



# Anti-programmed death ligand 1 (PD-L1) inhibitors in metastatic gastric cancer

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## ABSTRACT

Metastatic gastric cancer (GC) with limited therapeutic options has a poor prognosis, and therefore, major therapeutic advances are needed. Comprehensive genomic characterization has improved understanding of GC but a great majority of genomic profiling has not been effectively translated to the clinical benefit yet. The introduction of immunotherapy with anti-programmed death ligand 1 (PD-L1) antibody such as pembrolizumab or nivolumab resulted in a rapid paradigm shift in the field of medical oncology and their clinical indication has been expanding in the past few years. Now, the era of immunotherapy in metastatic GC has arrived with recent trial results in survival benefit from anti-PD-L1 antibody. Herein, we review the mechanisms of immunotherapy, clinical trials that have been conducted or are in progress, and the potential for PD-L1 as a predictive biomarker for GC.

**Keywords:** Gastric; Immune checkpoint; Neoplasms; Programmed cell death protein 1; Programmed death ligand 1

## INTRODUCTION

Gastric cancer (GC) is the second leading cause of cancer-related mortality worldwide, with an estimated 723,000 deaths in 2012 [1,2]. Several immune checkpoint inhibitors that block the key immune checkpoints, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and/or programmed death ligand 1 (PD-L1), had been approved by the U.S. Food and Drug Administration (FDA) in several cancer types including melanoma, bladder, and lung cancer. We extensively reviewed the current ongoing clinical research effort and translational research for GC regarding immune checkpoint inhibitors.

## IMMUNE CHECKPOINT INHIBITORS IN GC

Two anti-PD-L1 inhibitors, pembrolizumab and nivolumab, were approved by the U.S. FDA for the treatment of metastatic melanoma in 2014 [3,4]. Subsequently, immune checkpoint inhibitors have been approved by the U.S. FDA for lung cancer, renal cell carcinoma (RCC), Hodgkin's

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**Table 1.** Select clinical trials of immune checkpoint inhibitors for metastatic gastric cancer

Study (ClinicalTrials.gov identifier)	Phase	No.	Setting	Treatment	Results (primary end-point)	Ref
Ipilimumab CA184-162 (NCT01585987)	II	114	Maintenance after first-line	Ipilimumab vs. best supportive care after response or stability to platinum and fluoropyrimidine doublet	Negative 2.9 months vs. 4.9 months (irPFS)	[14]
Tremelimumab	II	18	Second-line	Tremelimumab 15 mg/kg every 90 day	1 partial response (ORR)	[15]
KEYNOTE-012 (NCT01848834)	Ib	36	First-line	Pembrolizumab 10 mg/kg once every 2 weeks	22% (ORR) in PD-L1 positive gastric cancer	[11]
KEYNOTE-059 (NCT02335411)	II	133	Third-line	Pembrolizumab 200 mg Q3W	16.4% (ORR)	[16]
CheckMate-032 (NCT01928394)	I/II	160	Second-line or later	Nivolumab 3 mg/kg Q2W (N3), nivo 1 mg/kg+ ipilimumab 3 mg/kg (N1+I3), or nivolumab 3 mg/kg+ipilimumab 1 mg/kg (N3+I1) Q3W×4 cycles, followed by nivolumab 3 mg/kg Q2W	16% (ORR): 14% (N3) 26% (N1+I3), and 10% (N3+I1)	[10]
ONO-4538-12 (NCT02267343)	III	493	Second-line or later	Nivolumab 3 mg/kg vs. placebo	5.3 months vs. 4.1 months (OS)	[12]
JAVELIN (NCT01772004)	Ib	89	Maintenance after first-line	Avelumab 10 mg/kg Q2W	9% (RR), 12 weeks (PFS)	[13]
		62	Second-line		10% (RR), 6 weeks (PFS)	

irPFS, immune-related progression-free survival; ORR, objective response rate; PD-L1, programmed cell death protein ligand 1; OS, overall survival; RR, response rate.

disease and head and neck cancer since then. Many studies have reported long-term responses to anti-PD-L1 antibodies with acceptable safety profiles in lung cancer [5], RCC [6], bladder cancer [7], and chemoresistant Hodgkin disease [8]. In addition, solid tumors with high mutational load or microsatellite instability (MSI-high) have shown dramatic response to pembrolizumab in recent trials including colon cancer, GC, endometrial cancer, etc. [9,10]. Based on this finding, pembrolizumab has been approved in MSI-high tumors in U.S. Table 1 lists selected clinical trials of immune checkpoint inhibitors for metastatic GC [10-16].

