Cancer Biol Med 2026. doi: 10.20892/j.issn.2095-3941.2025.0398

REVIEW

First-line immunotherapy for advanced HER2-negative gastric cancer: differences between Asian and non-Asian patients

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ABSTRACT Emerging evidence suggests that the efficacy of immunotherapy in patients with advanced HER2-negative gastric cancer differs between Asian and non-Asian populations. This review examines potential factors contributing to these disparities, including differences in demographic and clinicopathologic characteristics, somatic mutations, molecular subtypes, tumor immunity, *Helicobacter pylori (H. pylori)* infection, dietary habits, and gut microbiome composition. These factors may serve as predictors of immunotherapy response in gastric cancer patients. For example, the prevalence of molecular subtypes and somatic mutations have been linked to variations in immunotherapy efficacy between Asian and non-Asian populations. In addition, differences in *H. pylori* infection rates, dietary habits, and gut microbiota composition may influence systemic immune responses, and consequently, immunotherapy outcomes. Understanding the factors contributing to these disparities in immunotherapy response is crucial for optimizing treatment strategies and improving outcomes for patients with gastric cancer. Further research into the mechanisms underlying racial and ethnic disparities in immunotherapy response is needed to identify potential biomarkers predictive of immunotherapy response in diverse patient populations.

KEYWORDS Asia; gastric cancer; HER2-negative; immunotherapy

Introduction

Gastric cancer is a significant global health burden, ranking fifth in incidence and mortality[1]. Despite advances in treatment, the prognosis for advanced gastric cancer remains poor with a 5-year overall survival (OS) rate of < 10% for patients with advanced disease[2,3]. The introduction of immunotherapy has transformed the treatment landscape for gastric cancer. Several phase 3 studies have demonstrated that the combination of chemotherapy with immune checkpoint inhibitors (ICIs), including programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, can improve the survival of patients with advanced HER2-negative gastric cancer[4-8]. Based on this evidence immunotherapy in combination with chemotherapy has become the standard of care for previously untreated patients with advanced HER2-negative gastric cancer[9-12].

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Received July 21, 2025; accepted December 23, 2025;
published online February 27, 2026.
Available at www.cancerbiomed.org
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Emerging evidence has demonstrated variability in the efficacy of immunotherapy between different patient populations, particularly Asian and non-Asian patients[4,8,13-18]. However, the observed differences among Asian and non-Asian patients with advanced HER2-positive gastric cancer are inconsistent with the differences reported for patients with HER2-negative gastric cancer. The underlying factors contributing to these differences are unknown, although inherent differences in tumor characteristics between HER2-negative and -positive gastric cancers may have a role[19-21]. Understanding these disparities is crucial for optimizing treatment strategies and improving outcomes for all patients with gastric cancer. However, it is difficult to summarize the underlying reasons for the inconsistent outcomes of immunotherapy in different racial subgroups of patients with HER2-negative and -positive gastric cancer in a single review. Therefore, in this article only HER2-negative gastric cancer is discussed.

In this review the epidemiologic differences in HER2-negative gastric cancer between Asian and non-Asian patients are discussed and the immunotherapy response rates and outcomes in these populations are compared. Differences in etiology, clinicopathologic characteristics, mutation profiles, and immunologic landscapes between Asian and non-Asian patients are explored. The goal of this review is to highlight potential mechanisms contributing to the observed differences in immunotherapy efficacy. Recognizing population-specific differences in treatment response is essential for guiding the

selection of the most appropriate therapies for individual patients. Furthermore, understanding the mechanisms underlying disparities in immunotherapy efficacy may contribute to the further development of targeted and effective therapies, thereby leading to improved outcomes in diverse populations of patients with gastric cancer. Although subgroup analyses of clinical trials and several meta-analyses have addressed differences in response to immunotherapy in Asian and non-Asian populations, these studies did not comprehensively summarize and discuss the potential underlying mechanisms for these observations. In the current review the differences in outcomes to immunotherapy in Asian and non-Asian populations from epidemiologic, molecular, immunologic, and microbiome perspectives are investigated.

Global burden of gastric cancer is highest in Asia

According to the most recent Global Cancer Observatory (GLOBOCAN) data, an estimated 968,350 million new cases and 659,853 deaths were attributed to gastric cancer in 2022 with a worldwide age-standardized incidence rate (ASIR) of 9.2 per 100,000 person-years and an age-standardized mortality rate (ASMR) of 6.1 per 100,000 person-years[1].

Gastric cancer exhibits marked geographic variation in incidence and mortality with a disproportionate burden in Asian countries. According to GLOBOCAN 2022, gastric cancers in East Asia (South Korea, Japan, and China) account for nearly 54% of global gastric cancer cases[1]. In East Asian countries the ASIR of gastric cancer is 16.1 per 100,000 person-years and the ASMR is 9.2 per 100,000 person-years[1,22]. The burden of gastric cancer is particularly high in China, which accounts for 37% of new gastric cancer cases and 39.4% of all gastric cancer-related deaths worldwide[1,22]. In China 30%–40% of patients with gastric cancer are diagnosed at an advanced stage, which is associated with a poor prognosis[23]. Although the underlying reason for the disproportionate burden of gastric cancer in East Asian countries is not fully understood, environmental [e.g., prevalence of *Heliobacterium pylori (H. pylori)* infection], genetic (e.g., polymorphisms in *CDH1*), and lifestyle factors (e.g., high salt intake and consumption of smoked and pickled foods) may be contributing factors[1,24].

Temporal trends in the incidence and mortality of gastric cancer also differ between Asian and non-Asian countries. Although a decline in gastric cancer incidence has been observed in both Asian and non-Asian countries, the rates of decline differ[24,25]. For example, a relatively rapid decline in gastric cancer incidence over time has been reported in Japan and South Korea, perhaps due to widespread *H. pylori* screening programs and eradication, as well as early cancer screening programs utilizing gastroscopy[24,25]. In contrast, a slower decline in gastric cancer incidence has been observed in many Western countries with some subpopulations showing an increasing incidence[24,25]. These epidemiologic differences underscore the need for tailored approaches to gastric cancer prevention, screening, and treatment strategies for Asian and non-Asian populations.

