

The current management and biomarkers of immunotherapy in advanced gastric cancer

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Abstract

Background: Gastric carcinoma (GC) is the fourth most common cause of cancer-related death worldwide. Most patients are diagnosed at later stage, because of few treatment options, the prognosis is poor. In recent years, however, Immune checkpoint inhibitors (ICIs), such as anti-programmed death-1 (PD-1), anti-PD-L1, and anti-cytotoxic T lymphocyte antigen 4, have emerged as promising therapeutic agents in GC. Here, we summarize the current treatment and advances of immune checkpoint inhibitors in the advanced stage of GC.

Methods: WANFANG MED ONLINE, CNKI, NCBI PUBMED and clinicaltrials.gov were used to search literature spanning from 2000 to 2021, and all literatures about “advanced gastric or gastro-oesophageal junction cancer, Immune checkpoint inhibitors, PD-1, PD-L1, Cytotoxic T lymphocyte antigen 4, immune therapy” with detailed data were included.

Results: Nivolumab and pembrolizumab have been recommended for the third line or subsequent therapy in advanced GC. Nivolumab plus chemotherapy has been recommended for the first line treatment in advanced GC in China. Many other ICIs have been demonstrating encouraging efficacy. PD-L1, MSI-H, Epstein Barr virus, and TMB status maybe potential biomarkers for response to clinical outcomes for ICIs in GC.

Conclusion: ICIs have shown encouraging treatment efficacy and manageable safety profile in GC. Some biomarkers including PD-L1, MSI-H, EBV, and TMB status could evaluate the efficacy of ICIs in GC.

Abbreviations: 5-Fu = 5-fluorouracil, AGC = advanced gastric adenocarcinoma, CR = complete response, CSCO = Chinese society of clinical oncology, CTLA-4 = Cytotoxic T lymphocyte antigen 4, DCR = disease control rate, dMMR = DNA mismatch repair deficiency, EBV = Epstein Barr virus, FLOT = 5-fluorouracil + docetaxel + oxaliplatin + leucovorin, G/GEJ = Gastric or gastro-oesophageal junction, GC = gastric carcinoma, HER-2 = human epidermal growth factor receptor-2, HRR = homologous recombination repair, ICIs = immune checkpoint inhibitors, IPI = Ipilimumab, IV = intravenously, LAG-3 = lymphocyte activation gene 3, MIDS = mononuclear inflammatory cell density score, MSI = microsatellite-unstable/instability, nivo = nivolumab, ORR = objective response rate, OS = overall survival, PD-1 = programmed death-1, PFS = progression-free survival, PR = partial response, Q2W = every 2 weeks, SOX = S-1 plus oxaliplatin, TMB = tumor mutational burden, TPS = tumor proportion score, TRAEs = treatment-related adverse events, VEGF = vascular endothelial growth factor.

Keywords: cytotoxic T lymphocyte antigen 4, gastric carcinoma, immune checkpoint inhibitors, immunotherapy, programmed death-1

1. Introduction

Gastric carcinoma (GC) is one of the most common digestive malignancies worldwide with the fourth most common cause of cancer-related death.^[1] In China, the latest data from the National Cancer Center demonstrate that its morbidity and

mortality rank the second and the third respectively, which seriously endangers public health.^[2] Although with the progress of diagnosis and treatment technology, more than 50% of GC patients are still advanced at diagnosis, and the first-line treatment based on 5-fluorouracil (5-Fu) and platinum drugs in the advanced stage showed poor efficacy.^[3] And targeted

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drugs, trastuzumab which has been approved for first-line treatment of patients with human epidermal growth factor receptor-2 (HER-2)-positive GC also showed limited outcome.^[4] To date, both chemotherapy and targeted drugs face bottlenecks, and the median OS is difficult to break out 2 years. And the 5-year overall survival rate (OS) for advanced GC is only 10% to 15% worldwide.

Immune checkpoint inhibitors (ICIs), including anti- (programmed death-1) PD-1, anti-PD-L1, and anti-cytotoxic T lymphocyte antigen 4 (CTLA-4), are increasingly administered to those late-stage malignant tumor patients who have failed to multiple treatments, such as melanoma,^[5] non-small-cell lung cancer,^[6] and colorectal cancer,^[7] and have produced higher antitumor response. In recent years, however, ICIs have emerged as promising therapeutic agents in GC, and to date, nivolumab and pembrolizumab as the standard third therapy have been recommended in GC guidelines. Some biomarkers including PD-L1 have been shown the potential predictive outcome for GC patients receiving ICIs.

Here, we summary the advances and biomarkers of ICIs in advanced GC. WANFANG MED ONLINE, CNKI, NCBI PUBMED and clinicaltrials.gov were used to search literature spanning from 2000 to 2021, and all literatures about “advanced gastric or gastro-oesophageal junction cancer, Immune checkpoint inhibitors, PD-1, PD-L1, CTLA-4, immune therapy” with detailed data were included. Cases were excluded if they were duplicated or their information was too generalized.

