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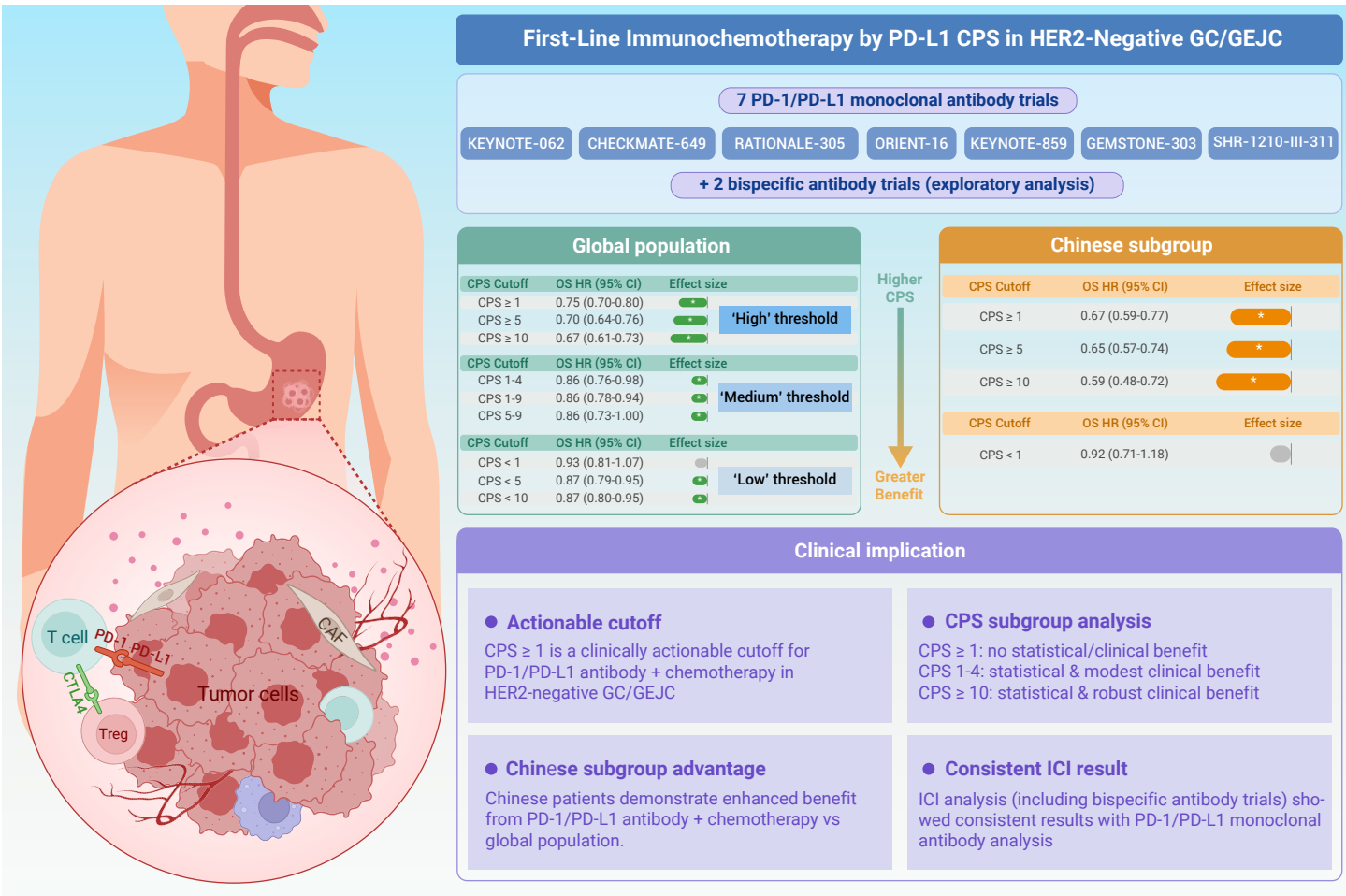
Received: June 11, 2026; Accepted: July 15, 2026; Published Online: July 24, 2026; https://doi.org/10.59717/j.xinn-oncol.2026.100030

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- This meta-analysis compared immunochemotherapy versus chemotherapy in HER2-negative gastric cancer.
- 7 monoclonal antibody trials were primary analysis, with two bispecific antibody trials as exploratory.
- Patients with PD-L1 CPS ≥1 showed significant survival benefit, while CPS <1 patients did not benefit.
- Chinese patients achieved greater benefits in OS/PFS than the global population.
- CPS ≥1 may serve as a practical cutoff for selecting first-line PD-1/PD-L1 antibody plus chemotherapy.

REVIEW Precision Medicine

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Efficacy of first-line immunochemotherapy by PD-L1 in HER2-negative gastric or gastroesophageal junction cancer: A meta-analysis

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Received: June 11, 2026; Accepted: July 15, 2026; Published Online: July 24, 2026; https://doi.org/10.59717/j.xinn-oncol.2026.100030

Citation: Xie T., Zhang X., Peng Z., et al. (2026). Efficacy of first-line immunochemotherapy by PD-L1 in HER2-negative gastric or gastroesophageal junction cancer: A meta-analysis. *The Innovation Oncology* **1**:100030.

Identifying optimal PD-L1 expression cutoff thresholds to guide programmed cell death protein-1/programmed death ligand-1 (PD-1/PD-L1) antibody combined with chemotherapy for patients with advanced HER2-negative gastric or gastroesophageal junction adenocarcinoma (GC/GEJC) remains a major challenge in clinical decision-making. This meta-analysis included nine randomized controlled trials of immunochemotherapy versus chemotherapy in patients with HER2-negative GC/GEJC; eight trials included Chinese patients. Among the global population, PD-1/PD-L1 antibodies plus chemotherapy significantly reduced mortality risk versus chemotherapy, with a positive association between CPS and overall survival (OS) benefit (CPS ≥1: HR_{OS} 0.75, 95% CI 0.70–0.80; CPS ≥5: HR_{OS} 0.70, 95% CI 0.64–0.76 and CPS ≥10: HR_{OS} 0.67, 95% CI 0.61–0.73; all p<0.0001 vs. chemotherapy), and an OS benefit for intermediate CPS cutoffs (1–4, 1–9, 5–9, <5 and <10). A similar trend was observed for progression-free survival (PFS). The OS and PFS benefits in Chinese patients were numerically greater versus the global population. Patients with CPS <1 did not benefit from immunochemotherapy. In conclusion, CPS ≥1 may be a clinically actionable cutoff for selecting PD-1/PD-L1 monoclonal antibody combined with chemotherapy in patients with HER2-negative GC/GEJC and Chinese patients derived a modestly greater OS and PFS benefit from that versus the global population. Analyses including studies of bispecific antibodies showed consistent results with those only including PD-1/PD-L1 antibodies.

INTRODUCTION

Gastric cancer has a high incidence and associated mortality rate.[1] The most common subtype of gastric cancer is gastric or gastroesophageal junction adenocarcinoma (GC/GEJC), which accounts for over 90% of all gastric cancers.[2] Patients with advanced or metastatic gastric adenocarcinoma have a poor prognosis, with a 5-year overall survival (OS) rate <35%.[3] Prior to the introduction of immunotherapy, patients with HER2-negative disease had a particularly poor prognosis due to a lack of treatment options beyond traditional chemotherapy. However, in recent years, the combination of immunotherapy with chemotherapy has improved the first-line treatment landscape for selected patients with HER2-negative GC/GEJC.[4]

Multiple phase 3 trials have evaluated first-line immunochemotherapy in patients with HER2-negative GC/GEJC, utilizing monoclonal antibodies against immune checkpoint molecules such as programmed cell death protein-1/programmed death ligand-1 (PD-1/PD-L1) as well as bispecific antibodies.[5-10] Collectively, the results of these trials show that immunochemotherapy improves overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) compared with chemotherapy alone, especially in patients with high PD-L1 expression.[11-14] Current treatment guidelines show some heterogeneity in PD-L1 threshold recommendations. The NCCN guidelines recommend PD-1 antibody combinations for a combined positive score [CPS] ≥1,while CSCO guidelines recommend PD-1 antibodies for all comer use, but they all endorse CPS ≥5 as a first-tier cutoff.[15] Furthermore, based on pooled data from the CheckMate-649, KEYNOTE-859, and RATIONALE-305 studies, in 2024 the US FDA Oncologic Drugs Advisory Committee (ODAC) advised restricting nivolumab/pembrolizumab/tislelizumab to patients with CPS ≥1.[16] However, as further data from phase 3 studies of immune checkpoint inhibitors (ICIs) become available, including studies of bispecific antibodies, the utility of immunochemotherapy in patients with low/intermediate PD-L1 expression (especially CPS 1–4) remains controversial due to equivocal results.[12] Therefore, a central clinical question remains: what is the optimal PD-L1 expression threshold for selecting first-line immunotherapy in patients with HER2-negative GC/GEJC, especially for monoclonal antibodies?