Better immunotherapy response in Asian *versus* non-Asian patients with advanced HER2-negative gastric cancer

Patients with advanced gastric cancer have a poor prognosis and chemotherapy has historically been the mainstay of treatment for this patient population[3]. Recently, the therapeutic landscape of immunotherapy for gastric cancer has evolved considerably, progressing from later-line treatments to first-line applications and from single-agent approaches to combination therapies. The efficacy of third-line treatment with ICIs in patients with advanced HER2-negative gastric cancer was investigated in the phase 2 KEYNOTE-059 and the phase 3 ATTRACTION-2 trials[26,27]. Pembrolizumab demonstrated comparable efficacy {Asian *vs.* non-Asian [objective response rate (ORR), 7.3% *vs.* 12.0%; 6-month progression-free survival (PFS) rate, 14.6% *vs.* 14.6%; 6-month (OS) rate, 68% *vs.* 46.2%]; **Table 1**} and safety profiles {Asian *vs.* non-Asian [any grade treatment-related adverse event (TRAE), 63.4% *vs.* 61%; grade 3–5 TRAE, 17.1% *vs.* 17.9% in Asian (n = 41) and non-Asian (n = 218) populations in third-line treatment]}, despite differences in PD-L1-positivity rates (41.5% and 60.1%, respectively) in the phase 2 global KEYNOTE-059 study cohort 1[26]. Despite slightly better survival in Asian patients, the disparity in sample sizes precluded drawing definitive conclusions[26]. In addition, Eastern Cooperative Oncology Group (ECOG) performance status, the extent of pretreatment, and the rate of PD-L1-positivity differed between the two populations, further complicating comparisons of treatment efficacy[26].

The phase 3 KEYNOTE-062 study was the first to show non-inferior efficacy of first-line pembrolizumab monotherapy versus standard-of-care chemotherapy in patients with advanced gastric cancer[14,15,28,29]. Subsequent randomized phase 3 trials, including CheckMate-649, ORIENT-16, RATIONALE-305, KEYNOTE-859, GEMSTONE-303, and COMPASSION-15, have demonstrated that adding ICIs to first-line chemotherapy can improve the survival of previously untreated patients with advanced unresectable or metastatic gastric cancer[4-8,30,31]. Data from these pivotal studies have led to ICIs combined with chemotherapy becoming the standard of care for the first-line treatment of patients with gastric or gastroesophageal junction cancer (GC/GEJC)[9-12].

Subgroup analysis of the global phase 2/3 trials of first-line immunotherapy for GC/GEJC, including CheckMate-649, KEYNOTE-062, KEYNOTE-859, and KEYNOTE-590, have shown that Asian patients may derive a stronger antitumor effect from ICIs plus chemotherapy than non-Asian patients

Table 1 Response rates in Asian and non-Asian patients with advanced gastric cancer who underwent treatment with immune checkpoint inhibitors in pivotal phase 2/3 trials

Treatment line	Study	PD-L1 expression	Treatment, pt number	ORR, % (95% CI)			PFS, months or % (95% CI), HR value			OS, months or % (95% CI), HR value		
				Asian patients	Non-Asian patients	Overall patients	Asian patients	Non-Asian patients	Overall patients	Asian patients	Non-Asian patients	Overall patients
Third	KEYNOTE-059[26]	Unselected	Pembrolizumab Asian: *n* = 41 Non-Asian, *n* = 218	7.3 (1.5–19.9)	12.8 (8.7–18.0)	12.0 (8.3–16.6)	6-mo PFS rate: 14.6	6-mo PFS rate: 14.6	6-mo PFS rate: 14.6	6-mo OS rate: 68.0	6-mo OS rate: 41.5	6-mo OS rate: 46.2
First	KEYNOTE-062[14,28,29]	PD-L1 CPS ≥ 1	Pembrolizumab Asian: *n* = 62 Non-Asian, *n* = 194	22.6 (12.9–35.0)	Not reported	14.8	Median: 4.1 (2.2–7.2), HR = 1.11	Not reported	Median: 2.0 (1.5–2.8), HR = 1.66	Median: 22.7 (14.3–28.5), HR = 0.54	Not reported	Median: 10.6 (7.7–13.8), HR = 0.91
	KEYNOTE-062[14,15]	PD-L1 CPS ≥ 1	Pembrolizumab + chemotherapy Asian: *n* = 64 Non-Asian, *n* = 193	53.1 (40.2–65.7)	Not reported	48.6	Median: 8.5 (7.0–10.3), HR = 0.64	Not reported	Median: 6.9 (5.7–7.3), HR = 0.84	Median: 16.5 (12.8–19.6), HR = 0.78	Not reported	Median: 12.5 (10.8–13.9), HR = 0.85
	CheckMate-649[4,13]	Unselected	Nivolumab + chemotherapy Chinese[a]: *n* = 99 Rest of world, *n* = 690	66.0 (55.0–76.0)[a]	Not reported	60.0 (55.0–65.0)	Median: 8.3 (6.2–12.3), HR = 0.57[a]	Not reported	Median: 7.7 (7.1–8.5), HR = 0.77	Chinese: median: 14.3 (11.5–17.5), HR = 0.61[a] Asian: 16.4, HR = 0.73	Median: White: 13.1, HR = 0.79	Median: 13.8 (12.6–14.6), HR = 0.80
	KEYNOTE-859[8,16]	Unselected	Pembrolizumab + chemotherapy Asian: *n* = 263 Non-Asian, *n* = 527	61.2 (55.0–67.1)	Not reported	51.3 (47.7–54.8)	Median: 8.4 (7.2–9.6), HR = 0.72	W Eur/Isr/N Am/Australia: HR = 0.79 Rest of world: HR = 0.77	Median: 6.9 (6.3–7.2), HR = 0.76	Median: 17.3 (14.8–19.5), HR = 0.71	W Eur/Isr/N Am/Australia: HR = 0.80 Rest of world: HR = 0.80	Median: 12.9 (11.9–14.0), HR = 0.78
	KEYNOTE-590[17,18]	Unselected	Pembrolizumab + chemotherapy Chinese[a]: *n* = 51 Rest of world, *n* = 322	37.3[a]	Not reported	45.0 (39.9–50.2)	Chinese: median: 6.2 (5.4–6.8), HR = 0.60[a] Asian: HR = 0.59	Non-Asian: HR = 0.70	Median: 6.3 (6.2–6.9), HR = 0.65	Chinese: median: 10.5 (7.9–19.3), HR = 0.51[a] Asian: HR = 0.64	Non-Asian: HR = 0.83	Median: 12.4 (10.5–14.0), HR = 0.73

[a]Data are for the Chinese subgroup.

CI, confidence interval; CPS, combined positive score; HR, hazard ratio; ITT, intention to treat; mo, month; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

(**Table 1**)[4,8,13-18]. In these studies the ORR after treatment with ICIs ranged from 22.6%–66.0% among Asian patients and from 14.5%–60.0% in the overall cohort. Similar differences in PFS and OS were reported. In global phase 2/3 trials the median PFS was 4.1–8.5 months for Asian patients [hazard ratio (HR) for ICI alone or with chemotherapy *vs.* chemotherapy range, 0.57–1.11] and 2.0–7.7 months for the overall cohorts (HR range, 0.65–1.66)[4,8,13-18]. The median OS was 10.5–22.7 months for Asian patients (HR range, 0.51–0.78) and 10.6–13.8 months for the overall cohorts (HR range, 0.73–0.91)[4,8,13-18].