This review aimed to summary the advances and biomarkers of ICIs in advanced GC using public available resources and do not require a statement from the ethics committee.

1.1. The current standard treatment of ICIs alone in advanced GC

Immune checkpoint inhibitors, including anti-PD-1, anti-PD-L1, and anti- CTLA-4, have been emerging as the novel treatment strategy for advanced GC. Nivolumab and pembrolizumab are the most common ICIs. To date, according to ATTRACTION-2 and KEYNOTE-059 study (Table 1), these two ICIs have been recommended for the later line treatment in NCCN guide since 2017(≥2 lines therapy) and guidelines of Chinese society of clinical oncology(≥3 lines, version 2020,CSCO). According to Checkmate 649 trial, nivolumab plus chemotherapy was recommended for the first line treatment in advance GC in CSCO guideline in 2021.

The recommendation of Nivolumab, a monoclonal antibody inhibitor of PD-1, was based on a phase III study called ATTRACTION-2 (NCT02267343), a multicenter study from 49 institutions in Japan, South Korea, and Taiwan of China, which was the first phase 3 study of ICIs in advanced GC.^[8] It was designed to investigate the efficacy and safety of nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer (G/GEJ cancer) who had been previously treated with two or more chemotherapy regimens. Patients were randomly assigned (2:1) to receive nivolumab (3 mg/kg intravenously [IV] infusion, every 2 weeks [Q2W]) or placebo. The primary endpoint was OS in the intention-to-treat population. The median follow-up was 8.87 months and 8.59 months in the nivolumab and placebo group, respectively. Results showed that Median OS was significantly longer in nivolumab compared with placebo group (5.26 vs 4.14 months, $p < 0.0001$), and 12-month OS rates were 26.2% with nivolumab and 10.9% with placebo. The OS benefit was observed regardless of tumor PD-L1 expression. According to the data of Attraction-2, nivolumab was approved for third- or later-line treatment of unresectable advanced or recurrent G/GEJ cancer in Japan, South Korea in 2017. The 2-year update data showed that 2-year OS was also higher in the nivolumab than in placebo group (10.6% vs 3.2%). For patients with a complete or partial response (CR or PR) in the nivolumab group, the long-term survival benefit of nivolumab was most evident, with the median OS as 26.6 months, the OS rates at 1 and 2 years were 87.1% and 61.3%, respectively.^[9] In CSCO guideline(2020), it was recommended for the third line or subsequent therapy in advanced GC.

The recommendation of pembrolizumab, another PD-1 inhibitor, was based on a phase II study called KEYNOTE-059 study (NCT02335411), open-label, single-arm, multicohort (three cohorts) study from 16 countries, and in which pembrolizumab as monotherapy and in combination with cisplatin+5-Fu with recurrent or metastatic G/GEJ adenocarcinoma.^[10] In cohort 1, patients who had received at least two prior therapies for their advanced disease received monotherapy with pembrolizumab (200 mg IV infusion, on Day 1 of each 3-week cycle for up to 24 months). Total of 259 patients enrolled, median (range) follow-up was 5.8 (0.5–21.6) months. Objective response rate(ORR) was 11.6% (30/259), with CR in 2.3% (6/259). Median (range) response duration (DOR) was 8.4months. ORR and median DOR were 15.5% (23/148) and 16.3months in patients with PD-L1-positive tumors, and 6.4% (7/109) and 6.9months in PD-L1-negative tumors, respectively. And all adverse reactions could be

Table 1
Clinical trials of the current third-line treatment of ICIs in advance GC.

Year	Study number	Phase	Study design	Disease	Effect
2017	NCT02267343 (Attraction-2)	III	nivolumab vs placebo	advanced G/GEJ	Median OS: 5.26 vs 4.14 mo 12-mo OS rates: 26.2% vs 10.9% 2-yr OS rate: 10.6% vs 3.2%
2017	NCT02335411 (Keynote-059)	II	cohort 1: pembrolizumab monotherapy	recurrent or metastatic G/GEJ	ORR was 11.6% Median DOR: 8.4 mo For PD-L1-positive vs negative: ORR: 15.5 vs 6.4 median DOR: 16.3 vs 6.9mo
2018	NCT02625623 (JAVELIN Gastric 300)	III	Avelumab vs physician's choice of chemotherapy (paclitaxel or irinotecan).	unresectable, recurrent, locally advanced, or metastatic GC/GEJC	ORR:2.2% vs 4.3% Median OS: 4.6 vs 5.0 months Median PFS: 1.4 vs 2.7 mo ($P > .99$)

tolerated, just 2 deaths were considered related to treatment. According to the data of keynote-059, FDA approved pembrolizumab with accelerated process for the treatment of patients with recurrent or metastatic G/GEJ adenocarcinoma and recommended for second-line or subsequent therapy for MSI-H/dMMR (microsatellite instability-High or DNA mismatch repair deficiency) tumor in NCCN guideline (Version 4, 2017).^[11] Update in Version 5.2017 of the NCCN, pembrolizumab also recommended for third-line or subsequent therapy for GC with PD-L1 levels by CPS (combined positive score ≥ 1). And it was recommended for the third line or subsequent therapy in advanced GC in version 2020 of CSCO guidelines.

