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Original article

Systematic review and adjusted indirect comparison of first-line immune checkpoint inhibitors in metastatic colorectal cancer

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ABSTRACT

Objectives: To evaluate the efficacy and safety of immune checkpoint inhibitors in the first-line treatment of microsatellite instability or mismatch repair-deficient metastatic colorectal cancer through a systematic review and adjusted indirect comparison, determining whether they are equivalent therapeutic alternatives.
Methods: A systematic literature search was conducted in PubMed and Embase following PRISMA 2020 recommendations. Phase III randomized controlled trials evaluating immune checkpoint inhibitors in microsatellite instability or mismatch repair-deficient metastatic colorectal cancer were eligible. Efficacy was assessed using Bucher's adjusted indirect comparison method, with progression-free survival as the primary endpoint. Therapeutic equivalence was evaluated according to the Equivalent Therapeutic Alternatives framework, applying a non-inferiority margin (Δ) of 0.65. Safety outcomes included overall and treatment-related adverse events, immune-related adverse events, discontinuations due to adverse events and grade 5 events.
Results: NI demonstrated a higher probability of superior efficacy over pembrolizumab, with an adjusted Hazard Ratio of 0.53 (95%CI 0.34 to 0.84) for progression-free survival, exceeding the equivalence margin. Thus, pembrolizumab and nivolumab + ipilimumab cannot be considered Equivalent Therapeutic Alternatives regarding efficacy. In terms of safety, nivolumab + ipilimumab was associated with fewer treatment-related grade ≥ 3 adverse events but higher rates of treatment discontinuation and immune-related adverse events compared to pembrolizumab.
Discussion: Nivolumab + ipilimumab appears to offer greater efficacy than pembrolizumab in first-line treatment of microsatellite instability or mismatch repair-deficient metastatic colorectal cancer, but with a distinct safety profile. Based on current interim data, these agents should not be regarded as equivalent therapeutic alternatives. Further data, including final efficacy analyses and quality-of-life assessments, are warranted to guide optimal treatment selection.
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Revisión sistemática y comparación indirecta ajustada en primera línea de inmunoterapia en cáncer colorrectal metastásico

Palabras clave:
Tumores colorrectales
Metástasis tumorales
Inestabilidad de microsatélite
Déficit en la reparación de errores de emparejamiento
Inhibidores de punto de control inmunitario
Nivolumab
Ipilimumab
Pembrolizumab

RESUMEN

Objetivos: Evaluar la eficacia y seguridad de los inhibidores de punto de control en el tratamiento de primera línea del cáncer colorrectal metastásico con inestabilidad de microsatélites o deficiencia en la reparación de apareamientos mediante una revisión sistemática y comparación indirecta ajustada, determinando si son alternativas terapéuticas equivalentes.
Métodos: Se realizó una búsqueda bibliográfica sistemática en PubMed y Embase siguiendo las recomendaciones de PRISMA 2020. Se seleccionaron los ensayos controlados aleatorizados de fase III que evaluaban los inhibidores de puntos de control inmunitario. La eficacia se evaluó mediante el método de comparación indirecta ajustada de Bucher, con la supervivencia libre de progresión como criterio de valoración principal. La equivalencia terapéutica se evaluó según el marco de alternativas terapéuticas equivalentes, aplicando un margen de no inferioridad de 0,65. Los resultados de seguridad incluyeron eventos adversos generales y relacionados con el tratamiento, eventos adversos relacionados con el sistema inmunitario, interrupciones debido a eventos adversos y eventos de grado 5.