Several systematic reviews have confirmed the superior efficacy of first-line treatment with ICIs plus chemotherapy in Asian patients with advanced gastric cancer[32-35]. Although both Asian and Western patients benefited from immunotherapy, Zhang et al.[32] reported that Asian patients demonstrated significantly superior OS to first-line immunotherapy compared to Western patients {Asian patients [HR, 0.65 (95% CI, 0.53–0.79)]}; Western patients [HR, 0.86 (95% CI, 0.72–1.04); $P = 0.04$] in a review involving 20 clinical trials[32]. PD-1 inhibitors were associated with better OS outcomes in the Asian patient population both as monotherapy (pooled HR, 0.66) and in combination with chemotherapy (pooled HR, 0.83) in a meta-analysis[35]. Two additional meta-analyses conducted by Parmar et al. and Liu et al. concluded that Asian patients derive greater benefit from ICIs compared to White patients[33,34]. These observations suggested improved immunotherapy efficacy in Asian patients compared to non-Asian patients with gastric cancer. However, it is essential to consider potential confounding factors and explore the underlying mechanisms contributing to these differences.

Despite the differences in ICI efficacy observed between Asian and non-Asian patients in phase 2/3 trials, the safety profile appears to be similar between these populations. In most studies involving ICI monotherapy for gastric cancer, grade 3–4 adverse events were observed in 10%–20% of patients, regardless of ethnicity[4,8,13-18]. However, a higher incidence of colitis and endocrinopathies has been observed in non-Asian patients[4,8,13-18].

Potential factors contributing to ethnic differences in the immunotherapy response

Differences in demographic and clinicopathologic characteristics between Asian and non-Asian patients

Racial differences in age of onset and gender ratio, and the impact on immunotherapy response

The racial differences in demographic and clinicopathologic characteristics that may impact immunotherapy response are summarized in **Table 2**. Findings from several studies suggest significant differences in the age and gender distribution of Asian and non-Asian patients with gastric cancer. Asian patients tend to be younger at the time of diagnosis; the median age at the time of diagnosis in Asian patients ranges from 59–67 years, whereas the median age at the time of diagnosis in non-Asian patients ranges from 64–69 years[36,37]. Data from 12,773 American patients with gastric cancer in the SEER database also showed a statistically significant difference in the mean age at the time of diagnosis between White and Asian patients (68.5 ± 13.6 *vs.* 66.8 ± 13.6 years; $P < 0.0001$)[37]. Furthermore, a higher male-to-female ratio has been reported in Asian gastric cancer populations (typically 2:1–3:1), whereas the ratio in non-Asians was closer to 1.5:1[40,41].

Differences in demographic characteristics may contribute to the higher efficacy of ICIs in Asian patients. For example, younger patients may have more robust immune systems and better overall health, potentially enhancing immunotherapy response[38]. Moreover, younger patients typically exhibit higher thymic output and T cell repertoire diversity, which are crucial for an effective ICI response[39]. An age-related decline in immune function, referred to as immunosenescence, affects multiple components of antitumor immunity, including reduced naive T cell production and impaired cytokine signaling[61]. Gender differences in immune function and hormonal influences may also affect treatment outcomes[43]. A meta-analysis has shown that sex hormones, particularly estrogen, may influence gastric cancer risk with women generally exhibiting a lower incidence compared to men[42]. This hormonal influence is further supported by findings that suggest estrogen may reduce the risk of gastric carcinogenesis[45]. In addition, the differential expression of estrogen receptors in gastric tissues may modulate immune responses, potentially leading to variations in tumor behavior and patient outcomes[44].

Racial differences in tumor location and histology, and the potential impact on the immunotherapy response

Racial differences in tumor location and histologic subtype have also been reported. For example, a higher proportion of proximal gastric tumors, including GEC cancer, was observed in White patients (29%–57%) than Asian patients (13%–33%)[36,37,40,46]. Furthermore, antral tumors tend to be more common in Asian patients than White patients. These differences in tumor location may influence local immune responses. For example, the frequency of chromosomal instability (CIN) is higher in gastric tumors in the GEC/cardia than other anatomic regions of the stomach[47]. This finding has been associated with a poor response to immunotherapy and might explain the lower response to ICIs among White patients compared to Asian patients[48]. In addition, myeloid-derived suppressor cells (MDSCs) are elevated in esophagogastric junction adenocarcinomas[50]. MDSCs have important roles in tumor progression and tumor immune

Table 2 Comparison of demographic and clinicopathologic characteristics between Asian and non-Asian patients with gastric cancer and impact on the immunotherapy response

Demographic and clinicopathologic characteristics	Racial differences	Supporting data	Impact on the immunotherapy response
Age of onset	Asian patients tend to be younger at the time of diagnosis[36,37].	Japan 59.0 *vs.* US 64.1[36]; Asian 66.8 *vs.* White 68.5[37]	• Younger patients may have more robust immune systems with better overall health, higher thymic output and diversity in T cell repertoire, potentially enhancing the immunotherapy response[38,39].
Gender ratio	A higher male-to-female ratio has been reported in Asian gastric cancer populations[40,41].	Male predominance: China 83.9% *vs.* US 75.8%[40]; Japan 71.0% male *vs.* 29.0% female[41]	• Gender differences in immune function and hormonal influences may affect treatment outcomes[42-45].
Tumor location	White patients exhibit a higher prevalence of proximal gastric tumors, including GEJC, whereas antral tumors are more frequently observed in Asian patients[36,37,40,46].	Proximal tumors more common in White patients: US 47% *vs.* Japan 23%[36]; non-Hispanic White men 57.0% *vs.* Asian men 17.0%[41]; US PGC 29.0–37.0% *vs.* China 13.0–33.0%[40] Distal/antral tumors more common in Asians: Antrum; Asian 39.9% *vs.* White 31.8%[37]; Japan; distal 56.0%, proximal 22.0%[46]	• Tumor location may affect local immune responses: higher CIN in GEJC is associated with a poorer response to immunotherapy[47,48]. • Increased levels of MDSCs in GEJC may promote immune evasion and reduce ICI effectiveness[49,50].
Histologic subtype	Asian patients tend to present with intestinal-type rather than diffuse-type histology[51].	Asian patients: intestinal 24.6% *vs.* diffuse 11.0%[51]	• Histologic subtypes are associated with different immune infiltration patterns; diffuse-type histology is linked with poorer outcomes[51].
Disease stage	Asian Americans tend to be diagnosed with gastric cancer at earlier stages than other racial groups in the US. Countries, such as Japan and South Korea, have a higher proportion of early-stage gastric cancer due to widespread screening programs[52,53].	Asian Americans: more localized disease at diagnosis (OR 1.61 *vs.* white, non-Latino)[52] Early-stage gastric cancer > 50% in Japan/Korea *vs.* ~20% in West due to screening[53]	• Earlier diagnosis may lead to better outcomes and enhanced immunotherapy responses[54].
Tumor burden	Within Asia, tumor burden at the time of diagnosis is lower in patients from Japan versus other Asian countries[55-57].	Lower tumor burden in Japan: OS 1.3 × longer in Japanese *vs.* others[58]; AGC median therapy duration, 10.2 mo[57]; ASIR 28.3 *vs.* China 30.6, Mongolia 43.7/100[56]	• Patients with low tumor burden may receive multiple lines of therapy, reducing the impact of first-line immunotherapy and improving overall survival but survival benefit of first-line immunotherapy is less pronounced[32,56,58-60].

