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REVIEW ARTICLE

Does immunotherapy change the treatment paradigm in metastatic gastric cancer?

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Abstract

Gastric cancer represents one of the leading causes of cancer-related death worldwide. Even if the last decade has witnessed an improvement in surgical and systemic treatments, with an increase of overall life expectancy, survival rates still remain unsatisfactory, especially for patients with metastatic disease. Systemic therapies represent the gold standard in the management of stage IV gastric cancer. In this scenario, the availability of effective second and third lines has represented for a long time the only hope to offer an overall survival improvement to these patients. Recently, the advent of immune checkpoint inhibitors has involved also gastric cancer with encouraging efficacy data in the metastatic setting, becoming integral part of the management of selected patients.

Keywords Metastatic gastric cancer · Systemic treatment · Immunotherapy · Clinical practice

Introduction

Gastric cancer still remains a global health burden, representing the 5th most common cancer and the 3rd leading cause of cancer-related death worldwide [1]. In western countries, most patients present advanced disease at diagnosis because of the belated clinical presentation and the lack of national screening programs. Undoubtedly, in the last decade, deeper knowledge of the disease molecular features, multidisciplinary management of patients, improvement of surgical and systemic treatments, early activation of simultaneous care and nutritional support have improved the overall life expectancy of these patients. However, survival rates still remain unsatisfactory, with a median survival that rarely exceed 12 months and only 5% of patients alive at 5 years in stage IV [2, 3].

In the metastatic setting, systemic therapies play the leading role. In first line, the combination of platinum plus fluoropyrimidine have represented hitherto the standard of care, having demonstrated a statistically significant benefit in overall survival (OS) compared to BSC in HER2-negative patients (median OS 9–11 months) [4]. This survival gain achieves 14–16 months with the addition of the monoclonal antibody anti-HER2 trastuzumab in patients with HER2-positive disease [5].

Oral fluoropyrimidines (i.e., capecitabine) and oxaliplatin are approved alternatives of 5-fluorouracil and cisplatin, respectively, having demonstrated non-inferiority in terms of efficacy and better tolerance [6–8].

In second line, the anti-VEGFR-2 ramucirumab, alone or in combination with paclitaxel, has showed a statistically significant survival benefit in previously treated GC patients compared to BSC, with a gain of 1.4 and 2.2 in median overall survival (mOS), respectively [9, 10]. In patients with good clinical conditions, third line chemotherapy has demonstrated to be superior in comparison with best supportive care (BSC). Trifluridine/tipiracil showed a statistically significant improvement in overall survival compared to placebo with a reduction of 31% in the risk of death. Also progression-free survival (PFS) was significantly improved

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(HR of 0.57; $p < 0.0001$) [11]. FOLFIRI is another well-established option in third line with a favorable safety profile in patients with preserved performance status and organ function [12, 13].

Except for HER2 and VEGFR-2, all the trials investigating target therapies in gastroesophageal/gastric cancer (GEJ/GC) showed underwhelming results [14–17].

For a long time, the only hope to offer an overall improvement in survival to advanced gastric cancer patients has been the availability of effective second and third lines of treatment. Recently, the advent of immune checkpoint inhibitors has finally involved also gastric cancer with several trials that have reported encouraging data of efficacy with a manageable safety profile in the metastatic setting, becoming integral part of the management of selected patients.

In this paper we provide an overview of the main studies that addressed the use of immunotherapies in metastatic GEJ/G adenocarcinoma, trying to translate the available results in clinical recommendation potentially useful in clinical practice.