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Resultados: Nivolumab + ipilimumab demostró una mayor probabilidad de eficacia superior con respecto a pembrolizumab, con una razón de riesgo ajustada de 0,53 (IC del 95%: 0,34 a 0,84) para la supervivencia libre de progresión, superando el margen de equivalencia. Por lo tanto, pembrolizumab y nivolumab + ipilimumab no pueden considerarse equivalentes en cuanto a la eficacia. En términos de seguridad, nivolumab + ipilimumab se asoció con menos eventos adversos de grado ≥3 relacionados con el tratamiento, pero con tasas más altas de interrupción del tratamiento y eventos adversos relacionados con el sistema inmunitario en comparación con pembrolizumab.
Discusión: Nivolumab + ipilimumab parece ofrecer una mayor eficacia que pembrolizumab en el tratamiento de primera línea del cáncer colorrectal metastásico con inestabilidad de microsatélites o deficiencia en la reparación, pero con un perfil de seguridad distinto. Según los datos provisionales actuales, estos agentes no deben considerarse alternativas terapéuticas equivalentes. Se necesitan más datos, incluidos análisis finales de eficacia y evaluaciones de la calidad de vida, para orientar la selección del tratamiento óptimo.
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Introduction

Metastatic colorectal cancer (mCRC) with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) represents a distinct molecular subtype characterized by a high tumor mutational burden due to defects in DNA mismatch repair mechanisms. This phenotype accounts for approximately 5% of mCRC cases and is associated with a greater immunogenicity and better prognosis in early stages, but with resistance to conventional chemotherapy in the metastatic setting.[1,2]

MSI-H/dMMR tumors may arise from inherited germline mutations (e.g., Lynch síndrome), or from sporadic hypermethylation of the MLH1 promoter.[1,3] These tumors typically generate a high load of neoantigens that elicit a strong immune response. Nevertheless, immune escape mechanisms can emerge during tumor progression, leading to poor prognosis outcomes and resistance to fluoropyrimidine-based regimens.[1,4]

Immune checkpoint inhibitors (ICIs) targeting programmed death receptor-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) have transformed the treatment landscape for this subgroup. Pembrolizumab and the combination of nivolumab plus ipilimumab have each demonstrated clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS) versus chemotherapy in patients with MSI-H/dMMR mCRC. However, direct head-to-head randomized trials comparing their relative efficacy and safety are lacking.

In this context, systematic reviews combined with adjusted indirect treatment comparisons (ITCs) provide an evidence-based approach to assess the comparative efficacy and safety of interventions that have not been directly compared in randomized clinical trials. These analyses are particularly relevant in health systems where therapeutic equivalence informs clinical decision-making and resource allocation.

The objective aim of this study was to perform a systematic review and adjusted indirect treatment comparison of the efficacy of first-line therapy in MSI/dMMR mCRC, assessing their potential positioning as Equivalent Therapeutic Alternatives (ETA), based on established non-inferiority thresholds and safety outcomes.

Methods

Study design

A systematic review and adjusted indirect comparison were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[5] The objective was to identify randomized controlled trials (RCTs) evaluating the efficacy and safety of immune checkpoint inhibitors (ICIs) as first-line therapy in patients with MSI-H or dMMR mCRC.

Search strategy and inclusion criteria

A comprehensive search was conducted in PubMed and Embase from inception to April 3, 2025, including all studies published within the last ten years. The search combined free-text terms and MeSH descriptors as follows: ((“Clinical Trial, Phase III” [Publication Type]) AND (“Colorectal Neoplasms”[Mesh] AND ((“Microsatellite Instability”[Mesh]) OR “DNA Mismatch Repair[Mesh]). A detailed reference screening was performed to identify randomized controlled trials comparing chemotherapy with ICIs in a comparable population and with similar follow-up durations. Reference lists of relevant publications were also manually checked. Only articles in English were considered.

Eligibility criteria

Studies were included if they met all of the following:

- Phase III design.
- dult population with MSI-H/dMMR metastatic colorectal cancer in the first-line setting.
- Reporting progression-free survival, overall survival, or sufficient data for indirect comparison.
- Availability of outcomes permitting adjusted comparison.

Non-randomized studies, not clinical trials or not phase 3, not first-line treatments, other cancer types or other mutations, non-metastatic, not chemotherapy-controlled, health-quality, molecular or other analyses (i.e: post-hoc analyses, subgroup-only reports) were excluded.