Avelumab, a human anti-PD-L1 IgG1 monoclonal antibody, demonstrated efficacy in various solid tumors. In a cohort of the phase I JAVELIN Solid Tumor trial, avelumab showed durable antitumor activity and an acceptable safety profile as first-line maintenance or second-line treatment of patients with advanced G/GEJ cancer.^[12] But in the randomised, phase III JAVELIN Gastric 300 trial (NCT02625623), which compared avelumab versus physician's choice of chemotherapy as third-line therapy in patients with advanced G/GEJ cancer.^[13] A total of 371 patients with unresectable, recurrent, locally advanced, or metastatic G/GEJ cancer were randomised to receive either avelumab (10 mg/kg, IV infusion, Q2W) or physician's choice of chemotherapy (paclitaxel 80 mg/m² on days 1, 8, and 15 or irinotecan 150 mg/m² on days 1 and 15, Q4W). All of the primary end point of improving OS (median, 4.6 vs 5.0 months, $P = .81$) or the secondary end points of progression-free survival (PFS) (median, 1.4 vs 2.7 months; $P > .99$) or ORR (2.2% vs 4.3%) showed no benefit in the avelumab versus chemotherapy arms, respectively, although avelumab showed a more manageable safety profile than chemotherapy. So avelumab failed to be recommended in guidelines.

1.2. The exploration of the late first-line treatment of ICIs and/or combined with chemotherapy in advanced GC

The Attraction-2 and Keynote-059 study confirmed that nivolumab and pembrolizumab monotherapy provided durable responses with manageable safety in patients with advanced G/GEJ adenocarcinoma that had progressed following second-line treatment. How about the effect of the monotherapy or combination therapy of ICIs in late first-line treatment? The data from Keynote-059 demonstrated promising antitumor activity of pembrolizumab monotherapy or plus chemotherapy as first-line therapy, but in the following phase 3 study, Keynote-062 (NCT02494583) is a negative study for effect of pembrolizumab in first-line treatment in advanced GC, and now other studies of ICIs as first line treatment are ongoing (Table 2).

In cohort 2 of Keynote-059 study, patients who had not received any previous therapy received pembrolizumab in combination with cisplatin and 5-Fu or capecitabine (Japan only).^[14] And in cohort 3, patients who showed PD-L1-positive received pembrolizumab monotherapy as the first-line therapy. Median follow-up was 13.8 months (range 1.8–24.1) and 17.5 months (range 1.7–20.7), respectively. The ORR was 2-fold higher in combination therapy than monotherapy (60.0% vs 25.8%). Median time to response was 2.1 months in both two cohorts, median response duration was 4.6 months and 9.6 months (cohort 2 vs cohort 3), respectively. Median OS and PFS was 13.8 months and 6.6 months in cohort 2, and 20.7 months and 3.3 months in cohort 3, respectively. The grade 3/4

treatment-related adverse events (TRAEs) in cohort 2 was 76.0% patients (19/25), none were fatal. While, grade 3–5 TRAEs in the monotherapy cohort was 22.6% (7/31). Pembrolizumab monotherapy or plus chemotherapy demonstrated manageable safety and promising antitumor activity as first-line therapy in advanced G/GEJ adenocarcinoma.

Keynote-062 (NCT02494583), is a phase 3 randomized, controlled, partially blinded interventional trial with untreated, advanced G/GEJ cancer with PD-L1 CPS ≥ 1 from 200 centers in 29 countries to evaluate the antitumor activity of pembrolizumab, pembrolizumab plus chemotherapy, or chemotherapy alone in patients.^[15] Total of 763 patients were randomized 1:1:1 (256:257:250) to pembrolizumab (200 mg), pembrolizumab plus chemotherapy (cisplatin 80 mg/m²/d on day 1 plus fluorouracil 800 mg/m²/d on days 1 to 5 or capecitabine 1000 mg/m² twice daily), or chemotherapy plus placebo. Primary end points were OS and PFS in patients with PD-L1 CPS ≥ 1 or ≥ 10 . Median follow-up was 29.4 (22.0–41.3) months. Results showed OS was similar in patients with CPS ≥ 1 (median, 10.6 vs 11.1 months) between pembrolizumab and chemotherapy group, but longer in patients with PD-L1 CPS ≥ 10 (median, 17.4 vs 10.8 months; HR, 0.69; 95% CI, 0.49–0.97), there was no statistically difference. Otherwise, the OS and PFS of Pembrolizumab plus chemotherapy were also not superior to chemotherapy in patients with CPS ≥ 1 or ≥ 10 (12.5 vs 11.1 months for OS with CPS ≥ 1 ; 12.3 vs 10.8 months for OS with CPS ≥ 10) (6.9 vs 6.4 months for PFS with CPS ≥ 1), although the CR rate was higher in pembrolizumab plus chemotherapy group (9.3% vs 5.6%). Grade 3 to 5 TRAEs was high in pembrolizumab plus chemotherapy group with 73%. It is regrettable that the data from Keynote-062 showed pembrolizumab monotherapy or plus chemotherapy is not superior to chemotherapy monotherapy.