Identifying an optimal PD-L1 cutoff is complicated by heterogeneity of PD-L1 assessment methods (differences in antibodies/platforms) and CPS cutoff selection across clinical trials of immunochemotherapy in HER2-negative GC/GEJC.[5-10] Furthermore, the reporting of CPS subgroup data is heterogeneous and often incomplete, precluding direct data pooling and threshold comparison. Phase 3 trials also differ substantially in geographic and ethnic composition, with almost half of trials being China-dominant or entirely China-based. Chinese patients show key differences from non-Chinese populations including genetic background, comorbidity profiles, tumor molecular features, lifestyle, and prior treatment patterns, all of which can affect the efficacy and toxicity of immunotherapy.[17] Therefore, analyzing the Chinese population separately may help further confirm regional and ethnicity-related differences in efficacy.

Previous meta-analyses have compared first-line immunochemotherapy regimens for patients with advanced HER2-negative GC/GEJC and evaluated the predictive ability of CPS.[11-14] However, these previous analyses predominantly relied on published aggregate data. This represents an important limitation, as the heterogeneous availability of subgroup and survival data preclude a comprehensive evaluation of a full range of CPS cutoffs and potential regional differences in efficacy. Therefore, we conducted a meta-analysis using the latest primary and follow-up data from phase 3 trials and used the KMSubtraction method,[18] to reconstruct data for unpublished subgroups. The present study aimed to answer the following key clinical questions. Is PD-L1 CPS a reliable predictive biomarker for outcomes to first-line immunochemotherapy, particularly PD-1/PD-L1 monoclonal antibodies, versus chemotherapy alone? Is there a "threshold-response" relationship with increasing CPS? Can patients with low PD-L1 expression benefit from PD-1/PD-L1 antibody? Are there differences in efficacy between Chinese and global populations when stratified by PD-L1 expression?

MATERIALS AND METHODS

This meta-analysis was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD420261394364) and performed and reported following the Preferred Reporting Items for Systematic Reviews (PRISMA) and meta-analysis extension statements.[19]

Data sources and search strategy

We systematically searched PubMed, Embase, Web of Science and the Cochrane Library, as well as congress abstracts from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), ASCO-GI, ESMO-GI and Chinese Society of Clinical Oncology (CSCO) annual meetings, for relevant studies published up to May 19, 2026. Key words used for the literature search included "gastric cancer" OR "gastro-esophageal" AND "HER2-negative" AND immunotherapy AND "first-line" AND "clinical trial" (Table S1). Reference lists of included studies were manually screened to identify potentially relevant trials. Only randomized phase 3 trials with sufficient

published data for risk of bias assessment were included. Unpublished trials without peer-reviewed data or adequate methodological reporting were excluded.

Study selection

Published randomized phase 3 trials were included if they met the following criteria: included patients with a confirmed diagnosis of HER2-negative advanced GC/GEJC; investigated the efficacy of first-line treatment with regimens combining an immune checkpoint inhibitor and chemotherapy; reported PD-L1 expression; compared two or more treatment arms and reported at least OS (defined as the time from randomization to death from any cause) or progression-free survival (PFS; defined as the time from randomization to disease progression or death from any cause) or duration of response (DoR, defined as the time from randomization to disease progression). Trials were excluded if they included patients with HER2-positive GC/GEJC or in which immunotherapy was utilised as a (neo)adjuvant therapy or used sequentially with chemotherapy. The literature search results were screened by two authors.

Data extraction and risk of bias

Data were extracted by two authors using a standard Excel template (Supplemental Materials). The extracted data included: author details, date of publication, trial name or ClinicalTrials.gov registration number, treatment regimens evaluated, PD-L1 expression scoring data, the PD-L1 assay used, number of patients in the intention-to-treat population, number of patients in PD-L1 subgroups, OS and PFS data (hazard ratio [HR] and 95% confidence intervals [CI], for the ITT and CPS subgroups, as available), and the information of objective response rate (ORR). Data were extracted for the entire study population and for Chinese patient subgroups, where reported, to generate global and Chinese patient data sets. Data were also stratified by PD-L1 CPS subgroups, with outcome data across different PD-L1 CPS expression subgroups extracted as comprehensively as possible to evaluate the intervention effects in populations with distinct PD-L1 expression levels. Risk of bias was assessed using the Cochrane Risk of Bias tool.[20] The most recently published or updated follow-up data from each clinical study was preferentially included.

Data synthesis and statistical analysis

Studies were assigned to each synthesis according to pre-specified intervention and subgroup criteria. We tabulated the treatment regimen, control arm, PD-L1 CPS expression, and population characteristics for each eligible trial, and then matched these characteristics against the planned synthesis groups. Trials were included in a given synthesis only if they evaluated the relevant intervention/comparator and reported sufficient outcome data for the corresponding overall or subgroup analysis. When subgroup results were not directly reported, we reconstructed the necessary subgroup data using KMSubtraction and included them in the relevant synthesis. Studies that did not meet the predefined criteria for a specific synthesis were excluded from that synthesis.

All analyses were performed in R version 4.2.2 using the survival, ggplot2, KMSubtraction, and IPDfromKM tools. In the event that summary data (HR and 95% CI for OS and PFS) were not reported for predefined PD-L1 subgroups, individual time-to-event data were estimated from Kaplan–Meier plots using validated graphical reconstruction algorithms according to Guyot et al.[21] and the IPDfromKM method.[22] Subsequently, the validated KMSubtraction tool[18,21] (based on bipartite matching and the Hungarian algorithm[23]) was applied to extract and reconstruct individual patient data (IPD) for unreported subgroups from the reported 'overall' population and 'subgroup' curves. All reconstructed data were verified by comparing survival probabilities at landmark time points and median survival values to ensure consistency and reliability before inclusion in the meta-analysis.

A meta-analysis was conducted to synthesize data from studies meeting the inclusion criteria, in overall (global) and Chinese patient populations, focusing on three key efficacy endpoints: OS, PFS, and ORR. Each endpoint was also synthesized across multiple CPS subgroups (CPS ≥1, CPS ≥5, CPS ≥ 10, CPS <1, CPS <5, CPS <10, CPS 1-4, CPS 1-9 and CPS 5-9). The PD-1/PD-L1 monoclonal antibody analysis as the primary analysis, with the ICI analysis (including bispecific antibodies) presented as exploratory analysis only. To account for potential inter-study heterogeneity, both common effects (fixed effect) and random effects models were considered. The choice between models was made based on a heterogeneity assessment using the Cochran's Q-test and I^2 statistic. A Q-test P-value <0.10 or I^2 >50% indicated substantial heterogeneity, warranting a random effects model, otherwise a fixed effects model was used. Sensitivity analyses were conducted to evaluate the robustness of findings by excluding individual studies in a stepwise manner.

Given that median OS and time-specific OS rates were not consistently reported across trials and are not suitable for direct meta-analytic pooling, HRs with corresponding 95%CIs were calculated for time-to-event endpoints (OS and PFS). For binary efficacy outcomes (ORR), pooled risk differences with 95% CIs were adopted. Descriptive data on median survival time in each individual trial is presented in Supplemental Materials.

RESULTS

Included studies and characteristics

In total, 587 unique literature search results were retrieved (Figure 1). After screening, nine randomized controlled trials including 7660 patients (immunochemotherapy: n=3752; chemotherapy only: n=3908) were selected for inclusion in the analysis (Table 1). These studies reported data for pembrolizumab, nivolumab, sintilimab, tislelizumab, sugemalimab, cadonilimab, camrelizumab and retlirafusp-α (a bispecific antibody against PD-L1 and TGF-β)[24] forming the 'immune checkpoint inhibitor (ICI)' analysis group. A subgroup of seven trials of PD-1/PD-L1 antibodies were included in the 'PD-1/PD-L1 antibodies' analysis group (KEYNOTE-062, KEYNOTE-859, CheckMate-649, ORIENT-16, RATIONALE-305, GEMSTONE-303, SHR-1210-III-311; PD-1/PD-L1 antibody + chemotherapy: n=3082; chemotherapy only: n=3237).