Data extraction and quality assessment

Two reviewers independently screened records, assessed full texts, and extracted data using a predefined template, including study design, treatment arms, baseline characteristics, sample size, follow-up time, and efficacy and safety outcomes. Any discrepancies were resolved by consensus or, if necessary, by a third reviewer.

Outcome measurements

OS was selected as the primary endpoint. If it was not available, progression-free survival (PFS, the time from randomization to first disease progression) was selected as the primary endpoint for the efficacy comparison.

Safety assessment included overall grade events, grade ≥ 3 adverse events, treatment-related adverse events, immune-related adverse events (any grade), grade ≥ 3 immune-related events, treatment discontinuation due to toxicity, grade 5 events. For all safety endpoints,

absolute risk reduction (ARR) and 95% confidence intervals were calculated.

Statistical analysis

An ITC was performed using Bucher's method, applying the Indirect Treatment Comparisons calculator of the Canadian Agency for Health Technology Assessment.[6] Hazard ratios with their confidence intervals were extracted from each eligible trial, using chemotherapy as the common reference arm.

To determine therapeutic equivalence, the ETA framework was applied.[7] This methodology establishes criteria for assessing whether two or more drugs can be considered Equivalent Therapeutic Alternatives in terms of efficacy. According to this framework, robust evidence is required, including high-quality studies, use of clinically relevant outcomes and assessment of the potential for serious or irreversible harm. A threshold value (Delta, Δ) was defined, representing the maximum acceptable difference as a clinical criterion of non-inferiority. In this study, the Δ value was set at 0.65 based on European Society for Medical Oncology's Magnitude of Clinical Benefit Scale (ESMO-MCBS) guidelines[8] for the described scenario, with its reciprocal, 1.54, used as the upper margin.

Additionally, *Shakespeare* et al.'s[9] calculator was used to estimate the likelihood that the observed HR exceeded the equivalence threshold.

All analyses were descriptive due to the limited number of available trials.

Results

Literature search

A literature review was conducted to identify articles published up to April 3, 2025 as summarized in Fig. 1. A total of 146 studies were retrieved and screened. After title, abstract, and full-text assessment, two phase III trials met the eligibility criteria and were included: CheckMate 8HW[10] and KEYNOTE-177.[11]

Both trials enrolled a similar population of adult patients with previously untreated (first-line) metastatic colorectal cancer characterized by MSI-H or dMMR.

Regarding the interventions, KEYNOTE-177 evaluated pembrolizumab at a dose of 200 mg every three weeks. CheckMate-8HW assessed the combination of nivolumab 240 mg plus ipilimumab 1 mg/kg every three weeks for four doses (12 weeks), followed by nivolumab 480 mg monotherapy as maintenance. As for the comparator, both trials utilized the same investigator's choice chemotherapy regimens (mFOLFOX6 or FOLFIRI with or without bevacizumab or cetuximab).

For the ITC, interim efficacy analyses were selected for both trials to ensure methodological consistency. This choice was based on the availability of comparable median follow-up durations: 32.4 months for KEYNOTE-177 and 31.5 months for CheckMate-8HW, as well as the absence of final results for the nivolumab plus ipilimumab trial at the time of this review. PFS was defined as the primary endpoint for efficacy comparison in both studies, as OS was not yet mature at CheckMate8HW.

Efficacy

Both pembrolizumab and nivolumab plus ipilimumab demonstrated statistically significant superiority over chemotherapy in terms of PFS. In KEYNOTE-177, the median PFS difference was 16.5 months, with a Hazard Ratio (HR) of 0.60 (95%CI 0.45 to 0.80). In CheckMate 8HW, the median PFS was not reached with an HR of 0.32 (95%CI 0.23 to 0.46).

The adjusted indirect comparison yielded an HR of 0.53 (95%CI 0.34 to 0.84) in favor of nivolumab plus ipilimumab. Using the predefined equivalence margin, the probability of a clinically relevant difference exceeding the equivalence margin was 81.18%, indicating a likely advantage for nivolumab plus ipilimumab. These results are illustrated in Fig. 2.