But the following Checkmate 649 study of nivolumab combined with chemotherapy showed durable responses in the late first-line treatment of advanced GC. Checkmate 649 (NCT02872116) was a randomized, multicenter, open-label, phase 3 study of Nivolumab plus Ipilimumab or Nivolumab in combination with chemotherapy versus chemotherapy (oxaliplatin plus fluoropyrimidine) in subjects with previously untreated advanced or metastatic G/GEJ cancer.^[16] Preliminary results showed that Nivolumab-plus-chemotherapy resulted in significant improvements in OS (14.4 vs 11.1 months, $p < 0.0001$) and PFS (7.7 vs 6.05 months, $p < 0.0001$) compared with chemotherapy in PD-L1 CPS ≥ 5 patients.^[17] And ORR was 60% versus 45% in PD-L1 CPS ≥ 5 patients ($p < 0.0001$). The 12-month PFS estimate was 36% versus 22%. Furthermore, the OS and PFS benefit was also observed with nivolumab plus chemotherapy versus chemotherapy in patients with PD-L1 CPS ≥ 1 and all randomised patients, respectively. But unstratified OS in patients with PD-L1 CPS < 1 . In subgroup of Chinese patients, OS and PFS were similar to that of all randomised patients. According to Checkmate 649 study, nivolumab combined with chemotherapy was recommended for the late first line therapy in advanced GC in PD-L1 CPS ≥ 5 patients in CSCO guideline in 2021.

Attraction-4 (NCT02746796), a randomized, phase II/III, two-part study, was to evaluate the safety and efficacy of nivolumab combined with S-1 or capecitabine plus oxaliplatin (SOX/CapeOX) as first-line therapy for unresectable advanced or recurrent HER2-negative G/GEJ cancer. In part 1 (phase II study), patients from 13 centers in Japan and South Korea were

Table 2
Clinical trials of the late first-line treatment of ICIs and/or combined with chemotherapy in advanced GC.

Year	Clinical number	Phase	Study design	Disease	Effect
2016	NCT02872116 (Checkmate-649)	III	Nivolumab+IPI or Nivolumab +chemotherapy or chemotherapy	advanced/metastatic GC	Nivo+chemotherapy vs chemo OS:14.4 vs11.1 months PFS 7.7 vs 6.05 months ORR 60% vs 45% (PD-L1 CPS ≥5) Completed date: October, 2022
2018	NCT02335411 (Keynote -059)	II	cohort 2: pembrolizumab +cisplatin and 5-FU or capecitabine cohort 3: pembrolizumab monotherapy for patients with PD-L1 -positive	recurrent or metastatic G/GEJ	cohort 2: ORR: 60.0%, Median OS 13.8 mo Median PFS 6.6 mo cohort 3: ORR 25.8%, Median OS: 20.7 mo, Median PFS: 3.3 mo
2019	NCT02746796 (Attraction-4)	II/III	Nivolumab(nivo) +S-1 or capecitabine plus oxaliplatin (SOX/CapeOX) (nivo +SOX vs nivo +CapeOX)	unresectable advanced or recurrent HER2(-) G/GEJ	part 1 (phase II study): ORR: 57.1% vs 76.5% Median OS was not reached in both groups; Median PFS: 9.7 vs 10.6 months. Part 2 (phase III study) is ongoing.
2019	NCT02915432	Ib/II	cohort 2: toripalimab (360 mg d1, Q3W) + CapeOX (as first-line treatment)	chemotherapy-naive advanced GC	ORR: 66.7%; DCR:88.9%. Grade 3 or higher TRAEs: 38.9%.
2020	NCT02494583 (Keynote-062)	III	Pembrolizumab(Pembro) vs Pembro + chemotherapy Or chemotherapy alone	untreated, advanced G/GEJ (PD-L1 CPS ≥1)	Pembro vs chemotherapy: Median OS: 10.6 vs 11.1 months(PD-L1 CPS ≥ 1) 17.4 vs 10.8 mo(CPS ≥ 10); Pembro vs combined chemotherapy: OS: 12.5 vs 11.1 mo(CPS ≥1); 12.3 vs 10.8 mo (CPS ≥10) PFS: 6.9 vs 6.4 months(CPS ≥1)
2020	NCT02625610 (JAVELIN Gastric 100))	III	Avelumab maintenance vs continued chemotherapy after 12 wk of first-line induction chemotherapy	Her2(-),locally advanced or metastatic GC or GEJC	Median OS : 10.4 vs 10.9 months 24-mo OS rate:22.1% vs 15.5% TRAEs: 61.3% vs 77.3%
2020	NCT03382600 (KEYNOTE-659)	IIb	cohort 1: pembrolizumab(pembro)+ SOX (oxaliplatin + TS-1)	PD-L1 positive, HER2-negative advanced G/GEJ(Japan)	ORR: 72.2%; DCR 96.3%. Median OS, DOR: not reached. 6-mo OS rate: 87.0%. Median PFS: 9.4 months. grade ≥3 TRAEs was 57.4%.
2016	NCT02678182 (maintenance therapy following by first-line chemotherapy)	II	HER-2 positive: trastuzumab HER-2negative: surveillance vs maintenance capecitabine vs anti-PD-L1 antibody	locally advanced or metastatic HER-2 positive or HER-2 negative oesophago-gastric adenocarcinomas	The study is ongoing(recruiting). Completed date: June, 2025
2016	NCT02872116 (Checkmate-649)	III	Nivolumab+IPI or Nivolumab +chemotherapy or chemotherapy	advanced/metastatic GC	Nivolumab+chemotherapy vs chemotherapy OS:14.4 vs11.1 mo PFS 7.7 vs 6.05 mo ORR 60% vs 45% (PD-L1 CPS ≥5) Completed date: October, 2022
2018	NCT03675737 (Keynote-859)	III	pembrolizumab or placebo +chemotherapy(investigator's choice of FP or CAPOX)	HER2(-) advanced/ metastatic GC	The study is ongoing(recruiting). Completed date: September, 2024
2018	NCT03615326 (Keynote-811)	III	pembrolizumab or placebo + trastuzumab +investigator's choice of FP(cisplatin + 5-fluorouracil) or CAPOX in the global cohort or SOX in the Japan-specific cohort.	advanced/metastatic HER2-positive GC	The study is ongoing. Completed date: March, 2024
2018	NCT03662659	II	BMS-986213(Relatlimab and or Nivolumab) or Nivolumab only + investigator's choice chemotherapy (XELOX or FOLFOX or SOX)	advanced G/GEJC	The study is ongoing. Completed date: August, 2024
2020	NCT04278222 (APICAL-GE)	II	Anlotinib Plus Toripalimab	advanced G/GEJC	The study is ongoing. Completed date: August, 2022
2015	NCT01585987	II	Ipilimumab(anti-CTLA-4) vs Best Supportive care following first-line chemotherapy	unresectable locally advanced/metastatic G/GEJ cancer.	Completed, Results are expected in the near future.