Immunotherapy in first line

The Keynote-062 was the first phase III trial evaluating the efficacy of immune checkpoint inhibitors in the first line setting [18] (Table 1). In this study, 753 patients with previously untreated, advanced GEJ/gastric cancer programed death-ligand 1 (PD-L1) combined positive score (CPS) ≥ 1, were enrolled in a ratio 1:1:1 to receive pembrolizumab alone, pembrolizumab plus chemotherapy or chemotherapy plus placebo every three weeks. Chemotherapy consisted in cisplatin plus fluorouracil/capecitabine. Primary endpoints were OS and PFS in PD-L1 CPS ≥ 1 and PD-L1 CPS ≥ 10 population. Pembrolizumab resulted not inferior to chemotherapy for OS in patients with CPS ≥ 1 (mOS 10.6 vs 11.1 months; HR 0.91; non-inferiority margin 1.2) with relatively shorter median PFS (2.0 months vs 6.4 months; HR 1.66) and lower ORR (15% vs 37%). In patients with CPS ≥ 10, pembrolizumab prolonged OS compared to chemotherapy (mOS 17.4 vs 10.8 months; HR 0.69), but this difference was not statistically tested because superiority was not demonstrated. The late separation of survival curves is comparable to what observed in the Keynote-061 trial [19], confirming the long-term survival benefit deriving from pembrolizumab. However, the greatest benefit in survival was recorded in MSI-H tumors with PD-L1 CPS ≥ 1 (mOS not reached with pembrolizumab vs 8.5 months with chemotherapy, HR 0.29). Pembrolizumab plus chemotherapy resulted not superior for OS compared to chemotherapy either in patients with CPS ≥ 1 (12.5 vs 11.1 months; HR 0.85) or CPS ≥ 10 (12.3 vs 10.8 months; HR 0.85). Even this time, OS was enriched in patients with microsatellite instability and PD-L1 CPS ≥ 1 (mOS not reached with pembrolizumab plus chemotherapy vs 8.5 months with chemotherapy alone). Nevertheless, the predictive value of PD-L1 CPS ≥ 10 was maintained even after exclusion of MSI-high tumors, suggesting the independent value of this biomarker. The updated results with additional 25 months of follow-up recently presented at the ASCO Gastrointestinal Cancers Symposium confirmed what was observed in the primary analysis [20].

Actually, the combination of pembrolizumab plus chemotherapy (CF/CAPOX) in first line is under investigation in the Keynote-859 trial, whose results are waiting [21].

Based on the results of nivolumab in heavily pretreated patients [22] and the assumption that oxaliplatin can enhance the activity of immune checkpoint inhibitors, the ATTRACTION-4 trial was conducted to evaluate the efficacy and safety of nivolumab plus chemotherapy (SOX/CapeOX) in previously untreated advanced or recurrent GEJ/gastric cancer patients [23] (Table 1). Similarly to ATTRACTION-2, this study enrolled only Asian patients. The co-primary endpoints, OS and PFS, were designed for all-comers, rather than a specific CPS value. At the interim analysis, nivolumab plus chemotherapy improved PFS compared to chemotherapy alone (mPFS 10.5 vs 8.3 months, respectively. HR 0.68, $p = 0.0007$). However, no statistically significant differences in OS were observed in the investigational arm compared with the control arm (mOS 17.5 vs 17.2 months, respectively. HR 0.90, $p = 0.257$). The objective response rate (ORR) was 57.5% in the nivolumab arm versus 47.8% in the placebo arm ($p = 0.0088$), with 19.3% of patients who experienced complete response ($n = 70$), and a disease control rate (DCR) of 71.8%. In both arms, the most common treatment-related adverse events were nausea, diarrhea and peripheral neuropathy.

More recently, the results of the global phase III CheckMate 649 trial were presented [24, 25] (Table 1). In this trial, 2031 patients with previously untreated advanced/unresectable or metastatic esophageal/GEJ/gastric adenocarcinoma were randomly assigned to receive nivolumab plus XELOX/FOLFOX ($n = 789$); XELOX/FOLFOX ($n = 833$); or nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab at 240 mg every 2 weeks ($n = 409$). Initially, the combination of nivolumab (N) plus chemotherapy (CT) and chemotherapy alone were compared with dual primary endpoints OS and PFS in PD-L1 CPS ≥ 5 patients. The updated results at 24 months of follow-up showed that, in this group, the combination of nivolumab plus chemotherapy provides a statistically significant benefit in overall survival (mOS 14.4 months) compared to chemotherapy alone (mOS 11.1 months) (HR 0.69, $p < 0.0001$) [26]. With longer follow-up, the OS and PFS improvement was confirmed even in the overall population (mOS 13.8 N + CT vs 11.6 CT, HR 0.79. mPFS 7.7 N + CT

Table 1 Study information and characteristics of trials (first line)