Eight of the included trials (KEYNOTE-859 China, CheckMate-649 China, ORIENT-16, RATIONALE-305 China, GEMSTONE-303, SHR-1210-III-311, COMPASSION-15, SHR-1701-III-307) included 3956 Chinese patients (immunochemotherapy: n=1899; chemotherapy only: n=2057) and were included in the Chinese subgroup analysis, including seven trials of PD-1/PD-L1 antibodies (n=1229; chemotherapy only: n=1386).

Due to the lack of PD-L1 CPS subgroup data in the ATTRACTION-4[25] and KEYNOTE-590[26] study publications, which resulted in selection bias, these two studies were not included.

A summary of the available data in each study included in this meta-analysis is provided in Tables S2 and S3. Of the CPS subgroup analyses, Checkmate-649 global study (OS data for CPS 1-4, 1-9 and 5-9; PFS data for CPS＜10, 1-4, 1-9 and 5-9), Checkmate-649 Chinese subgroup (OS and PFS data for CPS 1-4), KEYNOTE-859 Chinese subgroup (OS and PFS data for CPS＜1, ＜10 and 1-9), SHR-1210-III-311study (OS and PFS data for CPS＜1), and SHR-1701-III-307 study (OS and PFS data for CPS＜1 and 5), were reconstructed using KMSubtraction, and full detail is shown in Table S4. A summary of the risk of bias for each study is shown in Table S5. Tabulated synthesized data can be found in Appendix 1.

Global population analysis

Overall survival – global population. A detailed summary of OS data from each included study is provided (Figures S1-S2). Among all patients in the global population, combined treatment with PD-1/PD-L1 antibodies plus chemotherapy was associated with a significant reduction in the risk of mortality versus chemotherapy alone (HR_{OS} 0.77, 95% CI 0.73–0.82; p<0.0001) and this result was consistent among patients with CPS ≥1, ≥5 and ≥10 (Figure 2A). Furthermore, a positive association between CPS and OS benefit was observed (CPS ≥1; HR_{OS} 0.75, 95% CI 0.70–0.80, CPS ≥5; HR_{OS} 0.70, 95% CI 0.64–0.76 and CPS ≥10; HR_{OS} 0.67, 95% CI 0.61–0.73; p<0.0001 for all comparisons against chemotherapy alone). Using intermediate CPS cutoffs, 1–4, 1–9, 5–9, <5 and <10, a statistically significant survival benefit versus chemotherapy alone was also observed among all subgroups (HR_{OS} from 0.86–0.87; all p<0.05). Notably, patients with positive but low PD-L1 expression (CPS 1–4) also achieved a significant survival benefit (HR_{OS} 0.86, 95% CI 0.76–0.98; p=0.0188; Figure 2A). These findings suggest that the OS benefit of adding PD-1/PD-L1 antibodies to chemotherapy extends to

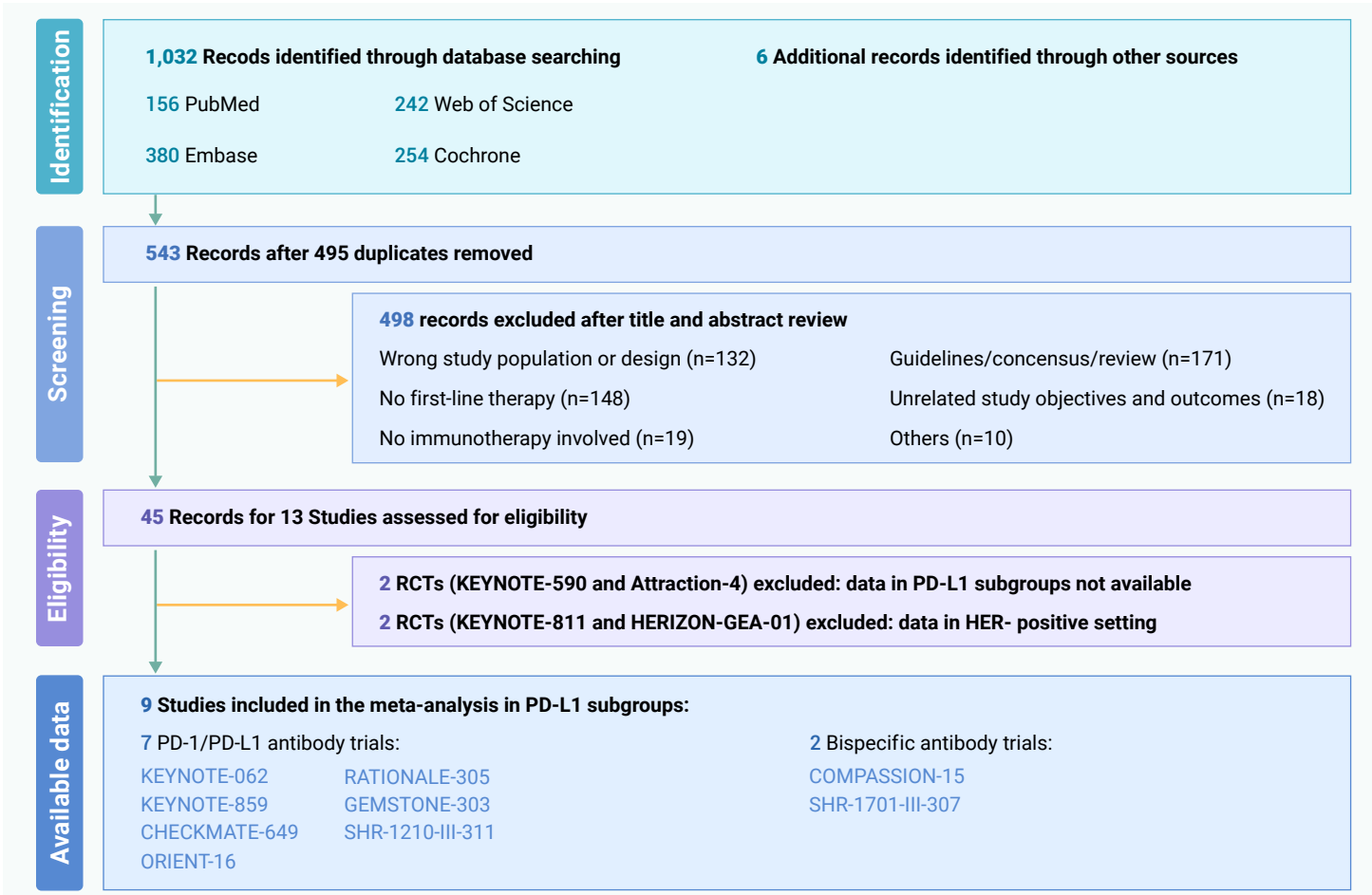

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart diagram PD-L1, programmed death ligand-1; RCT, randomized controlled trial.

patients with low-to-intermediate PD-L1 expression. No significant OS benefit was observed in patients with CPS <1 (HR 0.93, 95% CI 0.81–1.07; p=0.3120).

Consistent with the trend for improved efficacy observed in the PD-1/PD-L1 antibodies group analysis, significant OS improvements versus chemotherapy alone were also observed across all CPS strata except CPS <1 when including trials of PD-1/PD-L1 antibodies and bispecific antibodies (ICI analysis group, Figure S3). Furthermore, compared to the PD-1/PD-L1 antibodies analysis group, the HRs for OS were numerically lower for pooled data.

Progression-free survival – global population. A detailed summary of PFS data from each included study is provided (Figures S4-S5). Among all patients in the global population, treatment with PD-1/PD-L1 antibodies plus chemotherapy was associated with a significant reduction in the risk of disease progression versus chemotherapy alone (HR_{PFS} 0.76, 95% CI 0.71–0.81; p<0.0001). This result was consistent among patients with CPS ≥ 1, ≥5 and ≥10 and an association between higher CPS and greater PFS benefit was observed (Figure 2B). For the intermediate CPS cutoffs (1–4, 1–9, 5–9, <5 and <10) a statistically significant survival benefit versus chemotherapy alone was also observed among all subgroups. The analysis in the ICI group showed a comparable result, with a numerically lower HR_{PFS} in the total population and some of the CPS subgroups (Figure S6).

Objective response rate – global population. In the global patient population, PD-1/PD-L1 antibodies plus chemotherapy resulted in a higher chance of achieving an objective response (a complete or partial response) compared with chemotherapy (risk difference, 0.10; 95% CI 0.07, 0.12). ORR was correlated with PD-L1 expression level, and increased with higher CPS score (≥1, ≥5, and ≥10) (Figures S7 & S8A). A comparable result was observed in the ICIs group (Figures S8B & S9).