AGC, advanced gastric cancer; ASIR, age-standardized incidence rate; CIN, chromosomal instability; GEJC, gastroesophageal junction cancer; ICI, immune checkpoint inhibitor; MDSCs, myeloid-derived suppressor cells; mo, months.

escape[49] and may contribute to a lower efficacy of ICIs in patients with esophagogastric junction adenocarcinomas, who represent a considerable proportion of White patients with gastric cancer. Moreover, diffuse-type histology is more common in non-Asian patients than Asian patients, who tend to present with an intestinal-type histology[51]. Histologic subtypes have been associated with different immune infiltration patterns and may affect the immunotherapy response with diffuse-type histology being associated with treatment resistance and poorer outcomes[51].

Racial and regional differences in disease stage and tumor burden at the time of diagnosis, and the potential impact on immunotherapy outcomes

Racial or ethnic differences in disease stage at the time of diagnosis have been observed among patients with gastric cancer. Asian Americans have been reported to present with gastric carcinoma at less advanced stages compared to other racial groups in the United States, contributing to the superior survival rates among Asian patients[52]. The early stage of gastric cancer at the time of diagnosis in some Asian countries, such as Japan and South Korea, may be due to the widespread adoption of screening programs[53]. In contrast, most gastric cancer cases are diagnosed at advanced stages in Western countries. Earlier diagnosis may lead to better overall outcomes and a potentially enhanced immunotherapy response[54].

Regional differences in tumor burden have also been reported among patients with advanced gastric cancer. Even within Asia, the tumor burden of gastric cancer at diagnosis is usually lower in Japan and there also exists a disparity in immunotherapy efficacy between Japanese patients and patients from other Asian countries[55-57]. Due to the relatively low overall tumor burden in Japanese patients with advanced gastric cancer, Japanese patients can receive multiple lines of therapy, which may dilute the role of first-line immunotherapy. As a result, the absolute survival of Japanese patients with and without first-line immunotherapy for advanced gastric cancer tends to be longer than patients in other Asian countries[56,58,59]. However, the magnitude of survival benefit for Japanese patients who have received first-line immunotherapy is not as great as in other Asian countries[32,60].

Differences in somatic mutations between Asian and non-Asian patients with gastric cancer

Genetic and molecular differences have been reported between Asian and non-Asian patients with gastric cancer. This finding further contributes to variations in clinicopathologic characteristics and potentially to differences in immunotherapy response (**Table 3**). Genomic profiling of gastric tumors revealed distinct somatic mutation patterns in Asian and non-Asian patients. White patients with gastric cancer have higher rates *APC* (14.4% *vs.* 6.1%), *ARID1A* (32.1% *vs.* 20.7%), *KMT2A* (12.4% *vs.* 4.0%), *PIK3CA* (18.5% *vs.* 9.6%), and *PTEN* mutations (9.1% *vs.* 2.5%) compared to Asian patients[62]. In contrast, *TP53* (51.5% *vs.* 44.4%) and *CDH1* mutations (13.1% *vs.* 10.7%) are more common in Asian patients[62]. A comparison of US and Chinese populations further confirmed substantial differences in mutational frequencies across multiple genes[72].

Table 3 Comparison of differences in somatic mutations between Asian and non-Asian patients with gastric cancer and impact on the immunotherapy response

Somatic mutations	Racial differences: Asian *vs.* non-Asian	Impact on immunotherapy response
APC mutations	6.1% *vs.* 14.4%[62]	• Associated with poor immunotherapy response in colon cancer[63] • Has a vital role in gastric carcinogenesis[64]
PTEN loss	2.5% *vs.* 9.1%[62]	• Causes immune suppression and poorer responses to PD-1 inhibitors[65]
ARID1A mutations	20.7% *vs.* 32.1%[62]	• Associated with increased PD-L1 expression and higher TMB, leading to enhanced immunotherapy responses[66]
KMT2A mutations	4.0% *vs.* 12.4%[62]	• Associated with enhanced immunogenicity, increased infiltration of immune cells, higher levels of immune cell cytotoxicity, and potentially associated with a more favorable response to ICI therapy[67,68]
PIK3CA mutations	9.6% *vs.* 18.5%[62]	• Increases tumor sensitivity by upregulating PD-L1 and recruiting immune cells[69] • Yet also drive immune evasion and resistance through activation of immunosuppressive pathways[70,71]

ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden.

APC mutations are associated with immunotherapy resistance and gastric cancer progression

The observed differences in somatic mutations between Asian and non-Asian populations may impact the immunotherapy response because some mutations are associated with immunotherapy sensitivity or resistance. For example, mutations in the *APC* gene have been associated with a poor response to immunotherapy in patients with colon cancer[63]. Specifically, individuals with *APC* mutations have a lower tumor mutation burden (TMB), reduced expression of immune checkpoint molecules (e.g., PD-1, PD-L1, and PD-L2), lower levels of microsatellite instability (MSI-H), and fewer infiltrating CD8+ T cells and follicular helper T cells[63]. Furthermore, studies have suggested that *APC* mutations also have a vital role in gastric carcinogenesis, like the role in colorectal carcinogenesis[64].

PTEN loss drives immune suppression and reduces PD-1 inhibitor efficacy

Loss of *PTEN* in tumors can promote the secretion of cytokines that suppress the immune system, which can reduce the number of T cells that successfully enter the tumor site and limit T cell expansion[73,74]. Patients with *PTEN*-mutant tumors have been shown to have poorer responses to PD-1 inhibitors compared to wild-type tumors[65].

ARID1A mutations are associated with an enhanced immunotherapy response in gastric cancer

ARID1A mutations, the frequency of which is higher in White patients than Asian patients with gastric cancer, appear to be associated with enhanced responses to immunotherapy. It has been established that the presence of PD-L1 in gastric cancer tumors is strongly associated with the loss of *ARID1A*[66]. *ARID1A* deficiency leads to an increase in PD-L1 expression by activating the PI3K/AKT/mTOR signaling pathway[66]. Cancers with *ARID1A* mutations exhibit a higher TMB, which contributes to increased immune activity in the gastrointestinal system[75]. As a result, these cancers have a greater potential for immunotherapy responsiveness.

KMT2 mutations are associated with an improved immunotherapy response in gastric and other cancers

Mutations in *KMT2* may also influence patient responses to immunotherapy. A comprehensive clinical and bioinformatic analysis was conducted across 10 cancer types, including esophagogastric cancer, using 4 ICI-treated cohorts (n = 2069)[67]. The study showed that patients with mutations in the *KMT2* gene family experienced better OS, PFS, and ORR when treated with ICIs. Moreover, tumors with *KMT2* mutations exhibited enhanced immunogenicity, increased infiltration of immune cells, and higher levels of immune cell cytotoxicity, suggesting a tendency toward a 'hot tumor' phenotype[67]. Another study reported that patients with solid tumors and mutations in the *KMT2* gene family (specifically, *KMT2A/C*-mutations) gain greater benefit from ICI therapy than patients with wild-type tumors[68]. These findings suggested a potential correlation between *KMT2* mutations and a more favorable response to ICI therapy.

