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BRIEF REPORT

Microsatellite instability-high status as a pan-cancer biomarker for immunotherapy efficacy

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Abstract

Background Microsatellite instability-high (MSI-H) cancers are linked to exceptional benefit from immune checkpoint inhibitors (ICIs), but studies on their efficacy across various MSI-H cancer types are limited.

Methods Randomized clinical trials (RCTs) comparing ICIs to chemotherapy in advanced MSI-H/dMMR cancers were systematically reviewed. Eligible studies included 13 RCTs with 1633 MSI-H patients across colorectal, gastric, and endometrial cancers. Data were analyzed using hazard ratios for progression-free survival (PFS) and overall survival (OS), with subgroup analyses by tumor type. Statistical heterogeneity was assessed using Cochrane's Q and I^2.

Results Immunotherapy significantly improved PFS and OS in MSI-H patients, with an HR for OS of 0.35 (95% CI 0.27–0.46; $p < 0.00001$) versus 0.81 for MSS patients. PFS showed a 64% reduced risk of progression (HR = 0.36, 95% CI 0.28–0.46; $p < 0.0001$). Subgroup analyses highlighted PFS benefits across tumor types: colorectal (HR = 0.28, 95% CI 0.11–0.73), gastric (HR = 0.43, 95% CI 0.27–0.68), and endometrial cancers (HR = 0.34, 95% CI 0.27–0.42).

Conclusions This meta-analysis establishes MSI-H as a predictive biomarker for ICIs, supporting its role in therapy selection and underscoring the need for MSI-H/dMMR-focused clinical trials.

Keywords Microsatellite instability-high · Immune checkpoint inhibitors · Meta-analysis · Randomized trials · Overall survival

Introduction

Immunotherapy represents a major breakthrough in cancer treatment, particularly for tumors with microsatellite instability (MSI) or a mismatch repair deficiency (dMMR). The prevalence of MSI varies depending on the cancer type: 17–33% of endometrial cancers, 9–22% of gastric cancers, and 6–13% of colorectal cancers and with lower frequencies in other cancers (e.g., bladder, prostate, breast, renal cell carcinoma, pancreas, small cell lung cancer, thyroid, sarcomas) [1]. The prognosis of these advanced cancers has historically been poor due to resistance to conventional treatments such as chemotherapy [2, 3].

Early-phase clinical trials demonstrated that immune checkpoint inhibitors, such as anti-PD-1 and anti-PD-L1 therapies, revolutionized the management of these patients [4]. Anti-PD-1 therapies, like pembrolizumab and nivolumab, have shown remarkable efficacy in patients with MSI/dMMR cancers, yielding consistently high response rates and significant improvements in overall survival (OS), even at the metastatic stage.

In randomized immunotherapy trials for advanced cancers, very few focus specifically on MSI/dMMR patients. However, subgroup analyses of these studies show the substantial contribution of immunotherapy in gastroesophageal and gynecological cancers. Current studies and associated indications do not differentiate the role of microsatellite instability as a response marker. It appears both useful and necessary to conduct a meta-analysis of published randomized trials to better understand the benefit of immunotherapy across all MSI tumors, whether associated with Lynch syndrome or sporadic MSI.

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Methodology

Search strategy and inclusion criteria

For this study, a systematic search was conducted in the Embase, Medline, and The Cochrane Library databases up to October 1, 2024. Search terms included *cancer MSI-H/dMMR* AND *(immunotherapy OR nivolumab OR pembrolizumab OR dostarlimab OR durvalumab OR atezolizumab OR avelumab OR ipilimumab)*. Abstracts and presentations from relevant conferences (ASCO, ESMO) from 2010 to 2024 were also explored to identify unpublished studies. Eligible studies were randomized clinical trials (RCTs), published in English, comparing immunotherapy-containing treatments to chemotherapy for advanced MSI-H/dMMR tumors. The trials needed to report data on OS or progression-free survival (PFS). Retrospective studies, Phase I, or single-arm Phase II trials were excluded.