Chinese subgroup analysis

Overall survival – Chinese population. Compared with the global population, the meta-analysis of data from Chinese patients (n=2136) showed a numerically higher, significant reduction in mortality risk with PD-1/PD-L1 antibodies plus chemotherapy versus chemotherapy alone (HR_{OS} 0.72, 95% CI 0.66–0.80; p<0.0001) (Figures S10-S11). The lower HR_{OS} in Chinese patients versus the global cohort was consistent across the CPS cutoffs, with a positive association between increasing PD-L1 CPS and numerically improved HR_{OS}: CPS ≥1 (HR_{OS} 0.67 vs. 0.75 for Chinese vs. global), CPS ≥5 (HR_{OS} 0.65 vs. 0.70 for Chinese vs. global), and CPS ≥10 (HR_{OS} 0.59 vs. 0.67 for Chinese vs. global), indicating a greater survival advantage with PD-1/PD-L1 antibodies in Chinese patients with increasing CPS (Figure 3A-B). For CPS <1, <5 and <10, the magnitude of OS benefit in HR value in the Chinese population was comparable to or slightly improved relative to the global analysis, although some subgroups lacked sufficient data to draw definitive conclusions. Meta-analysis of intermediate CPS cutoffs (CPS 1-4, 1-9, and 5-9) was precluded as only a single study reported data for these subgroups. Therefore, these subgroups were not included in the pooled Chinese subgroup analysis. Consistent with the global analysis, no significant OS benefit was observed in patients with CPS <1 (HR_{OS}, 0.92; 95% CI 0.71–1.18; p=0.5001).

When studies of bispecific antibodies were also included in the meta-analysis, a similar trend for enhanced OS benefit versus chemotherapy alone in the Chinese versus global population was also observed (Figures 3 C-D; Figures S10 & S12). Consistent with the analysis of PD-1/PD-L1 inhibitors, the lower HR_{OS} in Chinese patients versus the global cohort was consistent across CPS ≥1, ≥5 and ≥10 subgroups, with a positive association between increasing PD-L1 CPS and improved HR_{OS}. In addition, patients with positive but low PD-L1 expression (CPS 1–4) achieved a significant survival benefit (HR_{OS} 0.71, 95% CI 0.56–0.90; p=0.0043; Figure S11). No significant OS benefit was observed in patients with CPS <1.

Progression-free survival – Chinese population. Chinese patients showed a numerically higher PFS benefit with PD-1/PD-L1 antibodies plus

Table 1. Summary of included studies and data sources.

Author/first reported year	Trial name	Region	Enrolled patients	Number of patients (IO+CT versus CT)	PD-L1 scoring method	PD-L1 assay	IO class	IO agent	CT backbone
Shitara/2019	KEYNOTE-062[43-45]	Global	CPS ≥1	257 versus 250	CPS	22C3	PD-1 antibody	Pembrolizumab	Cisplatin + 5-FU or capecitabine
Moehler/2020	CHECKMATE-649[5,31,46]	Global	All comer	789 versus 792	CPS	28.8	PD-1 antibody	Nivolumab	Oxaliplatin + FU or capecitabine
Xu/2021	ORIENT-16[6,47]	China	All comer	327 versus 323	CPS	22C3	PD-1 antibody	Sintilimab	Oxaliplatin + capecitabine
Rha/2023	KEYNOTE-859[9,48,49]	Global	All comer	790 versus 789	CPS	22C3	PD-1 antibody	Pembrolizumab	Oxaliplatin + capecitabine or cisplatin+5-Fu
Moehler/2023+ Rha/2023	RATIONALE-305[12,32,50,51]	Global	All comer	501 versus 496	CPS/TAP	SP263	PD-1 antibody	Tislelizumab	Oxaliplatin + capecitabine or Cisplatin+5-Fu
Zhang/2023	GEMSTONE-303[52]	China	CPS ≥5	241 versus 238	CPS	SP263	PD-L1 antibody	Sugemalimab	Oxaliplatin + capecitabine
Ji/2024	COMPASSION-15[27,28]	China	All comer	305 versus 305	CPS	22C3	PD-1/CTLA-4 bispecific antibody	Cadonilimab	Oxaliplatin + capecitabine
Peng/2024	SHR-1701-III-307[29,30]	China	All comer	365 versus 366	CPS	E1L3N	PD-L1/TGF-β bispecific antibody	Retlirafusp-α	Oxaliplatin + capecitabine
Peng/2026	SHR-1210-III-311[53]	China	All comer	177 versus 349	CPS	E1L3N	PD-1 antibody	Camrelizumab	Oxaliplatin + capecitabine

Abbreviations: CPS, combined positive score; CT, chemotherapy; FU, fluorouracil; IO, immunotherapy; PD-L1, programmed death ligand-1.

chemotherapy versus chemotherapy alone compared with the global population (HR_{PFS} 0.68, 95% CI 0.61–0.75; p<0.0001) (Figures S13-S14). The lower HR_{PFS} in Chinese patients versus the global cohort was consistent across the CPS subgroups with a trend for greater PFS benefit with increasing CPS score: CPS ≥1 (HR_{PFS} 0.65 vs. 0.75 for Chinese versus global), CPS ≥5 (HR_{PFS} 0.63 vs. 0.69 for Chinese versus global), and CPS ≥10 (HR_{PFS} 0.57 vs. 0.65 for Chinese versus global), indicating a greater reduction in risk of progression with PD-1/PD-L1 antibodies in Chinese patients with increasing CPS (Figures S13A-B). Only a single study reported data for the CPS 1–4, CPS 1–9 and CPS 5–9 subgroups, which precluded meta-analysis. When studies of bispecific antibodies were included in the analysis, a similar trend towards a numerically higher PFS benefit for Chinese patients versus the global cohort was observed (Figures S13 & S15).

Objective response rate – Chinese population. Chinese patients achieved numerically higher risk differences for objective response with PD-1/PD-L1 antibodies or immunotherapy plus chemotherapy versus chemotherapy alone compared with the global cohort (Figure 4A-B; Figures S16 & S17). This finding was consistent across the CPS ≥1, ≥5 and ≥10 subgroups. In particular, Chinese patients with a CPS ≥10 had an ORR improvement of over 25% compared with the global population.

DISCUSSION

The results of this meta-analysis of nine phase 3 trials further confirm the benefit of adding PD-1/PD-L1 monoclonal antibody to chemotherapy for the first-line treatment of patients with HER2-negative GC/GEJC, providing an up-to-date summary of the efficacy of immunotherapy in this patient population. The synthesis of data from studies of PD-1/PD-L1 monoclonal antibodies and bispecific antibodies showed good consistency with the results of the individual studies (including the studies of bispecifc antibodies COMPASSION-15[27,28] and SHR-1701-III-307[29,30]), further confirming the robustness of the findings. To our knowledge, our analysis also provides the most comprehensive evaluation to date of the correlation between PD-L1 expression level and the efficacy of immunochemotherapy. Previous meta-analyses have been limited by heterogeneous reporting of data for CPS subgroups in phase 3 trials.[11-14] To overcome this limitation, we utilized the KMSubtraction method to reconstruct data for unreported subgroups. Finally, the author conducted a meta-analysis of data from Chinese patients, which represents an important knowledge gap. Four recent meta-analyses have investigated outcomes of immunochemotherapy in patients with advanced gastric cancer.[11-14] However, only two of these studies analyses data in Asian subgroups, and none focused on Chinese subgroups.[13,14]

This analysis revealed efficacy benefits of first-line PD-1/PD-L1 antibody plus chemotherapy versus chemotherapy alone in patients with HER2-negative GC/GEJC, across multiple PD-L1 CPS cutoffs. The CPS cutoffs evaluated in this meta-analysis were deliberately selected to align with the stratification schemes employed in pivotal phase 3 trials that have established the current treatment paradigm. Specifically, CPS ≥1 and CPS ≥10 were prospectively defined in KEYNOTE-859 and KEYNOTE-062, and CPS ≥5 was all evaluated these phase III trials. These cutoffs correspond to active clinical debates regarding optimal patient selection: for example, some practitioners advocate for CPS ≥1 as a broad predictive criterion to maximize treatment access, while others argue that CPS ≥5 better enriches for meaningful clinical benefit. The intermediate categories—CPS 1–4, CPS 5–9 and CPS 1-9—were included to dissect this 'gray zone' of clinical equipoise, where treatment decisions are most uncertain and guideline recommendations diverge. Consistent with previous meta-analyses,[11-14] this study demonstrated PD-L1 CPS ≥1 was associated with a significantly improved OS (HR_{OS} 0.77, 95% CI 0.73–0.82; p<0.0001), PFS (HR_{PFS} 0.76, 95% CI 0.71–0.81; p<0.0001), and ORR (risk difference, 0.10; 95% CI 0.07, 0.12) versus chemotherapy alone. These benefits tended to increase further with increasing CPS expression levels (≥5 and ≥10). Importantly, the results suggest that even patients with low to moderate PD-L1 expression (CPS 1–4, 1–9, 5–9, and <5/10) achieve a statistically significant OS and PFS benefit from the addition of PD-1/PD-L1 antibody to chemotherapy. Many of the pivotal phase 3 trials of immunochemotherapy reported a stronger clinical benefit in patients with a CPS ≥5.[9,31,32] As a result, the effectiveness of PD-1/PD-L1in patients with a CPS of 1–4 is somewhat controversial, as reflected in the current NCCN guidelines, which recommend CPS ≥5 as the first-tier threshold for selecting pembrolizumab or tislelizumab combined with chemotherapy.[15] However, KEYNOTE-859 study[9] prospectively set CPS ≥1 as a pre-specified confirmatory endpoint and demonstrated that pembrolizumab plus chemotherapy yielded a more statistically significant survival benefit in patients with a CPS≥1 (HR_{OS}