Trial	Tumor location	Countries	Intervention groups	PD-L1 assay	Primary endpoints	Results
Keynote-062 Phase III NCT02494583	GEJ/Gastric adenocarcinoma HER2-negative	America Europe Asia Oceania	**Control arm** Cisplatin 80 mg/m^2 (day 1) plus 5FU 800 mg/m^2 (days 1–5) q3w, or Capecitabine 1000 mg/m^2 BID (days 1–14) q3w **Experimental arms** Pembrolizumab 200 mg (day 1) q3w Pembrolizumab 200 mg (day 1) q3w plus chemotherapy (as above)	IHC 22C3 PD-L1 status evaluated in all patients	OS CPS ≥ 1 CPS ≥ 10 PFS CPS ≥ 1	**OS Pembro vs CT** - CPS ≥ 1: mOS 10.6 m vs 11.1 m; HR 0.91 - CPS ≥ 10: mOS 17.4 m vs 10.8 m; HR 0.69 **OS CT + Pembro vs CT** - CPS ≥ 1: mOS 12.5 m vs 11.1 m; HR 0.85 - CPS ≥ 10: mOS 12.3 m vs 10.8 m; HR 0.85 **PFS Pembro vs CT** CPS ≥ 1: 2 m vs 6.4 m; HR 1.66 **PFS CT + Pembro vs CT** CPS ≥ 1: 6.9 m vs 6.4 m; HR 0.84
ATTRACTION-4 Phase III NCT02746796	GEJ/Gastric adenocarcinoma HER2-negative	Asia	**Control arm** Oxaliplatin 130 mg/m^2 (day 1) plus oral S-1 40 mg/m^2 (days 1–14), or capecitabine 1000 mg/m^2 BID (days 1–14) q3w **Experimental arm** Nivolumab 360 mg q3w plus chemotherapy (as above)	IHC 28–8 pharmDx kit (Dako, Santa Clara, CA, USA)	OS and PFS in all patients regardless CPS value	**OS Nivo vs CT** mOS 17.5 m vs 17.2 m; HR 0.90 **PFS nivo vs CT** mPFS 10.5 m vs 8.3 m; HR 0.68
Checkmate 649 Phase III NCT02872116	Esophageal GEJ Gastric adenocarcinoma HER2-negative	America Europe Asia Oceania	**Control arm** Capecitabine 1000 mg/m^2 BID (days 1–14) plus oxaliplatin 130 mg/m^2 (day 1) q3w, or Leucovorin 400 mg/m^2 (day 1), 5FU bolus 400 mg/m^2 (day 1), 5FU 1200 mg/m^2 (days 1–2) plus oxaliplatin 85 mg/m^2 (day 1) q2w **Experimental arm** Nivolumab 240 mg q2w or 360 mg q3w plus chemotherapy (as above)	ICH 28–8 pharmDX kit (Dako, Santa Clara, CA) PD-L1 status evaluated in all patients	OS and PFS in patients with PD-L1 CPS ≥ 5	**OS Nivo + CT vs CT** (minimum FU 12 months) mOS 14.4 m vs 11.1 m; HR 0.71 **PFS Nivo + CT vs CT** (minimum FU 12 months) mPFS 7.7 m vs 6 m; HR 0.68

GEJ gastroesophageal junction; *q3w* every 3 weeks; *q2w* every two weeks; *BID* bis in die, twice a day; *PD-L1* programed death-ligand 1; *CPS* combined positive score; *5FU* 5-fluorouracil; *HER2* human epidermal growth factor receptor 2; *IHC* immunohistochemistry; *OS* overall survival; *mOS* median overall survival; *PFS* progression-free survival; *mPFS* median progression-free survival; *m* months; *Pembro* pembrolizumab; *Nivo* Nivolumab; *CT* chemotherapy; *FU* follow-up; *HR* hazard ratio; *vs* versus

vs 6.9 CT, HR 0.79) across all key subgroups. However, is interesting to note that both in the CPS ≥ 5 group and in all randomized population, patients with peritoneal metastases and low baseline albumin seems to have less benefit from the combination therapy compared to patients without peritoneal disease and normal values of albumin. OS and ORR benefit with N + CT was increased across higher PDL-1 CPS cutoffs (≥ 1, ≥ 5, ≥ 10). This gain was maintained also after exclusion of MSI-high patients, which confirm to have the highest benefit from the combination. Even PFS2 (progression-free survival on subsequent therapy) favored the N + CT arm with a reduction of 25% in risk of death or disease progression on subsequent therapies (mPFS2 12.2 N + CT vs 10.4 CT, HR 0.75). No new safety signals were identified. Differently from the above-mentioned results, the combination of nivolumab plus ipilimumab did not significantly improve OS or PFS in PD-L1 CPS ≥ 5 patients and in all randomly assigned patients compared to chemotherapy. As expected, the only subgroup who benefit from the doublet immunotherapy was represented by MSI-high patients, where mOS was not reached versus 10 months with chemotherapy alone (HR 0.28).