Ambiguous role of PIK3CA mutations in immunotherapy outcomes, showing conflicting evidence of favorable and unfavorable correlations

PIK3CA mutations are relatively common in Epstein-Barr virus (EBV)-positive and microsatellite instability-high (MSI-H) gastric cancers[47] and are more common in White patients with gastric cancer[62]. *PIK3CA* mutations may upregulate PD-L1 *via* PI3K/AKT signaling, which could sensitize tumors to PD-1/PD-L1 inhibitors[69]. Gastric cancers with *PIK3CA* mutations are often accompanied by tumor-infiltrating lymphocytes in the peritumoral stroma, which are usually associated with enhanced responsiveness to immunotherapy and a favorable prognosis[76]. There is evidence that *PIK3CA* mutations are associated with better immunotherapy outcomes in elderly or *TP53*-mutated gastric cancer patients[77]. However, some studies showed that constitutive PI3K signaling can promote immunosuppressive mechanisms, such as recruitment of regulatory T cells (Tregs) and MDSCs, potentially dampening immunotherapy efficacy. *PIK3CA* mutations lead to activation of the PI3K pathway, which may contribute to resistance to ICIs by promoting tumor cell survival and immune evasion[70,71]. It has been reported that a subset of *PIK3CA*-mutant gastric cancers exhibit lower immune cell infiltration and consequently poorer survival outcomes[78].

Future studies are needed to confirm whether one or more of these somatic mutations have a role in the variation of immunotherapy efficacy among different ethnic groups. However, the presence of these genetic differences highlights the need for personalized treatment approaches that consider the unique molecular profiles of patients from different ethnic backgrounds. This phenomenon bears parallels to the development of EGFR-targeted therapies in non-small cell lung cancer. Initial clinical trials demonstrated superior efficacy among Asian populations, which was subsequently shown to be attributable to the higher frequency of *EGFR* mutations in Asian populations than Western populations[79,80].

Differences in molecular subtypes between Asian and non-Asian patients with gastric cancer

Gastric cancer is a heterogeneous disease with multiple molecular subtypes, each with distinct biological and clinical characteristics. The Cancer Genome Atlas (TCGA) project and the Asian Cancer Research Group (ACRG) have proposed novel classifications of gastric cancer based on molecular profiling of tumors[47,81]. The TCGA project has identified four major

molecular subtypes of gastric cancer: EBV-positive; MSI-H; genomically stable (GS); and CIN subtypes[47]. Similarly, the ACRG also described four molecular subtypes of gastric cancer based on sequencing analysis of 300 tumors: MSI subtype; microsatellite stable with epithelial-to-mesenchymal transition features (MSS/EMT); MSS/TP53 mutant; and MSS/TP53 wild-type[81].

Molecular subtype distribution varies across gastric cancer populations and regions

Studies have shown that the distribution of molecular subtypes of gastric cancer varies between populations (**Table 4**). A study that compared MSI in Japanese and European American patients showed that the frequency of MSI in Japanese gastric carcinoma specimens was higher than specimens from American patients of European descent (39% *vs.* 20%, respectively) and this difference was more significant in advanced gastric tumors (55% *vs.* 7.1%; $P = 0.02$)[82]. This finding suggests potential differences in the carcinogenesis process between these populations.

Assessment of the four molecular subtypes in Asian (Korea and Vietnam) and White populations (Canada, Poland, Germany, Russia, Ukraine, and USA) was performed using data from 295 subjects obtained from the National Cancer Institute TCGA and the Moffitt Cancer Center Total Cancer Care study[47,85]. Although the prevalence of the different molecular subtypes did not differ significantly between Asian and non-Asian populations, significant variations in the prevalence of different molecular subtypes were observed among countries (**Table 4**)[47,85]. Specifically, the CIN subtype was most stable across populations, with slightly higher prevalence in Poland (62.5%), the US (62.5%), and Germany (59%) than South Korea (45.2%) and Vietnam (54.5%). The GS subtype varied by country and was more common in some non-Asian populations (Ukraine, 35.9%; Poland, 18.8%; Russia, 18.1%; and Germany, 15.4%) than Asian populations (Vietnam, 29.5%; and South Korea, 6.5%). The additive incidence of MSI or EBV-positive GCs was approximately 20%–30% across the countries with South Korea an outlier (48.4% of GCs MSI or EBV-positive)[47,85].

However, the Asian cohort in the TCGA study consisted of only 75 patients, all of whom were from South Korea or Vietnam, which limits generalizability to all Asian subgroups[47,85]. In addition, it is unclear whether the TCGA molecular classification can be extrapolated into metastatic gastric cancers because most patients enrolled in the sequencing studies had locally advanced disease[47,81,89]. Therefore, these findings should be interpreted with caution and not overread and further data are needed.

Differences in the distribution of molecular subtypes between populations of gastric cancer patients may contribute to racial differences in immunotherapy outcomes. The presence of MSI-H and EBV in gastric cancer has been linked to a better response to ICIs[83,84,88]. In contrast, GS and CIN tumors typically have fewer infiltrating cytotoxic T cells. CIN tumors commonly display T-cell exclusion and are less likely to respond to PD-1/PD-L1 inhibitors than MSI-H or EBV-positive tumors[86,87]. This finding suggests that differences in molecular subtypes may account to some extent for the observed racial differences in ICI efficacy. However, the discrepancy between the subtype distribution and observed responses highlights the complexity of the factors influencing ICI treatment efficacy.

Differences in tumor immunity between Asian and non-Asian patients with gastric cancer

T cell activation is higher and FOXP3 is lower in non-Asian compared to Asian patients

The tumor microenvironment has a crucial role in modulating the response to immunotherapy. Several studies have

Table 4 Comparison of differences in molecular subtype distribution between Asian and non-Asian patients with gastric cancer and impact on immunotherapy response

Molecular subtype distribution	Differences across countries	Impact on the immunotherapy response
Incidence of MSI	39.0% in Japanese *vs.* 20.0% in European American[82]	• MSI is associated with a better immunotherapy response[83,84]
Incidence of CIN	South Korea 45.2%, Vietnam 54.5% *vs.* Poland 62.5%, US 62.5%, Germany 59.0%[47,85]	• CIN gastric cancers commonly display T-cell exclusion and respond less effectively to ICIs compared to MSI-H and EBV-positive tumors[86,87].
Incidence of GS	Vietnam 29.5%, South Korea 6.5% *vs.* Ukraine 35.9%, Poland 18.8%, Russia 18.1%, Germany 15.4%[47,85]	• GS tumors are associated with fewer infiltrating cytotoxic T cells and are less likely to respond to ICIs[86,87].
Additive incidence of MSI or EBV-positive	South Korea 48.4% *vs.* US 29.1%, Germany 25.7%, Poland 18.7%[47,85]	• MSI or EBV-positive gastric cancers are linked to a better response to ICIs[83,84,88].