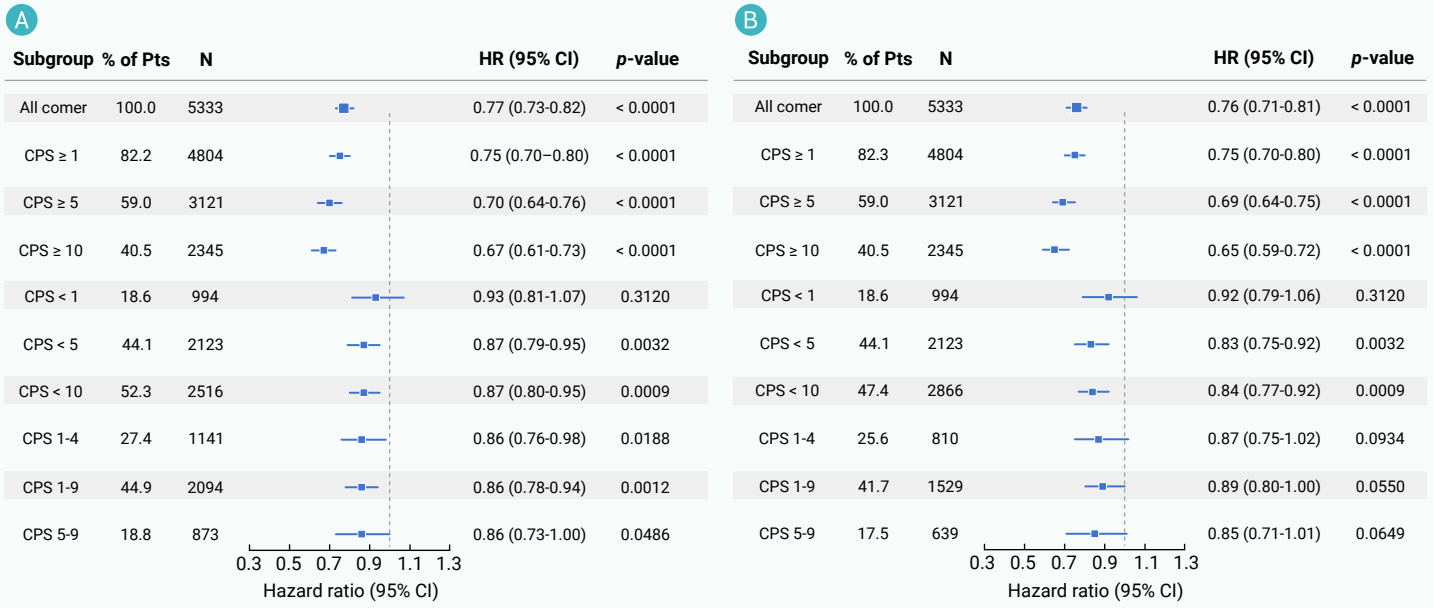

Figure 2. Global patient population: (A) overall survival and (B) progression-free survival for PD-1/PD-L1 antibodies plus chemotherapy versus chemotherapy alone stratified by PD-L1 CPS threshold CPS, combined positive score; PD-1, programmed cell death-1; PD-L1, programmed death ligand-1; Pts, patients.

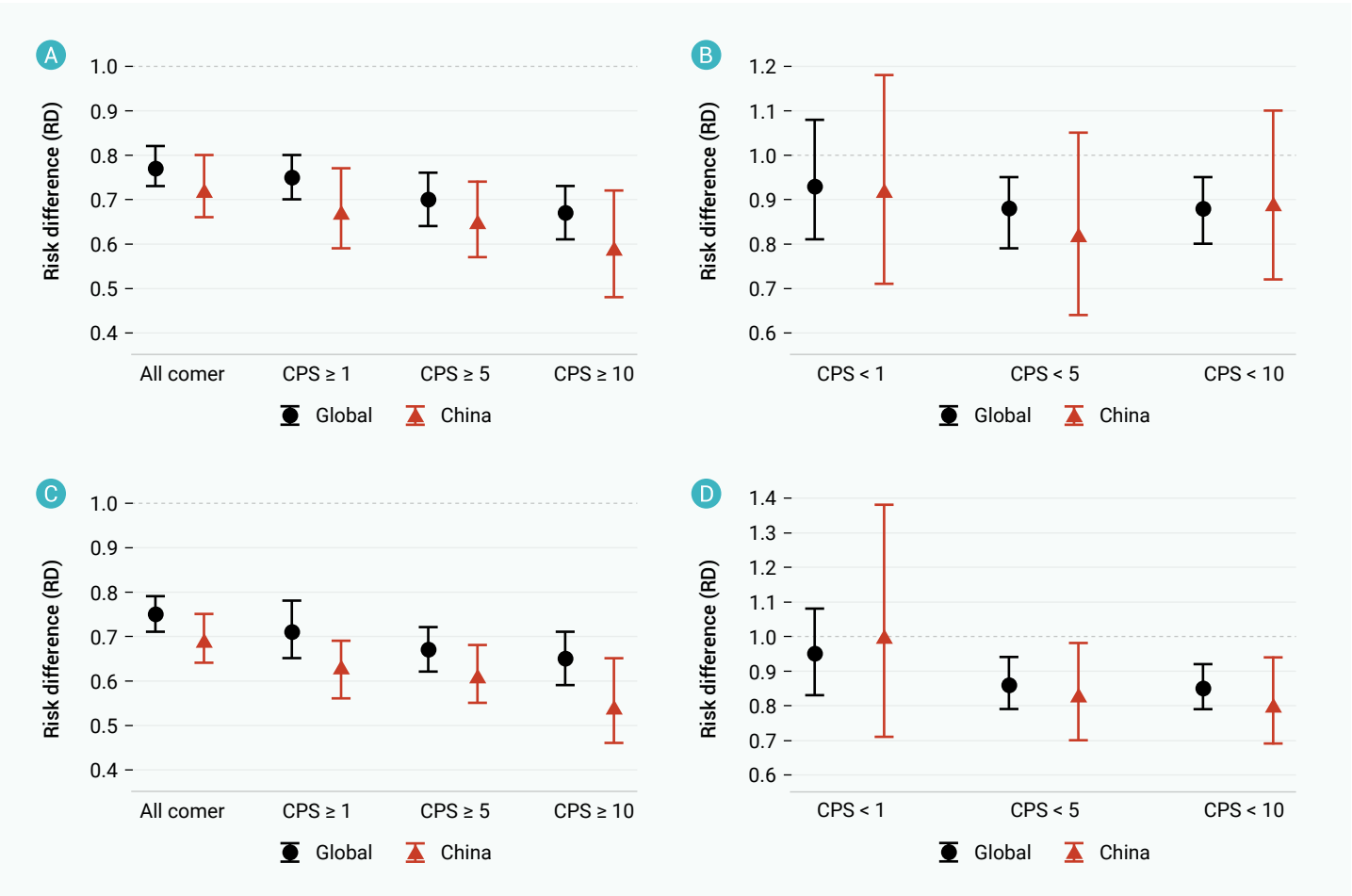

Figure 3. Comparison of hazard ratio for overall survival by PD-L1 CPS subgroup in China and global populations for studies of PD-1/PD-L1 antibodies (A & B) and immunotherapies (C & D) plus chemotherapy, versus chemotherapy alone.