In patients with HER2-positive metastatic GEJ/gastric cancer, the Keynote-811 trial, comparing CF or CAPOX plus trastuzumab ± pembrolizumab administered every 3 weeks, showed a statistically significant benefit in terms of objective response in the pembrolizumab arm (74%, 95% CI confidence interval [CI] 66–82%) in comparison with the placebo arm (52%, 95% CI 43–61%) [27]. Median duration of response was 10.6 months for patients treated with pembrolizumab and 9.5 months for those treated with placebo. The adverse reaction profile was consistent with the known pembrolizumab safety profile.

Based on the results of Checkmate 649, on April 2021, the Food and Drug Administration (FDA) approved nivolumab in combination with fluoropyrimidine and platinum chemotherapy for all advanced/metastatic GEJ/gastric HER2-negative adenocarcinoma in first line, regardless of the PD-L1 CPS value. On June of the same year, the European Medicines Agency (EMA) approved nivolumab plus chemotherapy for PD-L1 CPS ≥ 5 patients in the same setting.

Based on the results of Keynote-811, on May 2021 the FDA granted accelerated approval to pembrolizumab in combination with trastuzumab, fluoropyrimidine and platinum for patients with unresectable/metastatic HER2-positive GEJ/gastric adenocarcinoma.

Guidelines recommendations for immunotherapies in first line are summarized in Table 2.

Immunotherapy in second line

In 2018, Shitara et al. presented the results of their phase III Keynote-061 trial on the efficacy of pembrolizumab monotherapy compared with paclitaxel in 592 patients with GEJ/gastric cancer who progressed on first line chemotherapy with platinum and fluoropyrimidine [19] (Table 3). The study did not meet its primary endpoint, demonstrating not statistically significant differences in overall survival between the two treatment arms in the PD-L1 CPS ≥ 1 population (mOS 9.1 vs 8.3 months in the pembrolizumab and in the paclitaxel group, respectively; HR 0.82, $p = 0.0421$). However, the benefit of pembrolizumab arises with a long-term follow-up, where the estimated proportion of patients alive at 12 and 18 months was 40% and 26% respectively, compared to 27% and 15% with paclitaxel. Besides, the plateau of the survival curve at nearby 20 months observed in the pembrolizumab group supports the long-term benefit for this ICI in some patients. Patients with PD-L1 CPS ≥ 10 and with MSI-high tumors (regardless the CPS value) treated with pembrolizumab demonstrated better survival rates compared to those in the paclitaxel arm (mOS 10.4 vs 8 months, HR 0.64; mOS not reached vs 8.1 months, HR

Table 2 Guidelines recommendations for immunotherapies in first line

Guideline	First line
NCCN (2022)	HER2-negative: FOLFOX/CAPOX + nivolumab is considered one of preferred regimen for patients with PD-L1 CPS ≥ 5 and is considered appropriate for patients with PD-L1 CPS 1–4 HER2-positive: Fluoropyrimidine (5FU iv or capecitabine) and cisplatin plus trastuzumab plus pembrolizumab is recommended regardless PD-L1 CPS value
ESMO (2016)	No recommendation for immunotherapies in first line
CSCO (2021)	HER2-negative: FOLFOX/XELOX + nivolumab is recommended for PD-L1 CPS ≥ 5 patients Pembrolizumab monotherapy can be considered for PD-L1 CPS ≥ 1 patients if exist chemotherapy contraindications
JGCA (2018)	No recommendation for immunotherapies in first line

NCCN National Comprehensive Cancer Network; *ESMO* European Society for Medical Oncology; *CSCO* Chinese Society of Clinical Oncology; *JCGA* Japanese Gastric Cancer Association; *HER2* human epidermal growth factor receptor; *PD-L1* programed death-ligand 1; *CPS* combined positive score; *5FU* 5-fluorouracil; *iv* intravenous; *FOLFOX* Leucovorin 400 mg/m2 (day 1), 5FU bolus 400 mg/m2 (day 1), 5FU 1200 mg/m2 (days 1–2) plus oxaliplatin 85 mg/m2 (day 1) q2w; *XELOX (CAPOX)* Capecitabine 1000 mg/m2 BID (days 1–14) plus oxaliplatin 130 mg/m2 (day 1) q3w