5-Fu = 5-fluorouracil, CapeOX = Capecitabine plus oxaliplatin, DCR = disease control rate, TRAEs = treatment-related adverse events.

randomized (1: 1, 21 vs 18) to receive nivolumab (360 mg IV Q3W) plus SOX/CapeOX (S-1 40 mg/m², or capecitabine 1000 mg/m², both orally twice daily for 14 days, Q3W; oxaliplatin, 130 mg/m² on day 1, Q3W) until disease progression, unacceptable toxicity, or consent withdrawal.^[18] Median (range) follow-up time was 13.2 (12.2–15.2) months. Results showed that ORR was 57.1% (95% CI 34.0–78.2) with nivolumab plus SOX and 76.5% (95% CI 50.1–93.2) with nivolumab plus CapeOX. Median OS was not reached in both groups. Median PFS was 9.7 months (5.8– Not reached) and 10.6 months (5.6–12.5), respectively. Most frequent (>10%) grade 3/4 TRAEs were neutropenia (14.3%) in the nivolumab plus SOX group, and neutropenia (16.7%), anemia, peripheral sensory neuropathy, decreased appetite, type 1 diabetes mellitus, and nausea (11.1% each) in the nivolumab plus CapeOX group. No treatment-related death occurred. It suggests that nivolumab combined with SOX/CapeOX as first-line therapy is well tolerated and demonstrates encouraging efficacy. But only 5% patients were from Taiwan province of China. In part 2 (phase III study), the study was designed to compare nivolumab plus SOX/CapeOX versus placebo plus SOX/CapeOX, which is currently ongoing at 138 sites in Japan, South Korea, and Taiwan. We expect the encouraging data.

To date, many trials of ICIs in the late first line therapy in advanced GC are ongoing. NCT02915432 is a multi-center, open-label phase Ib/II clinical study to evaluate the safety and anti-tumor activity of toripalimab (a humanized anti-PD-1 monoclonal antibody) in advanced gastric adenocarcinoma (AGC), and the predictive survival benefit of tumor mutational burden (TMB) and PD-L1.^[19] In cohort 1, 58 chemo-refractory AGC patients received toripalimab (3 mg/kg d1, Q2W) as a monotherapy. In cohort 2, 18 chemotherapy-naïve AGC patients received toripalimab (360 mg d1, Q3W) plus capecitabine (oxaliplatin 130 mg/m² d1, capecitabine 1000 mg/m² bid d1-d14, Q3W) as first-line treatment. Primary endpoint was ORR. In cohort 2, the ORR was 66.7% and disease control rate (DCR) was 88.9%. Grade 3 or higher TRAEs was 38.9%. Toripalimab showed promising antitumor activity in AGC patients. Another study of Toripalimab, APICAL-GE (NCT04278222), a single center, single-arm phase II study, is to evaluate the efficacy and safety of Anlotinib plus toripalimab in advanced G/GEJ cancer as first-line treatment. The study is also ongoing and will be completed in 2022 (<https://clinicaltrials.gov/ct2/show/NCT04278222>).