## PEMBROLIZUMAB

The phase Ib study KEYNOTE-012 (NCT01848834) evaluated the safety and activity of pembrolizumab in PD-L1 positive GC (n=36). The primary endpoints were safety and response rate. The adverse events were manageable, and the response rate was 22% in PD-L1 positive GC patients who have failed to several lines of chemotherapy, thus very promising. There

was no correlation between PD-L1 expression and clinical responses to pembrolizumab in the KEYNOTE-012 trial but further biomarker analysis was not extensively performed due to limited tissue specimens from the cohort [11]. In KEYNOTE-059 (NCT02335411), in GC patients who received 2 prior lines of therapy (n=133), the objective response rate (ORR) was 16.4%; for those with PD-L1 positive tumors in the third-line setting (n=75), the ORR was 22.7%; in patients with PD-L1 negative tumors (n=58), the ORR was 8.6%. Hence, the ORR was higher in patients with PD-L1 positive tumors when compared with PD-L1 negative GC but importantly, responses were observed in patients with PD-L1 negative tumors [16]. Among the several ongoing trials, the KEYNOTE-061 (NCT02370498) is testing pembrolizumab versus paclitaxel after progression following a first-line platinum-based therapy. The KEYNOTE-062 trial (NCT02494583) is comparing pembrolizumab as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) in a first-line setting (Table 2). The two trials are currently ongoing. Currently, a phase II pembrolizumab trial (NCT02589496) which is a single-center trial

## PRECISION AND FUTURE MEDICINE

### Anti-PD-L1 inhibitors in gastric cancer

**Table 2.** Ongoing clinical trials of immune checkpoint inhibitors for gastric cancer

Study (ClinicalTrials.gov identifier)	Phase	Intervention	Primary end-points
<b>First-line</b>			
KEYNOTE-062 (NCT02494583)	III	Pembrolizumab vs. pembrolizumab, 5-FU, and cisplatin or capecitabine vs. 5-FU and cisplatin	PFS and OS
ONO-4538-37 (NCT02746796)	I/II	Fluoropyrimidine and platinum with or without nivolumab	PFS and OS
CheckMate 649 (NCT02872116)	III	Nivolumab and ipilimumab vs. 5-FU and oxaliplatin	OS
NCT02954536	II	Pembrolizumab in combination with trastuzumab and chemotherapy	6-month PFS
NCT02901301	IB/II	Pembrolizumab in combination with trastuzumab, capecitabine, and cisplatin	RP2D; 6-week ORR
NCT02864381	II	GS-5745 plus nivolumab vs. nivolumab alone	2-year ORR
<b>Maintenance after first-line</b>			
JAVELIN Gastric 100 (NCT02625610)	III	Avelumab or best supportive care after response or stability to oxaliplatin and fluoropyrimidine	3-year OS and PFS
PLATFORM (NCT02678182)	II	Durvalumab vs. capecitabine vs. trastuzumab vs. surveillance	PFS
<b>Second-line</b>			
KEYNOTE-181 (NCT02564263)	III	Pembrolizumab vs. irinotecan or paclitaxel or docetaxel	PFS and OS
KEYNOTE-061 (NCT02370498)	III	Pembrolizumab vs. paclitaxel	PFS and OS in PD-L1+tumors
KEYNOTE-063 (NCT03019588)	III	Pembrolizumab vs. paclitaxel	PFS and OS
D4190C00021 (NCT02340975) <sup>a)</sup>	Ib/II	Durvalumab vs. tremelimumab vs. durvalumab and tremelimumab	Phase Ib: DLT Phase II: ORR and 6-month PFS
NCT02999295	I/II	Nivolumab plus ramucirumab	DLTs and PFS
NCT02689284	Ib/II	Margetuximab in combination with pembrolizumab	MTD and MAD for margetuximab; duration of response; 12-month ORR
NCT03196232	II	Epacadostat with pembrolizumab	PFS
NCT02589496	II	Pembrolizumab	2-year RR
<b>Third-line</b>			
ONO-4538-12 (NCT02267343)	III	Nivolumab vs. placebo	OS
JAVELIN Gastric 300 (NCT02625623)	III	Avelumab and best supportive care vs. paclitaxel or irinotecan and best supportive care or best supportive care	2-year OS
NCT02935634	II	Nivolumab and ipilimumab vs. nivolumab and BMS-986016	ORR, DOR, and PFSR
NCT03122548	II	CRS-207 in combination with pembrolizumab	Adverse events
NCT02589496	II	Pembrolizumab as salvage therapy in metastatic GC (integrated genomic analysis)	ORR, genomic profiling