0.74, 95%CI 0.65-0.84, p< 0.0001), and a clear trend of clinical benefit was also observed in the subgroup with CPS 1-4 (HR_{OS} 0.78, 95%CI 0.64-0.95, p=0.0075). Similarly, the results in this study revealed a significant OS benefit for patients with a CPS of 1–4 in the global population even in studies solely focusing on PD-1/PD-L1 monoclonal antibodies. Of course, it should be noted that for certain subgroups the reduction in mortality risk was <20% and the upper limit of the 95% confidence interval was close to 1 (CPS 1-4: HR 0.86, 95% CI 0.76–0.98; p=0.0188 and CPS 1-9: HR 0.86, 95% CI 0.78–0.94;

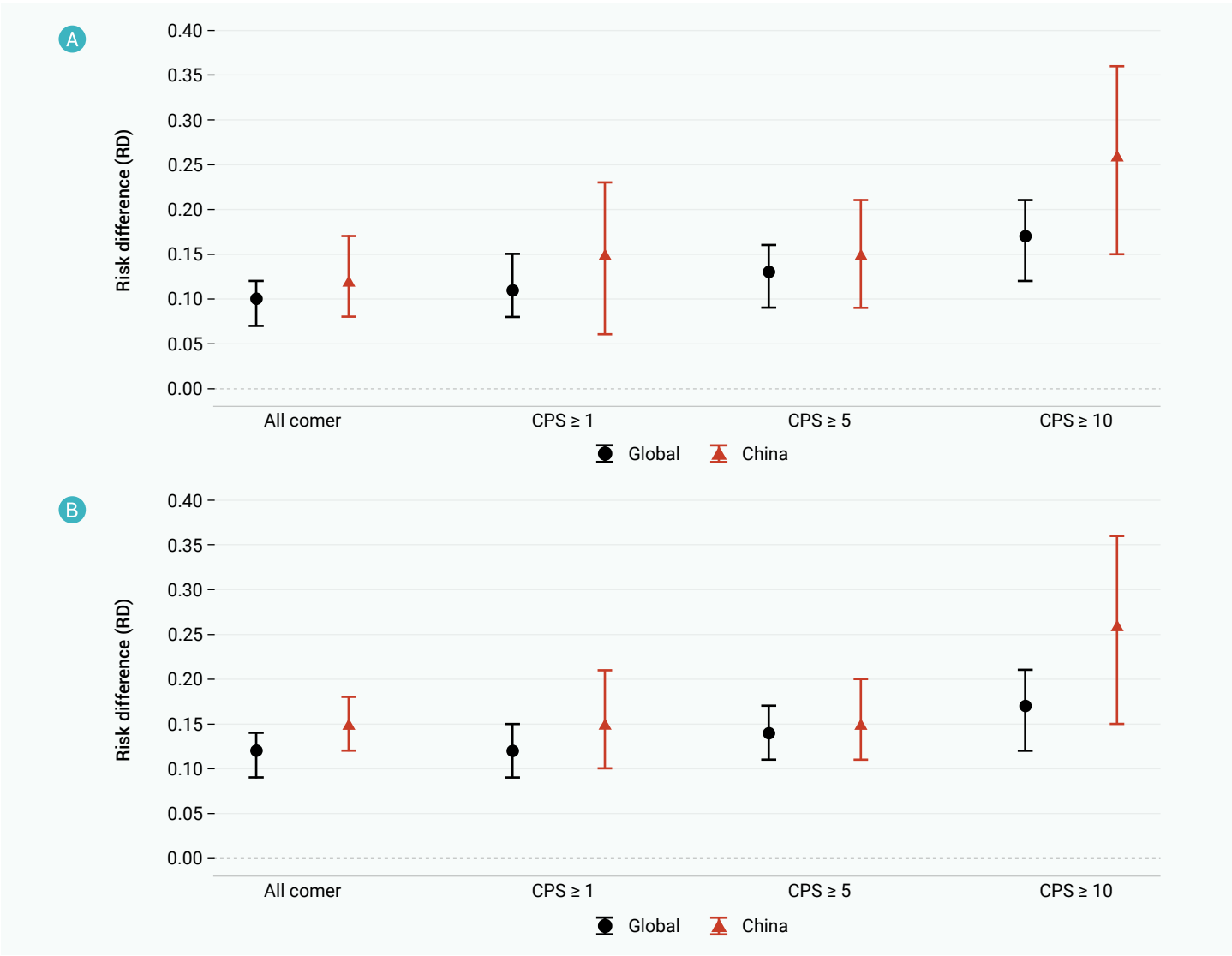

Figure 4. Comparison of China and global population: risk difference for objective response with (A) PD-1/PD-L1 antibodies and (B) immunotherapy, plus chemotherapy versus chemotherapy alone CPS, combined positive score; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1.

p=0.0012), therefore, these results require careful interpretation and prospective validation in larger cohorts is needed. Taken together, CPS ≥1 may be a reasonable threshold for considering PD-1/PD-L1 monoclonal antibody. For patients with CPS 1-4, PD-1/PD-L1 antibody represents a viable option, particularly when alternative treatments are limited, but the modest effect size warrants shared decision-making with patients. The ICI analysis involving bispecific antibodies showed consistent trends, their distinct mechanisms (e.g., dual PD-1/CTLA-4 or PD-L1/TGF-β blockade) may confer different biomarker dependencies. These agents require dedicated biomarker analyses in future trials.

Chinese patients achieved numerically greater improvements in OS, PFS, and ORR with first-line PD-1/PD-L1 antibody combined with chemotherapy versus chemotherapy alone compared with the global study populations. This observation was consistent across the majority of CPS strata investigated. These findings suggest the survival benefit of PD-1/PD-L1 antibody may be more significant in Chinese patients with positive PD-L1 expression. This is consistent with findings for Asian patient populations reported by previous meta-analyses.[13,14] Interestingly, the HR_{OS} value in the Chinese CPS ≥ 1 subgroup was 0.67 (95% CI 0.59–0.77), compared with 0.75 (95% CI 0.70–0.80) in the global population. This further indicates that CPS ≥1 may be a reasonable minimum threshold for selecting PD-1/PD-L1 antibody in the Chinese population, compared with >5 as recommended in the NCCN guidelines.[15] The differences in outcomes for Chinese versus global patients likely reflect differential demographic characteristics in Asian and Caucasian patients with gastric cancer,[17] with Asian patients tending to be younger at diagnosis[33,34] with a higher male-to-female ratio.[35,36] Other factors, such as earlier diagnosis in Asian versus Caucasian patients,[37,38] differences in tumour location and histological subtype,[33-35,39,40] and somatic mutation patterns,[41,42] may also result in differential responses to immunotherapy.

The results show that patients with CPS <1 do not derive an OS benefit from the addition of PD-1/PD-L1 antibodies to chemotherapy versus chemotherapy alone (HR_{OS} 0.93, 95% CI 0.81–1.07). This is consistent with the findings of prior meta-analyses.[11-14] A similar observation was made in the Chinese population (HR_{OS} 0.92, 95% CI 0.71–1.18), despite the overall greater efficacy with immunotherapy versus the global population. Overall, our findings align with the NCCN guideline recommendations and the US FDA Oncologic Drugs Advisory Committee (ODAC) advisory to restrict the use of immunotherapy to patients with CPS ≥1.[15,16] A similar trend was observed for bispecific antibodies. For example, a subgroup analysis of patients with CPS <1 in the COMPASSION-15 trial showed that cadonilimab combined with chemotherapy did not significantly improve OS versus chemotherapy alone (HR_{OS} 0.88, 95% CI 0.61–1.26) (See Appendix 1).[17] Similarly, reconstructed data for the CPS <1 subgroup in the SHR-1701-III-307 trial showed that retlirafusp-α combined with chemotherapy did not provide a survival benefit (HR_{OS} 4.70, 95% CI 1.65–13.38).[29,30] Based on these findings, the China National Medical Products Administration (NMPA) approved retlirafusp-α for first-line treatment in HER2-negative patients with CPS ≥1. Taken together, current data show that PD-L1 expression is an important predictor of outcome to

immunotherapy in patients with HER2-negative GC/GEJC. Individuals with CPS <1 are unlikely to benefit from immunotherapy, and further research is needed to explore novel treatment options for these patients.