KEYNOTE-659 (NCT03382600) is a non-randomised, multi-centre, open-label phase IIb study to evaluate the efficacy and safety of pembrolizumab plus chemotherapy as the first-line treatment in Japanese patients with PD-L1 positive, HER2-negative advanced G/GEJ cancer.^[20] In cohort 1, patients received pembrolizumab (200 mg Q3W) + SOX (oxaliplatin 130 mg/m² d1 Q3W + S-1 40 to 60 mg orally, BID d1–14, Q3W) combination therapy. The primary endpoint was ORR assessed by blinded independent central review. Secondary endpoints were DOR, DCR, time to response, PFS, OS and safety. The median follow-up was 10.1 months. ORR and DCR were 72.2% and 96.3%, respectively. The ORR was 73.9% in patients with CPS ≥ 1 to < 10 and 71.0% in those with CPS ≥ 10 . The median OS was not reached. The 6-month OS rate was 87.0%. Median DOR, time to response, PFS were as follows: not reached, 1.5 months, 9.4 months. The median PFS was not reached in patients with CPS ≥ 1 to < 10 and 8.1 months in those with CPS ≥ 10 , respectively. The grade ≥ 3 TRAEs was 57.4%. No treatment-related deaths occurred. Pembrolizumab plus SOX showed

encouraging efficacy and a manageable safety profile for the first-line treatment of HER2-negative advanced G/GEJ cancer. In cohort 2, the therapy was pembrolizumab + cisplatin (60 mg/m² Q3W) + TS-1 combination therapy, which is ongoing.

KEYNOTE-811 (NCT03615326) is an international, multi-center, randomized, double-blind, placebo-controlled, phase III study, evaluating the efficacy and safety of pembrolizumab in combination with trastuzumab and chemotherapy as first-line treatment of patients with advanced/metastatic HER2-positive GC.^[21] Patients will be randomly assigned 1:1 to receive pembrolizumab 200 mg or placebo (normal saline) + trastuzumab + investigator's choice of FP (cisplatin + 5-fluorouracil) or CapeOX in the global cohort or SOX in the Japan-specific cohort. The study is ongoing, and might be beneficial for patients with HER2-positive disease.

Keynote-859 (NCT03675737), another global Phase III study trials, is an ongoing study to evaluate pembrolizumab or placebo combination with investigator's choice of chemotherapy (FP: 5-fluorouracil 800 mg/m²/day on d1-5 + cisplatin 80 mg/m² d1 Q3W or CAPOX) in HER2(-) patients.^[22]

In recent years, new immunotherapy agents has been approved for cancer immunotherapy and obtained approval of clinical trials for the first therapy in advanced GC. Lymphocyte activation gene 3 (LAG-3) is expressed on activated T cells, natural killer cells or B cells, and functions to negatively regulate homeostasis of these cells. Anti-LAG-3 antibodies has been showed promising antitumor regimen for immunotherapy of solid tumors.^[23] Relatlimab, a Anti-LAG-3 antibody. NCT03662659 is a randomized, phase II study of Relatlimab (Anti-LAG-3) and Nivolumab plus Chemotherapy (investigator's choice chemotherapy: CapeOX or FOLFOX or SOX) Versus Nivolumab plus chemotherapy as First-Line Treatment in Patients With G/GEJ cancer. The primary endpoint is ORR. The secondary is Incidence of Adverse Events, incidence of Serious Adverse events, Incidence of death, DOR, OS and PFS. The study is recruiting, and will be completed in 2024 (<https://clinicaltrials.gov/ct2/show/NCT03662659>).

The role of maintenance therapy following completion of standard first-line chemotherapy for G/GEJ is unclear. JAVELIN Gastric 100 (NCT02625610), a global, open-label, phase III trial, answered this question.^[24] Eligible patients who had untreated, unresectable, human HER2-negative, locally advanced or metastatic GC or GEJ cancer, without progressive disease after 12 weeks of first-line chemotherapy with oxaliplatin plus a fluoropyrimidine were randomly assigned 1:1 (249:250) to avelumab 10 mg/kg every 2 weeks or continued chemotherapy. Both Median OS (10.4 vs 10.9) and 24-month OS rate (22.1% vs 15.5%) showed no statistically difference, as well as that of in the PD-L1-positive population.^[25] JAVELIN Gastric 100 failed to demonstrate superior OS with avelumab maintenance versus continued chemotherapy in patients with advanced GC or GEJ cancer overall or in a prespecified PD-L1-positive population. While, another ongoing study for maintenance therapy, platform (NCT02678182), a prospective, open label, multicentre, randomised phase II clinical trial, will evaluate the efficacy of maintenance therapies following completion of standard first-line chemotherapy in patients with locally advanced or metastatic HER-2 positive or HER-2 negative oesophago-gastric adenocarcinomas. Eligible patients will be randomised according to HER-2 status. HER-2 positive patients (~20%) will not be randomised and will be assigned maintenance single-agent trastuzumab (current UK standard), a comparator arm is in development. HER-2 negative