Statistical analysis

Statistical analyses were performed using RevMan software (version 5.4). Hazard ratios (HRs) derived from Cox proportional hazard models were used to compare treatment effects on survival outcomes. Studies were pooled using fixed- or random-effects models based on the inverse variance method. Subgroup interactions were assessed using an interaction test, expressed as *p*-values for subgroup differences. Heterogeneity between studies was measured with Cochrane's Q statistics and I^2.

Study selection and data extraction

Studies identified in the search were independently evaluated by two investigators (TL and GDG). Differences were resolved by consensus between authors. Eligible studies were extracted, and their results summarized in comparative tables. References of selected studies were cross-checked to identify any missing studies.

Results

The search yielded 13 randomized trials involving 1633 MSI-H/dMMR patients. These studies included 745 colorectal cancer (CRC) patients, 195 gastric cancer (GC) patients, and 693 endometrial cancer (EC) patients. Four studies focused on CRC [5–8], four on GC [9–12], and five on EC [13–17]. Only three studies were dedicated specifically to MSI-H/dMMR patients [5–7]. The study characteristics are summarized in Table 1.

Survival outcomes comparing MSI-H to MSS patients

For MSI-H patients, immunotherapy demonstrated a 65% reduction in the risk of death ($HR = 0.35$; 95% CI 0.27–0.46) compared to a 19% reduction for MSS patients

Table 1 Characteristics of randomized clinical trials included in the meta-analysis

Study	Line	Experimental arm	Patients MSI-H (Experimental/Control)	Total	Control arm	Tumor	Phase
Keynote-177	1L*	Pembrolizumab	153/154	307	Folfox ± tc Folfiri ± tc	Colorectal	III
CheckMate 8HW	1L*	Nivolumab + ipilimumab	202/101	303	Folfox ± tc Folfiri ± tc	Colorectal	III
AtezoTRIBE	1L	Atezolizumab + CT	8/5	13	Folfoxiri + Bevacizumab	Colorectal	2R
SAMCO-PRODIGE 54	2L*	Avelumab	61/61	122	Folfox ± tc Folfiri ± tc	Colorectal	2R
Keynote-062	1L	Pembrolizumab ± CT	17/14//19	50	Cisplatin + 5FU	Gastric	III
Keynote-061	2L	Pembrolizumab	15/12	27	Paclitaxel	Gastric	III
Keynote-859	1L	Pembrolizumab + CT	39/35	74	FP or Capox	Gastric	III
CheckMate-649	1L	Nivolumab + CT	23/21	44	Folfox Xelox	Gastric	III
Ruby	1L	Dostarlimab + CT	53/65	118	Carbo paclitaxel	Endometrial	III
AtTend	1L	Atezolizumab + CT	81/44	125	Carbo paclitaxel	Endometrial	III
NRG-Gy018	1L	Pembrolizumab + CT	46/49	95	Carbo paclitaxel	Endometrial	III
Duo-E	1L	Durvalumab + CT	112/113	225	Carbo paclitaxel	Endometrial	III
Keynote-775	2L	Pembrolizumab + lenvatinib	65/65	130	Doxorubicin paclitaxel	Endometrial	III
			889/744	1633			

CT (Chemotherapy), tc (Targeted therapy), Carbo (Carboplatin), FP (Fluoro Pyrimidin), * (Clinical trials dedicated to MSI patients)

(*HR* = 0.81; 95% CI 0.74–0.88) (Fig. 1). The difference between the two groups was statistically significant ($p < 0.00001$). PFS outcomes showed a 68% reduction in progression risk for MSI-H patients (*HR* = 0.32; 95% CI 0.26–0.40) compared to 27% for MSS patients (*HR* = 0.73; 95% CI 0.64–0.83) (Supplementary data 1).