One key limitation of this study was data availability. In Chinese subgroup, intermediate CPS cutoff analyses (CPS 1-4, 1-9, 5-9) were based on single-study data, precluding meta-analysis. This limits our ability to draw definitive conclusions about these subgroups in the Chinese population. Future trials with dedicated Chinese subgroup reporting for intermediate CPS ranges are needed. Meanwhile, some subgroup analyses included only two studies, which was too small to rule out the impact of publication bias. Small sample meta-analyses have inherent limitations such as insufficient statistical power and unreliable heterogeneity assessment. The use of KMSubtraction to reconstruct unreported subgroup data also could potentially introduce uncertainty, particularly for PD-L1 CPS subgroups where direct data were unavailable. While we validated reconstructed data against published survival probabilities, these estimates should be considered exploratory rather than definitive. In the future, large-scale prospective studies are needed to verify the conclusions. Secondly, in the global population, due to the relatively low number of studies of bispecific antibodies, the combined effect size may be more heavily weighted by the studies of monoclonal antibodies, resulting in insufficient representation of studies of bispecific antibodies. Therefore, the current analysis may not have sufficient power to detect the potential heterogeneity effect of studies containing bispecific antibodies. However, as the studies of bispecific antibodies included only Chinese patients, the weight of bispecific antibody studies in each subgroup was higher than for the global population.

CONCLUSION

The results of this meta-analysis of nine phase 3 clinical trials show that PD-1/PD-L1 antibody combined with chemotherapy results in superior OS, PFS and ORR outcomes compared with chemotherapy alone in global and Chinese patients with advanced HER2-negative GC/GEJC. A positive association was observed between higher PD-L1 CPS score and treatment outcome across all CPS thresholds evaluated, including intermediate cutoffs (1−4, 1−9, 5−9, <5 and <10). And CPS≥1 is supported as a practical cutoff for PD-L1/PD-L1 monoclonal antibody. Patients with a CPS <1 did not benefit from the addition of PD-1/PD-L1 antibody to chemotherapy. Chinese patients derived a modestly greater OS and PFS benefit from PD-1/PD-L1 antibody combined with chemotherapy versus chemotherapy alone compared with the global patient population. The addition of ICI analysis including studies of bispecific antibodies showed consistent results to those only including PD-1/PD-L1 antibodies.

REFERENCES

1. International Agency for Research on Cancer. (2025). GLOBOCAN cancer today. https://gco.iarc.fr/today/en. Accessed June 2025.
2. Patel A.K., Sethi N.S. and Park H. (2026). Gastric cancer: A review. *JAMA* **335**:439–450. DOI:10.1001/jama.2025.20034
3. Li Y., Feng A., Zheng S., et al. (2022). Recent estimates and predictions of 5-year survival in patients with gastric cancer: A model-based period analysis. *Cancer Control* **29**:10732748221099227. DOI: 10.1177/10732748221099227.
4. Wang Y. and Chong G. (2025). Immunotherapy in gastric adenocarcinoma - a rapidly evolving treatment landscape. *Crit. Rev. Oncol. Hematol.* **216**:104941. DOI:10.1016/j.critrevonc.2025.104941
5. Janjigian Y.Y., Shitara K., Moehler M., et al. (2021). First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): A randomised, open-label, phase 3 trial. *Lancet* **398**:27–40. DOI:10.1016/S0140-6736(21)00797-2
6. Xu J., Jiang H., Pan Y., et al. (2023). Sintilimab plus chemotherapy for unresectable gastric or gastroesophageal junction cancer: The ORIENT-16 randomized clinical trial. *JAMA* **330**:2064–2074. DOI:10.1001/jama.2023.19918
7. Moehler M.H., Kato K., Arkenau H.-T., et al. (2023). Rationale 305: Phase 3 study of tislelizumab plus chemotherapy vs placebo plus chemotherapy as first-line treatment (1L) of advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC). *J. Clin. Oncol.* **41**:286. DOI:10.1200/JCO.2023.41.4_suppl.286
8. Arkenau H.-T., Tabernero J., Cruz-Correa M., et al. (2024). Tislelizumab plus chemotherapy (chemo) versus placebo plus chemo as first-line treatment for locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma: RATIONALE-305 European/North American patient subgroup. *J. Clin. Oncol.* **42**:330. DOI:10.1200/JCO.2024.42.3_suppl.330
9. Rha S.Y., Oh D.Y., Yanez P., et al. (2023). Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): A multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol.* **24**:1181–1195. DOI:10.1016/S1470-2045(23)00515-6
10. Shen L., Ji J.F., Li Z.Y., et al. (2025). Final analysis of COMPASSION-15: Cadonilimab plus XELOX versus XELOX alone as first-line therapy for unresectable locally advanced/metastatic HER2-negative gastric/gastroesophageal junction adenocarcinoma. ESMO Congress 2025. Abstract No. 2098MO. Available from: https://www.esmo.org/congress-2025/abstracts/2098MO.
11. Formica V., Morelli C., Fornaro L., et al. (2024). PD-L1 thresholds predict efficacy of immune checkpoint inhibition in first-line treatment of advanced gastroesophageal adenocarcinoma. A systematic review and meta-analysis of seven phase III randomized trials. *ESMO Open* **9**:103967. DOI:10.1016/j.esmoop.2024.103967
12. Leone A.G., Mai A.S., Fong K.Y., et al. (2024). Immune checkpoint inhibitors in advanced gastroesophageal adenocarcinoma: A series of patient-level meta-analyses in different programmed death-ligand 1 subgroups. *ESMO Open* **9**:103962. DOI:10.1016/j.esmoop.2024.103962
13. Li J.B., Lai M.Y., Lin Z.C., et al. (2024). The optimal threshold of PD-L1 combined positive score to predict the benefit of PD-1 antibody plus chemotherapy for patients with HER2-negative gastric adenocarcinoma: A meta-analysis. *Cancer Immunol. Immunother.* **73**:132. DOI:10.1007/s00262-024-03726-1
14. Zhang W., Guo K. and Zheng S. (2025). Immunotherapy combined with chemotherapy in the first-line treatment of advanced gastric cancer: Systematic review and bayesian network meta-analysis based on specific PD-L1 CPS. *Curr. Oncol.* **32**:112. DOI:10.3390/curroncol32020112
15. National Comprehensive Cancer Network. (2026). Gastric Cancer (Version 2.2026). https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed July 6, 2026.
16. Food and Drug Administration Center for Drug Evaluation and Research. (2026). Oncologic Drugs Advisory Committee (ODAC) Meeting. https://www.fda.gov/media/184453/download. Accessed May 2026.
17. Zhao C., Ye S., Chen M., et al. (2026). First-line immunotherapy for advanced HER2-negative gastric cancer: Differences between Asian and non-Asian patients. *Cancer Biol. Med.* **23**:201–217. DOI:10.20892/j.issn.2095-3941.2025.0398
18. Zhao J.J., Syn N.L., Tan B.K.J., et al. (2022). KMSubtraction: Reconstruction of unreported subgroup survival data utilizing published Kaplan-Meier survival curves. *BMC Med. Res. Methodol.* **22**:93. DOI:10.1186/s12874-022-01567-z
19. Page M.J., McKenzie J.E., Bossuyt P.M., et al. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **372**:n71. DOI:10.1136/bmj.n71
20. Sterne J.A.C., Savović J., Page M.J., et al. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* **366**:l4898. DOI:10.1136/bmj.l4898
21. Guyot P., Ades A.E., Ouwens M.J., et al. (2012). Enhanced secondary analysis of survival data: Reconstructing the data from published Kaplan-Meier survival curves. *BMC Med. Res. Methodol.* **12**:9. DOI:10.1186/1471-2288-12-9
22. Liu N., Zhou Y. and Lee J.J. (2021). IPDfromKM: Reconstruct individual patient data from published Kaplan-Meier survival curves. *BMC Med. Res. Methodol.* **21**:111. DOI:10.1186/s12874-021-01308-8
23. Kuhn H.W. (1955). The Hungarian method for the assignment problem. *Nav. Res. Logist. Q.* **2**:83–97. https://doi.org/10.1007/978-3-540-68279-0_2
24. Liu D., Zhou J., Wang Y., et al. (2022). Bifunctional anti-PD-L1/TGF-βRII agent SHR-1701 in advanced solid tumors: A dose-escalation, dose-expansion, and clinical-expansion phase 1 trial. *BMC Med.* **20**:408. DOI:10.1186/s12916-022-02605-9
25. Kang Y.K., Chen L.T., Ryu M.H., et al. (2022). Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): A randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* **23**:234–247. DOI:10.1016/s1470-2045(21)00692-6
26. Sun J.M., Shen L., Shah M.A., et al. (2021). Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): A randomised, placebo-controlled, phase 3 study. *Lancet* **398**:759–771. DOI:10.1016/S0140-6736(21)01234-4
27. Shen L., Zhang Y., Li Z., et al. (2025). First-line cadonilimab plus chemotherapy in HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma: A randomized, double-blind, phase 3 trial. *Nat. Med.* **31**:1163–1170. DOI:10.1038/s41591-024-03450-4
28. Shen L., Zhang Y., Li Z., et al. (2025). 2098MO Cadonilimab (Cado) plus chemotherapy (chemo) versus chemotherapy as first-line (1L) treatment for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: Final results of the phase III COMPASSION-15 trial. *Ann. Oncol.* **36**:S1103. DOI:10.1016/j.annonc.2025.08.2719
29. Peng Z., Wang J., Zhang Y., et al. (2024). LBA60 phase III study of SHR-1701 versus placebo in combination with chemo as first-line (1L) therapy for HER2-negative gastric/gastroesophageal junction adenocarcinoma (G/GEJA). *Ann. Oncol.* **35**:S1250. DOI:10.1016/j.annonc.2024.08.2302
30. Peng Z., Wang J., Zhang Y., et al. (2025). 298P SHR-1701 plus CAPOX in patients with advanced gastric or gastroesophageal junction adenocarcinoma and PD-L1 combined positive score ≥1: A post-hoc analysis of a phase III study. *Ann. Oncol.* **36**:S1874. DOI:10.1016/j.annonc.2025.10.125
31. Janjigian Y.Y., Ajani J.A., Moehler M., et al. (2024). First-line nivolumab plus