CIN, chromosomal instability; EBV, Epstein-Barr virus; GS, genomically stable; ICI, immune checkpoint inhibitor; MSI, microsatellite instability.

shown that differences in tumor immunity may exist between Asian and non-Asian patients with gastric cancer (**Table 5**). A comprehensive study involving 1016 patients with gastric cancer from 6 Asian and 3 non-Asian cohorts revealed distinct gene expression profiles, indicating differences in the number and characteristics of different T cell subtypes in the tumor microenvironment[90]. Tumors from non-Asian patients were significantly enriched in T cell-related signatures, including CTLA-4 signaling. Immunohistochemical analysis confirmed higher expression of T cell markers (CD3, CD45R0, and CD8) and lower expression of the immunosuppressive T-regulatory cell marker (FOXP3) in non-Asian patients compared to Asian patients ($P < 0.05$)[90]. These findings suggested a more active T cell immune response in non-Asian patients with gastric cancer. A high infiltration of activated T cells within the tumor microenvironment is typically correlated with enhanced treatment efficacy in immunotherapy, whereas a predominance of immunosuppressive T cells often impedes therapeutic success[91,92]. The observed disparities in T cell subtypes between Asian and non-Asian populations are evidently inconsistent with the patterns observed in immunotherapy outcomes.

However, the tumor immune microenvironment is complex and varies by country and region, even within non-Asian populations. Analysis of biopsies from 95 European and 56 Latin American gastric cancer patients revealed two main immune clusters. Cluster 1 displayed heterogeneous infiltration and three subclusters: 1A (enriched for mast cells, B cells, and exhausted CD8+ T cells); 1B (very low immune-cell number); and 1C (dominated by macrophages and dendritic cells). Cluster 2 showed higher scores for B cells, CD8 T cells, cytotoxic cells, dendritic cells, neutrophils, natural killer cells, and T regulatory cells. The investigators reported that cluster 1A generally exhibited lower immune cell scores than cluster 2 and was enriched for antigen presentation, cytotoxicity, and immune cell adhesion and migration. In contrast, cluster 2 exhibited high inflammation and abundant T cells but lacked antigen presentation and cytotoxicity, suggesting an immune response targeting the microbiome rather than tumor cells[98]. This finding suggested that other constituents of the immune microenvironment and extrinsic factors beyond the immune milieu, collectively influence the complex immune response and ultimately determine the efficacy of immunotherapy in addition to T cells.

It is noteworthy that genetic variants in immune checkpoint genes may also exert ethnic-specific effects on clinical outcomes. A study investigating the prognostic significance of single nucleotide polymorphisms (SNPs) in immune checkpoint genes among patients with localized advanced gastric cancer from the US and Japan revealed contrasting results[93]. Specifically, carriers of the T allele of CD73 rs6922 in the US cohort exhibited significantly shorter OS compared to the G/G genotype (HR, 2.48; $P = 0.03$), whereas the same allele was associated with a longer OS (HR, 0.58; $P = 0.04$) in both univariate and multivariate analyses in the Japanese cohort. This divergent impact on OS between the two populations was statistically significant ($P = 0.002$)[93]. Nevertheless, due to limited available data, further research is needed to clarify these race-specific genetic influences.

Differences in tumor-associated neutrophils and macrophages between Asian and non-Asian patients may influence the immunotherapy response

Studies have shown that gastric tumors from Japanese patients have a significantly higher number of cells positive

Table 5 Comparison of differences in tumor immunity between Asian and non-Asian patients with gastric cancer and impact on immunotherapy response

Tumor immunity	Racial differences	Impact on the immunotherapy response
T cell subtypes	Higher expression of T cell markers (CD3, CD45R0, and CD8) and lower expression of the immunosuppressive T-regulatory cell marker FOXP3 in non-Asian *vs.* Asian patients ($P < 0.05$)[90]	• Activated T cells are associated with improved outcomes; suppressive T cells can lower effectiveness[91,92]. • Racial differences are inconsistent with treatment results, suggesting involvement of other immune and non-immune factors, and genetic differences in immune checkpoint genes[93].
Tumor-associated neutrophils and macrophages	Higher expression of the neutrophil marker (CD66b) in Japanese *vs.* White patients and higher expression of the macrophage marker (CD68) and higher CD68:CD3 ratios in White *vs.* Asian patients[90]	• Intratumoral neutrophils have high levels of PD-L1; inhibition of neutrophil-associated PD-L1 by PD-1 inhibitors can produce antitumor effects[94] • CD68+STING+ macrophages are associated with resistance to anti-PD-1/PD-L1 therapy[95].
PD-L1 CPS positivity	PD-L1 CPS prevalence is similar in Asian and non-Asian populations with gastric cancer[13,96,97].	• Higher PD-L1 expression predicts improved immunotherapy outcomes[4,5,8,13,96].

CPS, combined positive score; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

for the neutrophil marker (CD66b) than tumors from White patients[90]. CD66b, a marker commonly present in neutrophils, is characteristic of granulocyte activation. Intratumoral neutrophils exhibit considerably higher levels of the immunosuppressive molecule (PD-L1) than peripheral or non-tumorous neutrophils[94]. This finding leads to the suppression of T cell immunity within tumors. By inhibiting neutrophil-associated PD-L1 with PD-1 inhibitors, T cells remain in an activated state, resulting in antitumor effects[94].

Tumors from White patients with gastric cancer were shown to be significantly enriched in the macrophage marker (CD68) and had significantly higher CD68:CD3 ratios compared to tumors from Asian patients[90]. The STING pathway, which regulates the innate and adaptive immune system, is activated in macrophages in response to the presence of gastric cancer cells[99]. CD68+STING+ macrophages have been associated with resistance to anti–PD-1/PD-L1 therapy[95]. Therefore, future studies are needed to elucidate the potential role of differences in tumor infiltration by neutrophils and macrophages between Asian and non-Asian populations in racial disparities in immunotherapy response among patients with gastric cancer.