Based on the ETA criteria and the findings of this ITC, pembrolizumab and nivolumab plus ipilimumab cannot be considered ETA in terms of efficacy.

Safety

Safety outcomes were compared using ARR to evaluate differences in toxicity between treatments. The ARR for grade ≥ 3 treatment-related adverse events favored nivolumab plus ipilimumab, with a difference of 19.44% (95%CI 3.76 to 35.12). Conversely, treatment discontinuation due to adverse events (AEs) favored pembrolizumab, with a difference of −17.66% (95%CI -31.01 to −4.3).

Regarding irAEs, a marked difference was observed in favor of pembrolizumab over nivolumab plus ipilimumab. For irAEs of any grade, the ARR was −77.25% (95%CI, −89.3 to −65.1) and for grade ≥ 3 irAEs, −24.41% (95%CI -32.17% to −16.6). No significant differences were found in the remaining safety outcomes measured. All results are summarized in Table 1.

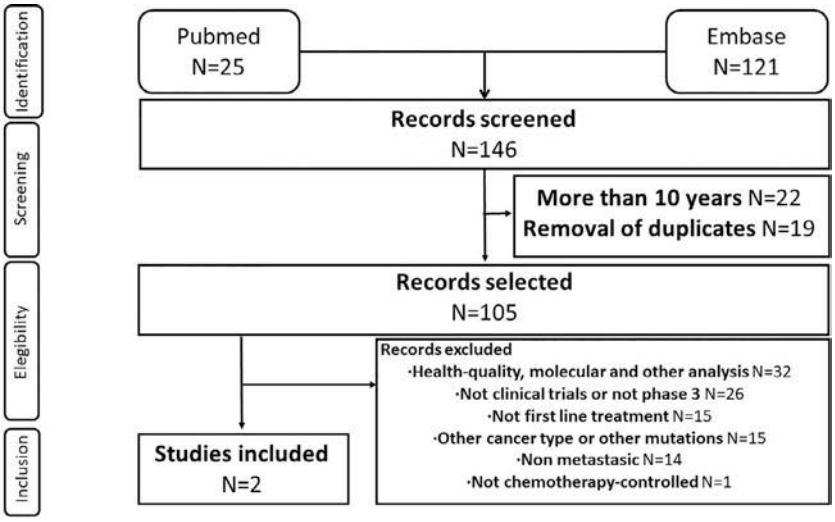

Fig. 1. Flow diagram of studies included and screened for the adjusted indirect comparison.