5-FU, 5-fluorouracil; PFS, progression-free survival; OS, overall survival; RP2D, recommended phase II dose; ORR, overall response rate; PD-L1, programmed cell death protein ligand 1; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; MAD, maximum administered dose; RR, response rate; DOR, duration of response; PFSR, progression-free survival rate.

<sup>a)</sup>Also in third-line study.

at Samsung Medical Center with integration of pre and post-biopsies has been completed patient accrual (n=60). This trial results, hopefully, may shed light into identifying a

subset of GC patients who may benefit the most from pembrolizumab.

**NIVOLUMAB**

In contrast to pembrolizumab, nivolumab has been investigated in patients regardless to PD-L1 status (both PD-L1 positive and negative GCs) and responses have been seen in both cohorts. Recently, in a randomized phase III trial ONO-4538 (NCT02267343), nivolumab was evaluated as a monotherapy versus placebo (2:1) in metastatic GC after second or later lines (n=493) [12]. The study reported significant prolongation of overall survival (OS) (5.3 months vs. 4.1 months) and disease-free survival (1.61 months vs. 1.45 months) in nivolumab arm when compared to best supportive care, respectively with statistical significance. This study documented a response rate of 11% and all comer GC patients were enrolled [12]. Based on this trial, nivolumab is expected to receive authority approval in Japan and Korea in late 2017 or early 2018. The GC cohort of CheckMate 032 [10] enrolled patients on nivolumab alone and two different doses of nivolumab in combination with ipilimumab. ORR was the highest with nivolumab 1 mg/kg with ipilimumab 3 mg/kg (26%, 12 of 46 patients), relative to the nivolumab 3 mg/kg (14%, 8 of 59 patients), or nivolumab 3 mg/kg with ipilimumab 1 mg/kg (10%, 5 of 49 patients) cohorts. In the nivolumab alone arm, response rate was higher in PD-L1-positive GC (27%) when compared to PD-L1 negative GC (12%); the highest response rate was observed in the combination arm (nivolumab 1 mg/kg with ipilimumab 3 mg/kg; 44% in PD-L1 positive and 21% in PD-L1 negative cohort) (Table 3). Given these notable find-

ings, a phase III trial CheckMate-649 (NCT02872116) is currently ongoing to enroll patients in nivolumab plus ipilimumab versus FOLFOX (oxaliplatin plus 5-fluorouracil) or XELOX (oxaliplatin plus capecitabine) as front-line therapy (Table 2).

**DURVALUMAB (MEDI-4736)**

Durvalumab is currently in a phase I study to evaluate its efficacy and safety in GC patients with GC (NCT01693562). Most frequent treatment-related adverse events were fatigue, nausea, and rash. Evidence of clinical activity has been seen across all histologies [17]. More recently, a phase II PLATFORM study (NCT02678182) is ongoing. The aim of this study is to evaluate the efficacy and safety of durvalumab for maintenance therapy in GC.

**AVELUMAB**

Another promising immune checkpoint inhibitor is avelumab. A large phase Ib JAVELIN trial (n=151) of first-line avelumab maintenance treatment reported a response rate of 9% with a median progression-free survival (PFS) of 12 weeks; second-line treatment reported a response rate of 10% with a median PFS of 6 weeks (NCT01772004) [18]. The adverse events reported were most common infusion reactions and fatigue [13]. Given the promising results of this trial, JAVELIN Gastric 100 (NCT#02625610) and JAVELIN Gastric 300 (NCT#02625623) phase III trials are underway (Table 2).