Table 3 Study information and characteristics of trials (second line)

Trial	Tumor location	Countries	Intervention groups	PD-L1 assay	Primary endpoints	Results
Keynote-061 Phase III NCT02370498	GEJ/Gastric adenocarcinoma HER2-negative who progressed on first line with platinum plus fluoropyrimidine	America Europe Asia Oceania	**Control arm** Paclitaxel 80 mg/m^2 days 1,8,15 q4w **Experimental arm** Pembrolizumab 200 mg (day 1) q3w	IHC 22C3	OS and PFS in patients with PD-L1 CPS ≥ 1	**OS Pembro vs CT** mOS 9.1 m vs 8.3 m; HR 0.82 **PFS Pembro vs CT** mPFS 1.5 m vs 4.1 m; HR 1.27

GEJ gastroesophageal junction; *q3w* every 3 weeks; *q4w* every 4 weeks; *PD-L1* programed death-ligand 1; *CPS* combined positive score; *IHC* immunohistochemistry; *OS* overall survival; *mOS* median overall survival; *PFS* progression-free survival; *mPFS* median progression-free survival; *m* months; *HR* hazard ratio; *vs* versus; *Pembro* pembrolizumab

0.42, respectively). Even patients with ECOG performance status 0 and primary tumor location in the GEJ had better survival with pembrolizumab compared to those treated with paclitaxel. On the other hand, patients with PD-L1 CPS < 1 had worse prognosis with pembrolizumab compared to paclitaxel (4.8 vs 8.2 months; HR 1.20). No improvement in PFS and response rate were observed with pembrolizumab in the ITT population, even if responses were more durable (median duration of response 18 months vs 5.2 months with pembrolizumab and paclitaxel, respectively). The safety profile was consistent to that reported with pembrolizumab in other studies. With two additional years of follow-up, pembrolizumab prolonged OS in PD-L1 positive patients across different cutoffs (≥ 1, ≥ 5, ≥ 10), while no significant differences were observed in PFS. ORR and duration of response (DoR) were higher in patients with PD-L1 CPS ≥ 10 [28].

The results of a phase I/II trial where nivolumab is combined with paclitaxel/ramucirumab suggest that this combination has promising antitumor activity with a manageable safety profile [29].

In 2017, FDA approved pembrolizumab for the treatment of adult and pediatric patients with unresectable/metastatic, MSI-high or mismatch-repair-deficient solid tumors (included GEJ/gastric cancer) that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Guidelines recommendations for immunotherapies in second line are summarized in Table 4.

Immunotherapy beyond the second line

The ATTRACTION-2 was in absolute the first randomized phase III study evaluating immunotherapy in patients with advanced GEJ/gastric cancer [22] (Table 5). In this trial, conducted exclusively in Asia, 493 heavily pretreated patients, unselected for PD-L1, were randomly assigned in a 2:1 ratio to receive nivolumab or placebo. Overall survival, primary endpoint of the study, was significantly longer in the nivolumab group compared to placebo (mOS 5.3 vs 4.1 months, respectively), with a reduction of 37% in the risk of death (HR 0.63; $p < 0.0001$). This survival benefit was observed across most subgroups and persists over time. An exploratory analysis according to PD-L1 expression showed that nivolumab improved overall survival regardless the PD-L1 status (mOS 5.22 in PD-L1-positive vs 6.05 months in PD-L1-negative patients). Nivolumab showed also a reduction of 40% in the risk of disease progression compared to placebo (HR 0.60; $p < 0.0001$) with mPFS of 1.6 versus 1.45 months, respectively. The ORR was 11.2%, even if no patients achieved CR. The DCR was superior in the nivolumab arm compared with placebo (40.3% vs 25%). Based on these results, nivolumab was approved in Asia as third or later-line in heavily pretreated GEJ/gastric cancer patients. The updated analysis at 3 years of follow-up confirmed the OS benefit (5.6% vs 1.9%) for nivolumab over placebo,

Table 4 Guidelines recommendations for immunotherapies in second line

Guideline	Second line
NCCN (2022)	Pembrolizumab is indicated for these subgroups of patients: - MSI-high or dMMR tumors - TMB high tumors (≥ 10 mutations/megabase)
ESMO (2016)	No recommendation for immunotherapies in second line
CSCO (2021)	Pembrolizumab is indicated in MSI-high patients
JGCA (2018)	No recommendation for immunotherapies in second line