patients (~80%) will be randomised 1:1:1 between surveillance only (current UK standard), maintenance capecitabine, or maintenance immunotherapy (anti-PD-L1 antibody). The primary outcome is PFS, the secondary endpoint is progression-free rate, OS and ORR. The study is recruiting, and will be completed in June 2025 (<https://clinicaltrials.gov/ct2/show/NCT02678182>). NCT01585987 is a randomized, phase II trial comparing the efficacy of sequential Ipilimumab(anti-CTLA-4) Versus Best Supportive care following first-line chemotherapy in patients with unresectable locally advanced/metastatic G/GEJ cancer. The study is complete, results are expected in the near future.

1.3. The exploration of the late second-line treatment of ICIs and/or combined with chemotherapy in advanced GC

As the only published second-line therapy for advanced G/GEJ cancer, Keynote-061(NCT02370498), a randomised, open-label, phase 3 study and done at 148 medical centers in 30 countries, is to evaluate the efficacy of pembrolizumab or paclitaxel monotherapy in patients with PD-L1 CPS of 1 or higher.^[26] Median follow-up was 9.1 months. The OS improved less than 1 month in pembrolizumab compared with the chemotherapy group(9.1 vs 8.3 months, $P = .042$), no significant differences were found in PFS and ORR(1.5 vs 4.1 months for PFS, 15.5% vs 13.6% for ORR). In subgroup analysis, PD-L1 CPS ≥ 5 (HR 0.73; 95%CI 0.52-1.03) and ≥ 10 (HR 0.64; 95% CI 0.41–1.02) showed better efficacy in patients treated with pembrolizumab. But the grade 3–5 TRAEs were declined in immunotherapy group(14% vs 35%). Pembrolizumab failed to improve OS and PFS compared with paclitaxel as second-line therapy for advanced G/GEJ cancer with PD-L1 CPS of 1 or higher. But pembrolizumab showed better safety than paclitaxel.

Some other studies of second-line therapy in GC are ongoing (Table 3). KEYNOTE-063(NCT03019588), another second-line therapy to compare the efficacy and safety of treatment with pembrolizumab versus paclitaxel in Asian PD-L1 positive advanced G/GEJ adenocarcinoma patients. It is a phase III,

randomized, open-label clinical trial, enrolled 360 participants who randomly assigned 1:1 to receive pembrolizumab (200 mg d1, Q3W for up to approximately 2 years) or paclitaxel (80 mg/m² d1, 8 and 15 of Q4W for up to approximately 2 years). NCT04140318 is a prospective, multi-centers, single arm phase II trial, to evaluate the efficacy and safety of Sintilimab (PD-1 inhibitor, 200 mg, Q3W) and nab-paclitaxel (125 mg/m², d1,d8, Q3W) in second line treatment of advanced G/GEJ adenocarcinoma. NCT04592211 is a phase Ib/II study to evaluate the efficacy of paclitaxel in combination with pembrolizumab and olaparib as a second line treatment in recurrent/advanced G/GEJ cancer with homologous recombination repair, mutation and microsatellite stable. The study will be completed in 2023.

PRODIGE 59(NCT03959293) is a randomised phase II study to evaluate FOLFIRI + Durvalumab vs FOLFIRI + Durvalumab and Tremelimumab in second-line treatment of patients with advanced GC.^[27] A safety analysis will be performed on 11 patients to ensure that treatment is well tolerated. Primary outcome is percentage of patients alive and without progression at 4 months. The study will be completed in 2024.

Patients with tumors refractory to anti-PD-(L)1 constitute a paramount priority in clinical oncology. BO-112, a synthetic nanoplexed doubled-stranded, noncodingRNA(poly I:C), has an antitumor activity and could increase the immune responses. It was reported that intratumoral BO-112 combined with anti-PD-1 agents had a manageable toxicity profile and produced evidence of clinical activity, and maybe a potential therapeutic tool to overcome primary resistance to anti-PD-1 therapy.^[28] KEYNOTE-A06 (NCT04508140) is an open, single arm, multicenter phase 2 trial including 2 cohorts to evaluate the safety, tolerability, and antitumor activity of BO-112 injected into a hepatic metastatic lesion in combination with pembrolizumab for colorectal or G/GEJ cancer with liver metastasis. Cohort 1 will enroll colorectal cancer patients with liver metastasis. In Cohort 2, gastric or G/GEJ patients who have received at least 1 prior standard of care systemic anticancer therapy for advanced/metastatic disease will receive BO-112 given intratumorally inside the liver metastasis at the dose

Table 3
Clinical trials of the late second-line treatment of ICIs and/or combined with chemotherapy in advanced GC.