Comparable PD-L1 positivity in Asian and non-Asian patients with gastric cancer

PD-L1 expression is a predictive biomarker to select patients likely to benefit from immunotherapy. Clinical trials, such as CheckMate-649, KEYNOTE-859, and ORIENT-16, have demonstrated that patients with PD-L1-positive gastric cancer tend to have better responses and improved survival with PD-1/PD-L1 inhibitors[4,5,8,13,16]. No significant differences were observed in the prevalence of PD-L1 combined positive score (CPS) between global and Asian populations in the three pivotal phase 3 clinical trials assessing PD-L1 expression using the CPS. The percentages of patients with a CPS ≥ 1 were 82%, 78.2%, and 84% in the CheckMate-649, KEYNOTE-859, and ORIENT-16 studies, respectively. Notably, CheckMate-649 and KEYNOTE-859 were global studies, whereas ORIENT-16 was conducted exclusively in a Chinese population. Although the Chinese subgroup showed a slightly higher CPS-positive rate than the global population in CheckMate-649 (CPS ≥ 1: 88% *vs.* 82%) and KEYNOTE-859 (CPS ≥ 1: 81% *vs.* 78.2%)[13,96], this difference may be attributed to the limited sample size of the subgroup. A retrospective study analyzed PD-L1 expression in tumor samples from 574 gastric cancer patients (329 from Korea and 245 from the US) collected between 2003 and 2017[97]. The overall prevalence of CPS ≥ 1 was 67.4% with similar PD-L1-positivity observed in South Korean (68.7%) and US (65.7%) samples. These findings suggested no significant difference in PD-L1 CPS expression between Asian and non-Asian populations. Considering the observed differences in the tumor immune microenvironment between Asian and non-Asian patients with gastric cancer, Mao et al.[100] developed an Asian-specific immune-related gene prognostic index based on sequencing analysis of tumors from 364 Asian patients with gastric cancer. Mao et al.[100] found that Asian patients had unique immune cell compositions in the tumor microenvironment compared to non-Asian patients. Mao et al.[100] also developed and validated a prognostic model based on seven immune-related genes that could effectively predict survival specifically in Asian patients with gastric cancer.

Differences in *H. pylori* infection between Asian and non-Asian patients with gastric cancer

H. pylori infection is a well-established risk factor for gastric cancer and is more prevalent in Asian populations than in non-Asian populations[101]. *H. pylori* has emerged as the most significant infectious cause of cancer worldwide with an ASIR of 8.7 cases per 100,000 person-years and an estimated 810,000 attributable cases of cancer. The ASIR of *H. pylori* infection-related cancer was highest in eastern Asia, reaching 17.6. In contrast, the ASIR of *H. pylori* infection-related cancer was lowest in northern Europe and North America (3.1 and 2.8, respectively)[102].

Differences in the prevalence of *H. pylori* infection may contribute to the observed variations in the immunotherapy response between Asian and non-Asian patients with gastric cancer. Two US-based retrospective studies involving patients treated with ICIs for gastric cancer showed that patients with *H. pylori* infection had a significantly shorter median PFS and OS[103,104]. These results suggested that *H. pylori* infection is associated with inferior survival outcomes in ICI-treated patients with gastric cancer. In contrast, a larger study from Peking University Cancer Hospital & Institute in China showed that *H. pylori*-positive patients had a significantly longer PFS and showed a trend toward improved OS with ICI therapy[105]. These contradictory findings suggested that the impact of *H. pylori* infection on the immunotherapy response may differ between Asian and non-Asian populations.

Studies have shown that there is considerable variation among *H. pylori* strains isolated from individuals from different geographic regions and the host-*H. pylori* strain interactions likely differ in relation to regulation of immune and inflammatory responses in the gastric mucosa[106-108]. *H. pylori* strains from East Asia have an 'East Asian' type of *CagA* that is more potent and predominantly comprises a single type, while the Western type *CagA* is less active and comprises many different types generated by intragenomic recombination[106,108]. East Asian *H. pylori* strains can induce significantly higher secretion of IL-8, a major chemotaxin that elicits inflammatory responses, than Western strains[106]. Moreover, Asian strains more often carry putative virulence factors (e.g., *hopQ type I*, *vacA s1*, and *m1* genotypes and *CagA*-positive), which are associated with higher gastric mucosal inflammation in

infected individuals[107]. *H. pylori* infection in Asian populations, which often exhibit higher inflammatory levels, may therefore contribute to observed differences in immunotherapy efficacy between Asian and non-Asian groups. However, further studies are needed to clarify the mechanisms underlying these disparities.

The effects of *H. pylori* on the tumor microenvironment in patients with gastric cancer remain controversial and have been extensively reviewed elsewhere[109]. *H. pylori* infection can trigger the expression of PD-L1 and infiltration of MDSCs, which can lead to immune escape. Hedgehog (HH) signaling, which is activated by infection, induces PD-L1 expression and the proliferation of gastric cancer cells. This results in cancer cells becoming resistant to immunotherapy[109]. In contrast, *H. pylori* virulence factors, including CagA, VacA, BabA, and HP-NAP, can act as antigens or adjuvants to enhance tumor immunity. The stimulation of autoantibodies during antigen processing and presentation, followed by T cell activation and proliferation, can improve the host antitumor immune response, which results in cancer cell elimination and suppresses metastasis[109]. The mechanistic role of *H. pylori* infection in modulating immunotherapy response and the contribution to the observed differences in immunotherapy efficacy between Asian and non-Asian populations remain to be elucidated.

Differences in dietary habits and the gut microbiome between Asian and non-Asian patients with gastric cancer

Fermented foods, red meat, and dairy intake shape ethnic variations in the gut microbiota composition

Dietary habits and the gut microbiome have emerged as important modulators of immune function and cancer therapy response[110]. Asian diets are comprised of higher consumption of fermented foods (e.g., kimchi and miso) and greater intake of green tea and soy products[111]. In contrast, non-Asian diets typically include higher consumption of red meat and processed foods and low intake of fermented foods and probiotics[112].

Dietary factors, such as overall diet quality and intake of specific food components, may have a role in ethnic differences in the gut microbiome composition and contribute to disparities in gut microbiome-related health outcomes among racial and ethnic groups[113]. Asian populations tend to have a higher abundance of *Bifidobacterium* and *Lactobacillus* species[114-117]. Moreover, some studies have reported greater microbial diversity in Asian populations compared to Western populations[114,116,118]. Consumption of dairy and alcohol appears to contribute to differences in *Bifidobacterium* abundance between White and Japanese populations in the US. Compared to White individuals with the highest consumption of both dairy and alcohol, Japanese Americans had a higher abundance of *Bifidobacterium*, which was positively mediated by lower alcohol intake and would have been even higher if not for the negative mediation by a lower dairy intake[119]. This higher abundance of *Bifidobacterium* in Asian populations may partially contribute to the better efficacy of immunotherapy in Asians than in non-Asians.