NCCN National Comprehensive Cancer Network; *ESMO* European Society for Medical Oncology; *CSCO* Chinese Society of Clinical Oncology; *JCGA* Japanese Gastric Cancer Association; *MSI* microsatellite instability; *dMMR* mismatch-repair deficiency; *TMB* Tumor Mutational Burden

Table 5 Study information and characteristics of trials (third line)

Trial	Tumor location	Countries	Intervention groups	PD-L1 assay	Primary endpoints	Results
ATTRACTION-2 Phase III NCT02267343	GEJ/Gastric adenocarcinoma HER2-negative	Asia	**Control arm** Placebo **Experimental arm** Nivolumab 3 mg/kg q2w	IHC 28–8 pharmDx kit (Dako, Santa Clara, CA, USA) assessed retrospectively on tumor cells PD-L1 tumor expression not required for enrollment	OS and PFS in all patients, regardless PD-L1 expression	**OS nivo vs CT** mOS 5.3 m vs 4.1 m, HR 0.63 **PFS nivo vs CT** mPFS 1.6 m vs 1.45 m, HR 0.60
Keynote-059 Phase II NCT02335411	GEJ/Gastric adenocarcinoma HER2-negative	America Europe Asia Oceania	**Control arm** Placebo **Experimental arm** Pembrolizumab 200 mg q3w	IHC 22C3 PD-L1 status evaluated in all patients	ORR and safety -All patients -PD-L1 positive	**ORR in favor of pembro** - 11.6% all patients - 15.5% PD-L1 positive vs 6.4% PD-L1 negative

GEJ gastroesophageal junction; *q2w* every 2 weeks; *q3w* every 3 weeks; *PD-L1* programed death-ligand 1; *CPS* combined positive score; *IHC* immunohistochemistry; *OS* overall survival; *mOS* median overall survival; *PFS* progression-free survival; *mPFS* median progression-free survival; *m* months; *HR* hazard ratio; *vs* versus; *Nivo* nivolumab; *Pembro* pembrolizumab

regardless PD-L1 expression [30]. By note, patients with a rapid onset of treatment-related adverse events (TRAEs) showed a prolonged survival compared to patients without TRAEs (mOS 7.95 vs 3.81, HR 0.49).

Starting from the phase Ib trial Keynote 012 [31], also pembrolizumab showed promising activity with a manageable safety profile in heavily pretreated G/GEJ cancer patients. The results of this trial were confirmed in 2018 in the multicenter phase II Keynote-059 study [32] where an objective response rate of 11.6% was observed, with 2.3% of patients treated with pembrolizumab who experienced CR. Even if this benefit was recorded in the overall population, patients with PD-L1-positive tumors (CPS ≥ 1) experienced higher response rates (15.5% vs 6.4%) and a longer DoR (16.3 vs 6.9 months) compared to the PD-L1 negative group (Table 5). Based on these results, on September 2017, FDA granted accelerated approval for pembrolizumab as single agent for the treatment of recurrent locally advanced or metastatic GEJ/gastric adenocarcinoma with PD-L1 CPS ≥ 1 after two or more previous lines of therapy.

Nivolumab and Pembrolizumab have demonstrated similar efficacy and represents two valid options in third or later-line. However, the different definition of PD-L1 in the ATTRACTION-2 (staining in 1% or more of tumor cells using immunohistochemistry) compared to the CPS used in the most recent trials, the limited sample size of the PD-L1-positive subgroup (12.3% and 16.1% in the nivolumab and in the placebo group, respectively), the retrospective nature of this evaluation and the exclusive enrollment of Asian patients have to be considered for the interpretation and application of these results in clinical practice.

Guidelines recommendations for immunotherapies in third line are summarized in Table 6.