Survival results for MSI-H patients

Regarding progression-free survival (PFS), the benefit was 64%, with a hazard ratio (HR) of 0.36 (95% CI 0.28–0.46; $p < 0.0001$). By cancer type: colorectal cancer: HR = 0.28 (95% CI 0.11–0.73), gastric cancer: HR = 0.43 (95% CI 0.27–0.68), endometrial cancer: HR = 0.34 (95% CI 0.27–0.42) (Fig. 2).

Regarding overall survival (OS), the benefit was 54%, with an HR of 0.46 (95% CI 0.34–0.61; $p = 0.0008$). By cancer type: colorectal cancer: HR = 0.78 (95% CI 0.59–1.02), gastric cancer: HR = 0.35 (95% CI 0.23–0.51), endometrial cancer: HR = 0.37 (95% CI 0.26–0.53) (Supplementary data 2).

Discussion

To our knowledge, this is the first meta-analysis of randomized trials evaluating MSI status as a predictive biomarker of immunotherapy efficacy across cancer types with a high frequency of microsatellite instability. Our results demonstrate that MSI status is a key predictive biomarker for improved survival, with equivalent progression-free survival (PFS) benefits across these cancers, reflecting homogeneous efficacy regardless of the tumor's primary site.

Comparison of results between cancer types

The benefit in overall survival (OS) appears significant for gastric cancer (GC) and endometrial cancer (EC), with HRs of 0.35 and 0.37, respectively, while being more limited for colorectal cancer (CRC) (*HR* = 0.78). However, the OS results of the *CheckMate 8HW* study have not yet been published, even though the PFS results are extremely favorable for MSI-H patients (*HR* = 0.28).

The current question concerns whether to use monotherapy or a combination of immune checkpoint inhibitors. The Phase 3 *CheckMate 8HW* trial compared also nivolumab