chemotherapy for advanced gastric, gastroesophageal junction, and esophageal adenocarcinoma: 3-year follow-up of the phase III CheckMate 649 trial. *J. Clin. Oncol.* **42**:2012–2020. DOI:10.1200/jco.23.01601
32. Qiu M.Z., Oh D.Y., Kato K., et al. (2024). Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial. *BMJ* **385**:e078876. DOI:10.1136/bmj-2023-078876
33. Maruyama M., Takeshita K., Endo M., et al. (1998). Clinicopathological study of gastric carcinoma in high- and low-mortality countries: Comparison between Japan and the United States. *Gastric Cancer* **1**:64–70. DOI:10.1007/s101200050056
34. Wang J., Sun Y. and Bertagnolli M.M. (2015). Comparison of gastric cancer survival between Caucasian and Asian patients treated in the United States: Results from the Surveillance Epidemiology and End Results (SEER) database. *Ann. Surg. Oncol.* **22**:2965–2971. DOI:10.1245/s10434-015-4388-4
35. Zhao L., Niu P., Zhao D., et al. (2021). Regional and racial disparity in proximal gastric cancer survival outcomes 1996-2016: Results from SEER and China National Cancer Center database. *Cancer Med.* **10**:4923–4938. DOI:10.1002/cam4.4033
36. Xing Y., Hosaka H., Moki F., et al. (2024). Gender differences in patients with gastric adenocarcinoma. *J. Clin. Med.* **13**:2524. DOI:10.3390/jcm13092524
37. Theuer C.P., Kurosaki T., Ziogas A., et al. (2000). Asian patients with gastric carcinoma in the United States exhibit unique clinical features and superior overall and cancer specific survival rates. *Cancer* **89**:1883–1892. DOI:10.1002/1097-0142(20001101)89:9<1883::aid-cncr3>3.3.co;2-8
38. Chiarello M.M., Fico V., Pepe G., et al. (2022). Early gastric cancer: A challenge in Western countries. *World J. Gastroenterol.* **28**:693–703. DOI:10.3748/wjg.v28.i7.693
39. Yao J.C., Schnirer II, Reddy S., et al. (2002). Effects of sex and racial/ethnic group on the pattern of gastric cancer localization. *Gastric Cancer* **5**:208–212. DOI:10.1007/s101200200036
40. Wu S.P., Keshavjee S.H., Yoon S.S., et al. (2023). Survival outcomes and patterns of care for stage II or III resected gastric cancer by race and ethnicity. *JAMA Netw. Open* **6**:e2349026. DOI:10.1001/jamanetworkopen.2023.49026
41. Jia F., Teer J.K., Knepper T.C., et al. (2017). Discordance of somatic mutations between Asian and Caucasian patient populations with gastric cancer. *Mol. Diagn. Ther.* **21**:179–185. DOI:10.1007/s40291-016-0250-z
42. Gilmore G.A., Barakat M., Chaudhary U.B., et al. (2019). Genomic profile of gastric cancer in the United States versus East Asia. *J. Clin. Oncol.* **37**:45. DOI:10.1200/JCO.2019.37.4_suppl.45
43. Tabernero J., Van Cutsem E., Bang Y.-J., et al. (2019). Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study. *J. Clin. Oncol.* **37**:LBA4007. DOI:10.1200/JCO.2019.37.18_suppl.LBA4007
44. Shitara K., Van Cutsem E., Bang Y.J., et al. (2020). Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: The KEYNOTE-062 phase 3 randomized clinical trial. *JAMA Oncol.* **6**:1571–1580. DOI:10.1001/jamaoncol.2020.3370
45. Zhao J.J., Yap D.W.T., Chan Y.H., et al. (2022). Low programmed death-ligand 1-expressing subgroup outcomes of first-line immune checkpoint inhibitors in gastric or esophageal adenocarcinoma. *J. Clin. Oncol.* **40**:392–402. DOI:10.1200/JCO.21.01862
46. Janjigian Y.Y., Moehler M.H., Ajani J.A., et al. (2025). Nivolumab (NIVO) + chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 5-year (y) follow-up results from CheckMate 649. *J. Clin. Oncol.* **43**:398. DOI:10.1200/JCO.2025.43.4_suppl.398
47. Xu J., Jiang H., Pan Y., et al. (2023). Abstract CT078: First-line treatment with sintilimab (sin) vs placebo in combination with chemotherapy (chemo) in patients (pts) with unresectable gastric or gastroesophageal junction (G/GEJ) cancer: Final overall survival (OS) results from the randomized, phase III ORIENT-16 trial. *Cancer Res.* **83**:CT078. DOI:10.1158/1538-7445.Am2023-ct078
48. Rha S.Y., Wyrwicz L., Weber P.E.Y., et al. (2025). KEYNOTE-859: 4.5-year median follow-up of pembrolizumab plus chemotherapy for previously untreated advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. *J. Clin. Oncol.* **43**:4036. DOI: 10.1200/JCO.2025.43.16_suppl.4036.
49. European Medicines Agency. (2023). Keytruda Assessment Report (Procedure No. EMEA/H/C/003820/II/0135). Committee for Medicinal Products for Human Use (CHMP). October 12, 2023.
50. Cruz-Correa M., Oh D.Y., Kato K., et al. (2026). Tislelizumab + chemotherapy in gastric cancer: Long-term RATIONALE-305 randomized trial follow-up. *Adv. Ther.* **43**:165–183. DOI:10.1007/s12325-025-03415-0
51. Moehler M., Oh D.Y., Kato K., et al. (2024). 397MO Tislelizumab (TIS) plus chemotherapy (CT) vs placebo (PBO) plus CT in HER2-negative advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma (GC/GEJC): PD-L1 biomarker analysis from RATIONALE-305. *Ann. Oncol.* **35**:S160–S161. DOI:10.1016/j.annonc.2024.05.312
52. Zhang X., Wang J., Wang G., et al. (2025). First-line sugemalimab plus chemotherapy for advanced gastric cancer: The GEMSTONE-303 randomized clinical trial. *JAMA* **333**:1305–1314. DOI:10.1001/jama.2024.28463
53. Peng Z., Zhang Y., Xu H., et al. (2026). Camrelizumab plus CAPOX with camrelizumab based maintenance versus CAPOX alone as initial treatment for gastric or gastro-oesophageal junction adenocarcinoma: Randomised phase 3 trial. *BMJ* **392**:e086115. DOI:10.1136/bmj-2025-086115

FUNDING AND ACKNOWLEDGMENTS

This study is supported by Noncommunicable Chronic Diseases-National Science and Technology Major Project（2023ZD0511600）and Beijing Natural Science Foundation (L254087). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors sincerely thank Mrs. Chenxi Ma, Jing Qian and Nan Xiao from The Medical Affairs GI team, MSD China for their scientific support.

AUTHOR CONTRIBUTIONS

Tong Xie contributed to the conception and design of the study, data analysis and interpretation of data. Xiaotian Zhang, Zhi Peng, Yakun Wang, and Lin Shen contributed to the conception and design of the study and interpretation of data. Tong Xie and Lin Shen Yin prepared the first draft of the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

Lin Shen is an Editorial Board member of The Innovation Oncology and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors report no conflict of interest.

DATA AND CODE AVAILABILITY

All of the data underlying this paper have been provided in the Appendix. Appendix 1 includes full details of the data synthesis for each included study.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-oncol.2026.100030