Gut microbiome variations may influence immunotherapy outcomes in gastric cancer across ethnicities

Mounting evidence suggests that the gut microbiome can modulate systemic immune responses[120]. Therefore, racial differences in dietary habits and gut microbiome composition may have a role in the observed differences in immunotherapy response between Asian and non-Asian patients with gastric cancer. For example, diets rich in fermented foods and fiber increase gut microbiome diversity and enhance immune responses[121]. Certain bacterial species, including *Akkermansia muciniphila* and *Bifidobacterium* species, are associated with enhanced immunotherapy efficacy[122]. *Bifidobacterium* species are commonly used as probiotics because they can generate short-chain fatty acids (SCFAs) and exhibit beneficial immunomodulatory effects[123]. The microbiome can influence both local and systemic immune responses and may also impact the efficacy of immunotherapy. It has been shown that the antitumor sensitivity of monoclonal antibodies targeting PD-1 or PD-L1 can be affected by *B. longum* and *B. breve*[124]. Furthermore, 16S ribosomal RNA sequencing analysis to examine the impact of various commensal microbiota on antitumor immunity revealed that commensal *Bifidobacterium* species can enhance antitumor immunity and improve the efficacy of anti-PD-L1 therapy[125]. The study also showed that *Bifidobacterium* enhanced dendritic cell function, leading to better CD8+ T cell priming and accumulation in the tumor microenvironment. Oral administration of *Bifidobacterium* alone or combined with PD-L1-specific antibody therapy significantly improves tumor control[125]. Another study investigated the association between the gut microbiome and clinical responses to anti–PD-1/PD-L1 immunotherapy in patients with gastrointestinal cancer[126]. Patients with a favorable response to treatment had a higher abundance of *Prevotealla*, *Bifidobacterium*, and *Lachnospiraceae* species. Gut bacteria capable of producing SCFAs are positively associated with treatment response. Differences in microbial pathways related to nucleoside and nucleotide biosynthesis, lipid biosynthesis, sugar metabolism, and SCFA fermentation were observed between responders and non-responders[126]. A metagenomic study of the gut microbiome in metastatic or unresectable HER2-negative GC/GEJC patients also showed that a higher relative abundance of *Lactobacillus* was associated with greater microbiome diversity and a significantly better response to anti-PD-1/PD-L1 immunotherapy with a trend toward improved PFS[127]. However, there are limited comparative data on the microbiome composition and immunotherapy response between Asian and non-Asian populations. The role of the gut microbiome in shaping immune responses and the interactions with dietary factors warrant further investigation in large cohorts of patients with gastric cancer.

Demographic and clinicopathological characteristics
Age of onset: Asian patients tend to be younger at the time of diagnosis[36,37]
Sex ratio: Higher male-to-female ratio in Asian patients[40,41]
Tumor location: Higher prevalence of proximal gastric tumors in White patients[36,37,40,46]
Histological subtype: Asian patients tend to present with intestinal-type rather than diffuse-type histology[51]
Disease stage: Countries such as Japan and South Korea have higher proportion of early-stage gastric cancer[52,53]
Tumor burden: Tumor burden at diagnosis is lower in patients from Japan[55-57]
Somatic mutations[62]
Higher APC mutations in White patients
Higher PTEN loss in White patients
Higher ARID1A mutations in White patients
Higher KMT2A mutations in White patients
Higher PIK3CA mutations in White patients
Molecular subtype distribution
MSI: 39.0% in Japanese vs. 20.0% in European American[82]
CIN: South Korea 45.2%, Vietnam 54.5% vs. Poland 62.5%, US 62.5%, Germany 59.0%[47,85]
GS: Vietnam 29.5%, South Korea 6.5% vs. Ukraine 35.9%, Poland 18.8%, Russia 18.1%, Germany 15.4%[47,85]
Additive incidence of MSI or EBV-positive: South Korea 48.4% vs. US 29.1%, Germany 25.7%, Poland 18.7%[47,85]
VS.
Potential factors contributing to ethnic differences in first-line immunotherapy response in patients with advanced HER2-negative gastric cancer
T cell subtypes: Higher expression of T cell markers (CD3, CD45R0, CD8) and lower expression of the immunosuppressive T-regulatory cell marker FOXP3 in non-Asian vs. Asian patients[90]
Tumor-associated neutrophils and macrophages: Higher expression of neutrophil marker CD66b in Japanese vs. White patients, higher expression of macrophage marker CD68 and higher CD68/CD3 ratios in White vs. Asian patients[90]
PD-L1 CPS prevalence: Similar in Asian and non-Asian patients[13,96,97]
Tumor immunity
Dietary habits: Higher intake of fermented food, red meat, and dairy in Asians vs. non-Asians[111]
Gut microbiome: Higher abundance of Bifidobacterium in Asians vs. non-Asians[114-117]
Dietary habits and gut microbiome
Higher prevalence of H. pylori infection in Asians than in non-Asians[101]
East Asian type of CagA is more potent[106,108]
Asian strains more often carry putative virulence factors, which are associated with higher gastric mucosal inflammation[107]
Helicobacter pylori infection

Figure 1 Potential factors contributing to ethnic differences in the immunotherapy response in Asian versus non-Asian patients with HER2-negative gastric cancer. APC, adenomatous polyposis coli; CIN, chromosomal instability; CPS, combined positive score; EBV, Epstein-Barr virus; GS, genomically stable; MSI, microsatellite instability; PD-L1, programmed death-ligand 1.

Critical view

The emerging evidence summarized in this review suggests that the response to immunotherapy in patients with gastric cancer varies between Asian and non-Asian populations (**Figure 1**). This review represents the first extensive summary of the factors that may account for the variations in immunotherapy efficacy between Asian and non-Asian populations, including differences in demographic and clinicopathologic characteristics, somatic mutations, molecular subtypes, tumor immunity, *H. pylori* infection, dietary habits, and gut microbiota composition. One or more of these factors may serve as predictors of the immunotherapy response in patients with gastric cancer. Understanding the mechanisms underlying racial disparities in the immunotherapy response could help tailor treatment strategies for different patient populations and improve patient outcomes.

In future clinical study designs it may be worth considering prospectively stratifying randomized clinical trials by geographic region and ethnicity, ensuring that the sample sizes in each major ethnic stratum are sufficient to provide reasonable power for clinically meaningful subgroup analyses, and when appropriate, preplanning interaction tests to assess treatment-by-ethnicity heterogeneity. It is likewise crucial to pursue translational mechanistic research. Integrating genomics, immune profiling, microbiome analysis, and related techniques enables comprehensive characterization of tumor intrinsic features, the immune microenvironment, specific driver mutations, and biomarker expression across different ethnic groups. Using functional approaches, such as *in vitro* T-cell reactivity assays and organoid or patient-derived xenograft (PDX) co-culture systems, allows discovery and validation of actionable targets and can directly inform biomarker-driven clinical research in defined populations.

Acknowledgements

Editorial support for this review was provided by Rude Health Consulting Limited and was funded by MSD China.

Grant support

This manuscript was funded by MSD China. This work was supported by grants from Non-communicable Chronic Diseases-National Science and Technology Major Project (Grant No. 2024ZD0520600).

Conflict of interest statement

Meng Chen and Jing Qian are employees of MSD China; the other authors have no conflicts of interest to declare.

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Cite this article as: Zhao C, Ye S, Chen M, Qian J, Xu J. First-line immunotherapy for advanced HER2-negative gastric cancer: differences between Asian and non-Asian patients. Cancer Biol Med. 2026; 23: 201-217. doi: 10.20892/j.issn.2095-3941.2025.0398