Table 6 Guidelines recommendations for immunotherapies in third line

Guideline	Third line
NCCN (2022)	Pembrolizumab is indicated for these subgroups of patients: - MSI-high or dMMR tumors - TMB high tumors (≥ 10 mutations/megabase)
ESMO (2016)	No recommendation for immunotherapies in third line
CSCO (2021)	Nivolumab monotherapy is recommended as third- or further-line Pembrolizumab monotherapy is indicated for PD-L1 CPS ≥ 1 patients
JGCA (2018)	Nivolumab monotherapy is recommended as third- or further-line

NCCN National Comprehensive Cancer Network; *ESMO* European Society for Medical Oncology; *CSCO* Chinese Society of Clinical Oncology; *JCGA* Japanese Gastric Cancer Association; *MSI* microsatellite instability; *dMMR* mismatch-repair deficiency; *TMB* Tumor Mutational Burden

Discussion

The above-mentioned results show that immunotherapy can improve survival outcomes in metastatic GEJ and gastric cancer patients. However, especially in the first line, is not completely clear which patients can really benefit from this treatment, resulting in a lack of unanimous consensus regarding patients who can be offered immunotherapy. In the CheckMate 649 trial [24], the survival benefit resulting from the addition of nivolumab to chemotherapy was reported in the overall population and across all PD-L1 CPS subgroups ($\geq 1, \geq 5, \geq 10$). However, was not clarified if the advantage in all randomly patients was driven by the CPS ≥ 5 subgroup, where the primary endpoint was to be met. A recent study, even with the limits of univariate nature of survival analysis, showed that the subgroup of patients with PD-L1 CPS 1–4 in the CheckMate 649 trial and the subgroup of patients with PD-L1 CPS 1–9 in the Keynote-062 trial seem not gain any survival benefit from the addition of immunotherapies to chemotherapy, thus raising a series of questions about the real advantage in these subset of patients [33].

Across the principal studies investigating immunotherapies in GEJ/G cancer, patients with microsatellite instability showed the best results in terms of objective response and survival, irrespective of the PD-L1 CPS status. Since 2014, the Cancer Genome Atlas project identified the microsatellite instable genomic subtype as an excellent candidate for immunotherapies, due to its high intrinsic mutation rate (including genes encoding targetable oncogenic signaling proteins) [34]. Also Epstein-Barr virus (EBV)-positive tumors (roughly 9% of all GC), in the light of their biological characteristics as PI3KCA mutations, DNA hypermethylation and amplification of JAK2, PD-L1 and PD-L2, seem to display better response when treated with immunotherapy [35].

The results of the main studies with immunotherapies must be read also in the light of immunological differences among Eastern and Western GC patients. In fact, non-Asian patients exhibit higher rates of gene signature related to T-cell activity, including CTLA-4 signaling. Also, they present a TILs enriched-microenvironment, higher T-cell (CD3, CD45R0, CD8) and lower Treg-cell (FOXP3) markers expression compared to Asian patients [36]. On the other hand, the prevalence of MSI-H and EBV-positive subtypes results similar between Asian and non-Asian populations (MSI-H 22% for TCGA and 23% for ACRG classifications, respectively; EBV-positive 9% for TCGA and 8.3% reported in Asia, respectively) [37]. Even efficacy and toxicity of immune checkpoint inhibitors seem to be similar, without significant differences in treatment-related or immune-mediated/infusion-related AEs.

Another key point that has to be considered is malnutrition, with consequent cachexia and sarcopenia, that are often detected in GEJ/gastric cancer patients and that are strictly associated to higher morbidity and mortality [38, 39]. Even if, at present, no data concerning the impact of malnutrition on response to immune checkpoint inhibitors (ICIs) in GC patients are available, in other cancer types it has been clearly demonstrated that chronic inflammation at the base of malnutrition directly affect immune system and subsequently response to immunotherapy [40].

Concluding, immune checkpoint inhibitors have demonstrated a significant efficacy with a good safety profile in selected metastatic GEJ/gastric cancer patients, becoming integral part of their treatment, especially in first line, where the combination of nivolumab plus chemotherapy can be considered the new standard of care. To date, immunotherapies have not changed the treatment management of second and third line, where paclitaxel plus ramucirumab (second line) and trifluridine/tipiracil or FOLFIRI (third line), still represent the gold standard. Even nowadays, the availability of efficacious second and third lines is essential for the opportunity to prolong significantly the global survival and to control the unavoidable symptoms evolution that heavily affects the quality of life of these patients.

Together with HER2, the evaluation of microsatellite instability, PD-L1 CPS value and EBV status should be performed in all metastatic patients to better select those who can benefit from immunotherapies. The identification of new biomarkers capable to identify all patients who can benefit from ICIs is highly desirable for the near future, thus extending their use to a wider population.

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