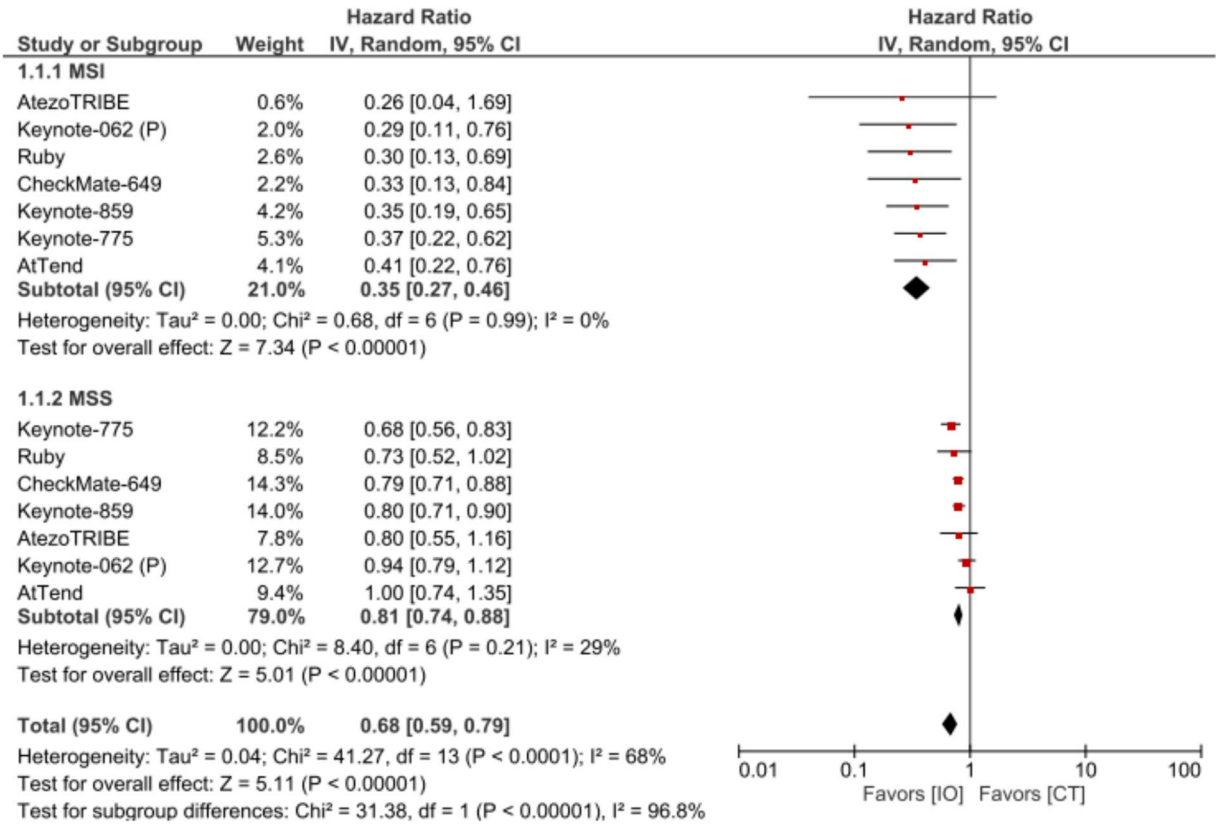

Fig. 1 Forest plot showing overall survival (OS) for anti-programmed cell death protein 1 (PD-1)-based treatment in MSI-high and MSS metastatic cancer patients

