robustly confirm the efficacy of immunotherapy as an upfront systemic treatment for patients with dMMR/MSI-H mCRC, corroborating and strengthening findings from the KEYNOTE-177 trial that established the anti-PD-1 pembrolizumab as the new standard of care.[3,8] However, the most clinically relevant question is not addressed yet, that is PFS and overall survival with ipilimumab + nivolumab versus nivolumab alone.

Although acknowledging the limitations of cross-trial comparisons, the effort to estimate the relative benefit of dual checkpoint inhibition over PD-1 blockade alone is completely understandable. Curve reconstruction using the IPDfromKM method provides useful information, but these need to be cautiously interpreted. In fact, although reconstructed curves lead to the conclusion that the association of ipilimumab and nivolumab improves PFS compared with pembrolizumab alone, and is able to overcome the initial crossover of the PFS curves in the KEYNOTE-177 trial, thus dramatically reducing the percentage of early treatment failures, some limitations should be taken into account.

First, IPD reconstructed with this method do not contain any information about covariates from the original dataset, unless they are graphically represented in the Kaplan–Meier graph. Therefore assessing whether homogenous and consistent criteria were adopted in different trials is essential. Further, in the case of comparable inclusion/exclusion criteria, a certain degree of heterogeneity in patients' selection, potentially weighing on final results, may exist.[9] In this regard, it should be well acknowledged that, although in both KEYNOTE-177 and CheckMate-8HW trials

the enrollment was based on the local testing of MSI/MMR, a central confirmation was carried out only in the latter using either immunohistochemistry or PCR-based tests, and only patients with centrally confirmed MSI-H/dMMR status were included in the primary endpoint analysis.[6,10] Notably, a significant percentage of cases (15%) identified as MSI-H/dMMR through local testing failed to be confirmed by central testing. Although feasible local testing offers the clear advantage of shorter screening phases for clinical trial enrollment and reflects real-life scenarios, these findings highlight an urgent need to investigate the reasons behind the significant discrepancy in results. Differences in adopted technologies and procedures must be examined, and reliable diagnostic algorithms need to be developed for pathologists to minimize the risk of MSI-H/dMMR misdiagnosis in daily practice, given the critical role of this biomarker in determining the therapeutic approach for impacted patients. From a cost/effectiveness perspective, although testing both MMR by immunohistochemistry (IHC) and MSI by restriction fragment length polymorphism-PCR or next-generation sequencing in each case may not be sustainable, and often even not needed, in cases of indeterminate MMR protein expression, the analysis of MSI by restriction fragment length polymorphism-PCR or next-generation sequencing should be recommended.[11,12] It should also be mentioned that the confidence of pathologists worldwide in the interpretation of IHC has improved in recent years, alongside the performance of available antibodies for IHC.

With regard to the comparison of the PFS curves achieved with ipilimumab + nivolumab and with pembrolizumab in the CheckMate-8HW trial and in the KEYNOTE-177 trials, respectively, the exclusion of patients with microsatellite stable/mismatch repair-proficient tumors in CheckMate-8HW and not in KEYNOTE-177 might significantly influence the apparent efficacy of the combination immunotherapy in preventing primary resistance. In fact, at least a percentage of early progressors in the pembrolizumab arm of the KEYNOTE-177 trial, conducted at a time when MMR testing was less established in the routine activity of pathologists than nowadays, might be explained by MSI-H/dMMR misdiagnosis, and excluding those patients would have likely reduced the early failures at the 3-month landmark analysis at least from 30% to 15%. Only the indirect comparison of results from the nivolumab arm of the CheckMate-8HW trial and the pembrolizumab arm of the KEYNOTE-177 trial might confirm or refute this hypothesis.

Second, the IPDfromKM algorithm does not accept input for censoring marks, and censored observation survival times are estimated using the modified i-KM method, which introduces some level of uncertainty. Moreover, the duration of follow-up for patients in the KEYNOTE-177 and CheckMate-8HW trials is highly different, being 73.3 months in the last PFS update and 23.4 months, respectively.[6,10] Consequently, the message of reconstructed curves with regard to the longer-term observations should be interpreted cautiously as a result of the much lower numbers at risk in the ipilimumab + nivolumab group than in the pembrolizumab group.

Finally, although the safety profile of the combination schedule used in the CheckMate-8HW trial appears highly acceptable and reassuring, estimating the clinical benefit magnitude of adding anti-CTLA-4 to upfront therapy in the entire population of patients with MSI-H/dMMR mCRC, as well as in relevant subgroups, is essential. This assessment will help properly integrate this treatment option into daily patient care, with careful consideration of financial sustainability, especially in public health care systems. From a precision medicine perspective, the identification of molecular and/or clinical predictors of benefit from the combination immunotherapy, compared with anti-PD-1 alone, would definitely help select patients' subgroups for whom the addition of the anti-CTLA-4 agent is needed and reduce the financial toxicity related to the incorporation of this treatment option into clinicians' therapeutic armamentarium. CheckMate-8HW will certainly be able—and was actually designed—to provide these pressing answers. The longer we have to wait before the planned number of progression events is reached for the primary analysis, the more pronounced the favorable impact of immunotherapy on these patients' life expectancy will be.

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Available online xxx

https://doi.org/10.1016/j.esmoop.2024.103483

FUNDING

None declared.

DISCLOSURE

CC reports honoraria from Amgen, Bayer, Merck, Roche, and Servier; carries out consulting or advisory roles for Amgen, Bayer, MSD, and Roche; is on the speakers' bureau for Servier; reports research funding from Bayer, Merck, and

Servier; and reports travel, accommodations, and expenses covered by Roche and Servier. FP reports institutional research grants from BMS, Incyte, Agenus, Amgen, Lilly, and AstraZeneca, and personal fees from BMS, MSD, Amgen, Merck-Serono, Pierre-Fabre, Servier, Bayer, Takeda, Astellas, Johnson & Johnson, Rottapharm, Ipsen, AstraZeneca, GSK, Daiichi-Sankyo, Seagen, and BeiGene. DR has received honoraria from Amgen, MSD, Takeda, and Pierre-Fabre. DS is on the advisory board for Angen, Janssen, Astellas, Bayer, Servier, Novartis, MSD, Merck, Pfizer, and Ipsen. DM, AS, EB, FC, and VP have declared no conflicts of interest.

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