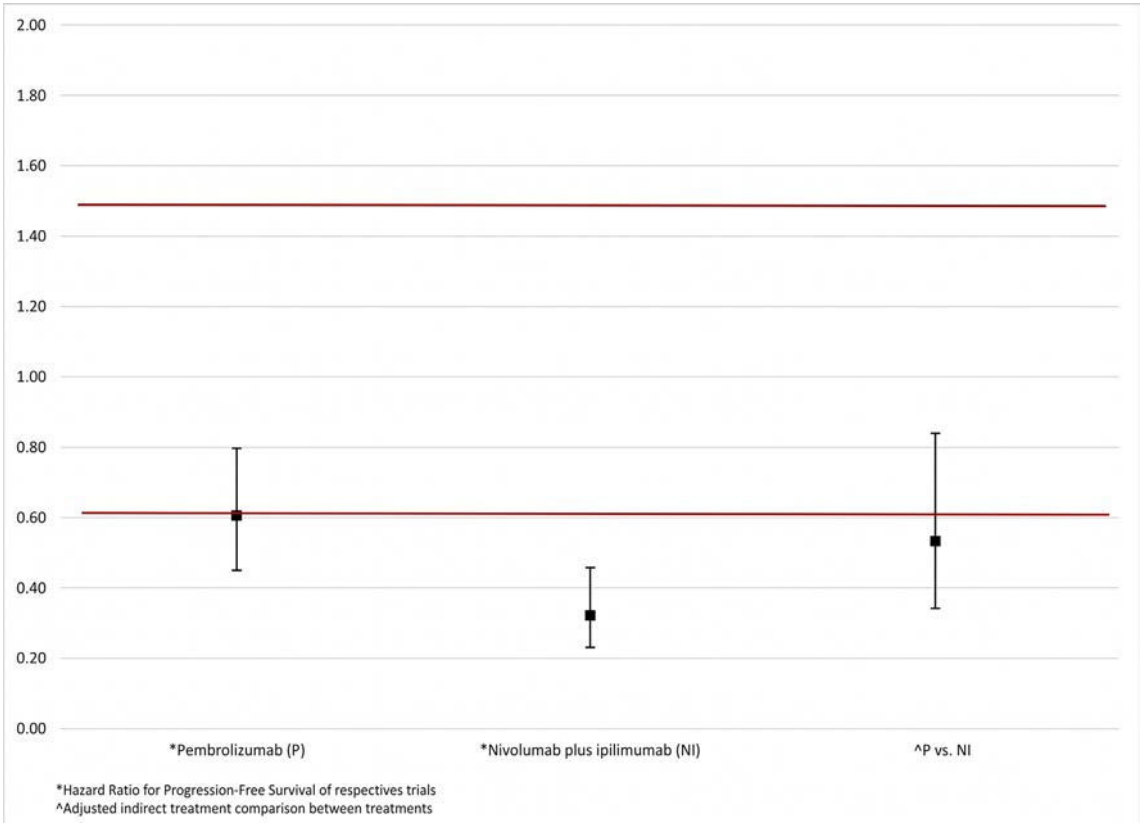

Fig. 2. Comparison of Hazard Ratios for Progression-Free Survival: pembrolizumb, nivolumab plus ipilimumab and adjusted indirect comparison between trials.

Discussion

In this systematic review and adjusted indirect comparison, nivolumab plus ipilimumab appeared to provide greater progression-free survival than pembrolizumab in the first-line treatment of metastatic colorectal cancers with MSI-H/dMMR. This difference may be related to the addition of CTLA-4 inhibition, introducing a complementary mechanism of action that could enhance antitumour activity. It has been hypothesized that this mechanism could help overcome resistance associated with RAS mutations, which was suggested in a subgroup analysis of the pembrolizumab trial but not observed in the nivolumab plus ipilimumab trial. Nevertheless, establishing consistency and biological plausibility requires comparable subgroup data, which were not available. Differences in the format and presentation of subgroup outcomes across trials prevented any valid cross-trial subgroup assessment or positioning.

With regard to safety, pembrolizumab showed a higher incidence of grade ≥ 3 treatment-related AEs, whereas treatment discontinuation due to toxicity was more frequent with nivolumab plus ipilimumab. Interpretation of these findings requires caution because the two trials used different versions of the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 in the pembrolizumab trial and version 5.0 in the nivolumab plus ipilimumab trial. Furthermore, both trials were open-label, which may introduce subjectivity in attributing AEs and contribute to differences in safety reporting. An adjustment was necessary for grade 5 AEs, as the nivolumab plus ipilimumab trial initially included deaths due to disease progression, which are not classified as grade 5 in CTCAE v5.0; these were excluded from this category in the CheckMate8HW.

Real-world evidence comparing these regimens in other tumor types has shown higher rates of grade ≥ 3 or 4 irAEs and grade 5 AEs with nivolumab plus ipilimumab.[12] Our findings are consistent with this pattern for irAEs, although a discrepancy was observed in the occurrence of grade 5 AEs. It should be noted that safety data alone are insufficient for determining overall tolerability, particularly in the absence of quality-of-life assessments, which may help mitigate subjectivity in AE attribution.

Another aspect to consider is prior treatment exposure. Although the nivolumab plus ipilimumab trial included a small proportion of

Table 1
Absolute risk reduction for safety outcomes comparing pembrolizumab versus nivolumab plus ipilimumab using the common chemotherapy arm as reference. Negative values indicate a lower incidence with pembrolizumab.