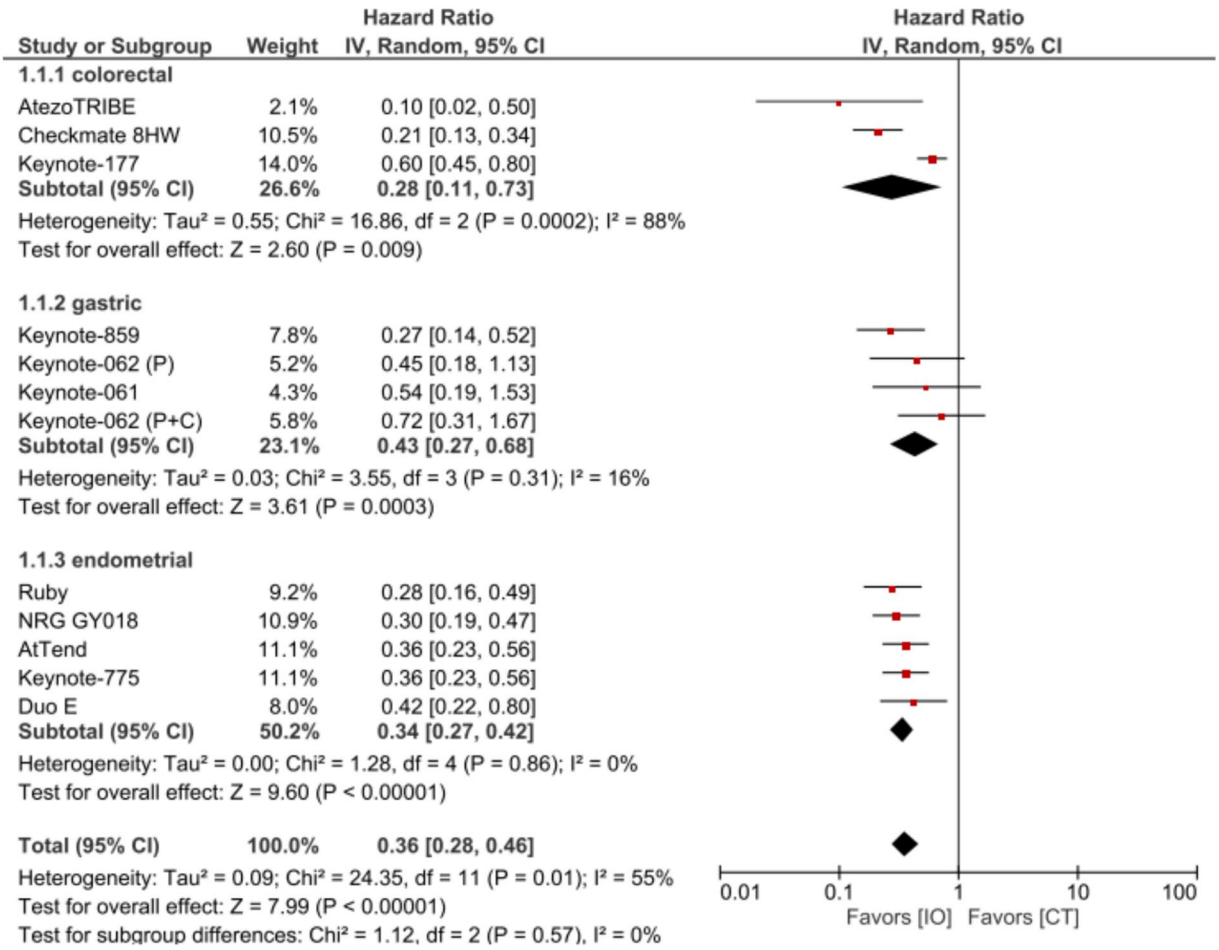

Fig. 2 Forest plot showing progression-free survival (PFS) for anti-programmed cell death protein 1 (PD-1)-based treatment in MSI-high metastatic cancer patients

plus ipilimumab to nivolumab alone in patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer. The results showed a significant improvement in progression-free survival with the combination (HR 0.62; $p = 0.0003$), suggesting that nivolumab plus ipilimumab could become a new standard of care for this patient population [18]. Furthermore, combining chemotherapy with immunotherapy, as is done in GC and EC, has proved highly effective. Only the *AtezoTRIBE* study addresses this option for CRC, but it includes only a small number of MSI-H patients. Further studies are needed to clarify this question.

Limitations and future perspectives

Although our analysis presents promising results, certain limitations must be highlighted. Firstly, the included studies exhibit heterogeneity regarding therapeutic combinations, which are often used as first-line treatments. Secondly, while the interaction between MSI status and immune checkpoint inhibitors (ICIs) is significant for OS and PFS in analyzed cancers, the number of MSI-H patients remains low in certain subgroups, particularly in gastric cancer, limiting the statistical power for PFS conclusions. However, the benefit remains clear. Moreover, data on objective response rates (ORR) were often incomplete, especially for MSI tumors, making direct comparisons of tumor responses across organ sites difficult. Finally, although MSI tests are reliable, false positives are still possible, especially if only one method is used. An integrated approach (PCR + IHC or NGS) can improve diagnostic accuracy.

Health authorities could consider the importance of MSI status for drug approval decisions. In 2023, the US Food and Drug Administration (FDA) granted accelerated approval for pembrolizumab in adult and pediatric patients with unresectable or metastatic MSI-H/dMMR solid tumors. This was the first tissue/site-agnostic FDA approval, encouraging treatment approaches based on tumor biology rather than organ of origin [19].

Future studies should include larger numbers of MSI-H patients in dedicated clinical trials, particularly for cancers with low MSI prevalence. Additionally, translational studies are necessary to explore mechanisms of primary resistance to ICIs in MSI-H tumors, especially in patients with low PD-L1 expression, which could influence immunotherapy responses. The relationship between MSI status, tumor mutational burden (TMB), and PD-1/PD-L1 expression is complex and varies according to tumor type. PD-1/PD-L1 expression varies according to tumor type, and does not systematically coincide with high MSI or TMB [20]. A thorough understanding of the relationship between these biomarkers is crucial to improving the use of immunotherapy in these patients.

Conclusion

This meta-analysis provides robust evidence supporting the efficacy of immune checkpoint inhibitors in MSI-H patients across colorectal, endometrial, and gastric cancers. These results reinforce the role of MSI status as a predictive biomarker for immunotherapy and highlight the need for tailored clinical strategies to optimize patient outcomes in this specific population.

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Author contributions T.L.and G.DG. wrote the manuscript and fully carried out this analysis. G.DG. supervised this work. All authors have given their consent for publication.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interests The authors declare that they have no competing interests.

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