**Table 3.** Selected clinical trials evaluating PD-L1 as a predictive biomarker

Study (ClinicalTrials.gov identifier)	Phase	No.	Setting	Treatment	Results according to PD-L1	Ref
<b>Pembrolizumab</b>						
KEYNOTE-012 (NCT01848834)	Ib	36	First-line	Pembrolizumab 10 mg/kg once every 2 weeks	24% vs. 17% (ORR) in PD-L1 positive and negative, respectively However, no correlation of PD-L1 expression with clinical responses to pembrolizumab	[11]
KEYNOTE-059 (NCT02335411)	II	133	Third-line	Pembrolizumab 200 mg Q3W	22.7% vs. 8.6% (ORR) in PD-L1 positive and negative, respectively	[16]
<b>Nivolumab</b>						
CheckMate-032 (NCT01928394)	I/II	160	Second-line or later	Nivo 3 mg/kg Q2W (N3), nivo 1 mg/kg+ipi 3 mg/kg (N1+I3), or nivo 3 mg/kg+ipi 1 mg/kg (N3+I1) Q3W×4 cycles, followed by nivo 3 mg/kg Q2W	27% vs. 12% (ORR), in PD-L1 positive and negative, respectively	[10]

PD-L1, programmed cell death protein ligand 1; ORR, overall response rate.

## ATEZOLIZUMAB (MPDL-3280A)

A phase I dose-escalation study was conducted to evaluate the pharmacokinetics and safety of atezolizumab. In this trial, atezolizumab monotherapy was administered in patients with non-selected solid tumors, including one GC patient. The ORR was 21% (NCT01375842).

## PD-1/PD-L1 EXPRESSION AND PATIENT OUTCOME

Melanoma, RCC, and non-small cell lung cancer express high levels of PD-L1, ranging from 66% to 100% [19-21]. In a study of 102 GC samples, Wu et al. [22] have demonstrated using an immunohistochemical approach that 42.2% of the samples had PD-L1 overexpressing tumor cells. They also showed that PD-L1 is undetectable in normal gastric tissue controls and only weakly detectable in gastric adenomas [22]. Similarly, PD-L1 overexpression was found in 40% of cases of advanced GC from the phase Ib KEYNOTE-012 trial data [11]. Another Chinese study (n=111) reported PD-L1 positivity in 63% of GC resection specimens [23].

The high PD-L1 expression has been identified as a negative prognostic marker in melanoma [24], RCC [25], and lung cancer [26]. Additionally, PD-L1 upregulation has been detected in gastrointestinal malignancies, such as pancreatic, colorectal, and GC, correlating with poor prognosis [27,28]. Likewise, high PD-L1 expression in GC was associated with nodal metastases, advanced stage, and poor outcome [22,23]. Recently, a small cohort study showed that resected GC patients with a higher CD8+ T-cell density have a higher PD-L1 expression and worse clinical outcome [29]. These biological features in GCs are comparable to those seen in other cancers in which immune checkpoint inhibitors have demonstrated early success. PD-L1 overexpression may also play a role as a predictive response biomarker in GC.

Nevertheless, no biomarker is absolute to predict response to immune checkpoint inhibitors. Hence, an integrated analysis of mutational load, microsatellite instability, needs to be analyzed in responders and non-responders to immune checkpoint inhibitors in GC. The impact of Epstein-Barr Virus status and microsatellite instability status on response to immune checkpoint inhibitors in GC will be very interesting.

## CONCLUSION

In spite the development of targeted agents such as trastu-

zumab and ramucirumab, precision medicine for GC patients has still a long way to go. Based on the promising early trial results in GC with anti-PD-L1 antibodies such as pembrolizumab, nivolumab, and avelumab, the practice guideline and pattern in metastatic GC patients will be rapidly changed in the next few years. Especially, given the high percentage of MSI-high in GC (up to 20%), the impact of immunotherapy in these patients will be substantial. With upcoming KEYNOTE 061, KEYNOTE 062 trials, and CheckMate trials, the positioning of immune checkpoint inhibitors in GC will be refined and tuned in the next few years. In addition, identification of responders versus non-responders to immunotherapy will very likely facilitate and improve survival outcome in GC following immunotherapy.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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## PRECISION AND FUTURE MEDICINE

### Anti-PD-L1 inhibitors in gastric cancer

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