Safety endpoints	ARR_{CT-P}	ARR_{CT-NI}	ITC_{P-NI}
AEs	1.92% (95%CI, −1.00 to 4.77)	−1.27% (95%CI, −4.68 to 2.13)	3.64% (95%CI, −0.82 to 8.1)
Grade ≥ 3 AEs	21.41% (95%CI, 11.00 to 31.83)	19.05% (95%CI, 7.03 to 31.06)	2.36% (95%CI, −13.54 to 18.26)
Grade ≥ 3 treatment-related AEs	44.17% (95%CI, 34.02 to 54.31)	24.73% (95%CI, 12.77 to 36.68)	19.44% (95%CI, 3.76 to 35.12)
Any grade irAEs	−18.3% (95%CI, −27.2 to −9.02)	−58.95% (95%CI, −66.9 to −51.00%)	−77.25% (95%CI, −89.3 to −65.1)
Grade ≥ 3 irAEs	−7.05% (95%CI, −12.19 to −1.92)	−17.36% (95%CI, −23.18 to −11.54)	−24.41% (95%CI, −32.17 to −16.6)
Treatment discontinuation due to AEs	−1.84% (95%CI, −9.44 to 5.77)	15.82% (95%CI, 4.84 to 26.80)	−17.66% (95%CI, −31.01 to −4.3)
Grade 5 AEs	0.97% (95%CI, −3.71 to 5.66)	−2.00% (95%CI, −3.94 to −0.06)	2.97% (95%CI, −2.1 to 8.04)

ARR: absolute risk reduction; AEs: adverse events; CI: confidence Interval; CT: chemotherapy; irAE: inmune-related adverse event; ITC: indirect treatment comparison; NI: nivolumab + ipilimumab; P: pembrolizumab.

patients with previous therapy (1% treated for metastatic disease, 3% with neoadjuvant therapy and 30% with adjuvant therapy), the very low rate of second-line metastatic treatment (1% of participants) supports its interpretation as a true first-line population.

Given the absence of a direct comparative trial, adjusted ITC may support clinical decision-making algorithms, especially in public healthcare systems where therapeutic equivalence influences reimbursement and drug positioning. These results may also inform future pharmacoeconomics evaluations, as differences in efficacy and safety could impact resource utilization and patient quality of life.

Although pembrolizumab and nivolumab plus ipilimumab are the most widely used ICIs in this setting, additional studies are evaluating other immunomodulatory drugs combined with chemotherapy. This evidence should also be considered when establishing therapeutic positioning.

Finally, this comparison was based on interim data: mature results from ongoing trials are required to confirm both efficacy positioning and safety profile. Taken together, these considerations frame the context in which the comparative value of both regimens must be interpreted and lead to the overall conclusions of this review.

In conclusion, nivolumab plus ipilimumab and pembrolizumab cannot be considered equivalent therapeutic alternatives in terms of efficacy in the first-line treatment of MSI/dMMR mCRC. The available evidence suggests that nivolumab plus ipilimumab may offer greater efficacy; however, comparative data on safety and quality of life are still needed to establish their definitive therapeutic positioning.

Contribution to scientific literature

This study suggests that nivolumab plus ipilimumab might offer greater efficacy than pembrolizumab.

Artificial intelligence disclosure

The authors declare that no generative artificial intelligence or artificial intelligence-assisted technologies were used in the preparation of this manuscript or during the conduct of the research.

Congress abstract

A preliminary article of this study was presented by the same author at the 70th SEFH congress (October 2025).

CRediT authorship contribution statement

Y. Reyes-de-la-Mata: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **S. Fénix-Caballero:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **F.J. Salmerón-Navas:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization.

Ethical considerations

This study was conducted in accordance with international ethical principles for the reporting and publication of biomedical research information.

No informed consent needed (no patients involved).

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None.

Conflict of interest

None.

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