Study number	Phase	Study design	Disease	Effect or study status
NCT02370498 (Keynote-061)	III	Pembrolizumab vs paclitaxel monotherapy	previously treated advanced G/GEJ with PD-L1 CPS ≥ 1	ORR:15.5%vs13.6% Median OS: 9.1 vs 8.3 mo PFS: 1.5 vs 4.1 months grade 3–5 treatment-related Ads: 14% vs 35%.
NCT03019588 (Keynote-063)	III	Pembrolizumab vs paclitaxel	PD-L1 positive advanced G/GEJ (Asian)	The study is terminated (Business Reasons).
NCT04140318 (NCC2070)	II	Sintilimab+ nab-paclitaxel	advanced G/GEJ	The study is ongoing Completed date: October, 2022
NCT04592211	Ib/II	olaparib+pembrolizumab+ paclitaxel	recurrent/advanced G/GEJ Cancer With (HRR mutation and MSS	The study is ongoing Completed date: May, 2023
NCT04508140 (KEYNOTE-A06)	II	BO-112 given intratumorally inside the liver metastasis + intravenous pembrolizumab	colorectal or G/GEJ with liver metastasis	The study is ongoing. Completed date: July, 2023.
NCT03959293 (PRODIGE 59)	II	FOLFIRI + Durvalumab vs FOLFIRI + Durvalumab+ Tremelimumab	advanced GC	The study is ongoing. Completed date: July, 2024.
NCT04178460	Ib	Niraparib combined with MGD013	Advanced or Metastatic G/GEJ Failed Prior Treatment	The study is ongoing. Completed date: December, 2024

HRR = homologous recombination repair, MSS = mutation and microsatellite stable.

of 1gm in 1.2ml in combination with intravenous pembrolizumab given at the fixed dose of 200 mg(Q3W, with a maximum duration of 35 cycles). The study is ongoing and will be completed in 2023 (<https://clinicaltrials.gov/ct2/show/NCT04508140>).

To date, some new ICIs obtain approval of clinical trials for the second-line or subsequent therapy in advanced GC. NCT04178460 is a open-label, single-arm, multicenter, phase Ib dose escalation and expansion clinical study to assess the safety and antitumor activity of niraparib(a selective PARP1 and PARP2 inhibitor) in combination with MGD013 (bispecific antibody that targets both PD-1 and LAG-3) in patients with advanced or metastatic GC who failed prior treatment.

1.4. Neoadjuvant/adjvant immunotherapy in advanced GC

For locally advanced GC, evidence showed that neoadjuvant therapy could improve the rate of surgical resection and reduce recurrence and metastasis.^[29] Cancer immunotherapy drugs that block PD-1 or PD-L1 facilitate endogenous antitumor immunity, and have demonstrated durable efficacy in patients with advanced/metastatic cancers.^[30] More recently, the use of ICIs for the adjuvant treatment of patients with surgically resectable melanoma has also demonstrated efficacy by improving relapse-free survival and improving OS.^[31] Up to now, there are some ongoing trials on neoadjuvant/adjvant immunotherapy in GC (Table 4). Keynote-585(NCT03221426) is a phase 3, randomized clinical trial to evaluate the efficacy of pembrolizumab or placebo combined chemotherapy (FP or XP for 3 cycles prior to surgery, and 14 cycles after surgery) in the neoadjuvant (prior to surgery) or adjuvant (after surgery) treatment of previously untreated patients with G/GEJ adenocarcinoma.^[32] Patients was randomly assigned (1:1) to receive pembrolizumab or placebo every 3 weeks in combination with FP(cisplatin plus 5-

fluorouracil) or XP (cisplatin plus capecitabine), according to investigator choice. Furthermore, a separate safety cohort will evaluate 5-fluorouracil + docetaxel + oxaliplatin + leucovorin (FLOT) as a potential chemotherapy option. The study is ongoing and will estimate to be completed in2024 (<https://clinicaltrials.gov/ct2/show/NCT03488667>) is another phase 2 study to evaluate the antitumor activity and safety/tolerability of the combination (mFOLFOX + Pembrolizumab) (before and after surgery) in patients with potentially resectable G/GEJ cancer. The study is completed in2023.

ATTRACTION 05(NCT03006705) is a multicenter, double-blind, randomized study in Asian, to evaluate the efficacy and safety of postoperative adjuvant chemotherapy with Nivolumab or placebo in combination with S-1 or CapeOX, in pStage III GC (including esophagogastric junction cancer) after D2 or more extensive lymph node dissection. The primary endpoint is relapse-free survival. Patients will receive nivolumab(360mg Q3W) or placebo plus S-1(40 - 60 mg bid orally in 28 days, followed by 14 days off) or CapeOX(Oxaliplatin 130 mg/m² d1 +Capecitabine 1000 mg2 bid orally in 14 days, Q3W). The study is estimated to be completed in 2023 (<https://clinicaltrials.gov/ct2/show/NCT03006705>).

NCT04592913 is another phase 3, randomized clinical trial to evaluate the efficacy of durvalumab or placebo combined with FLOT chemotherapy given before surgery (neoadjuvant) and after surgery (adjuvant) in resectable (removable by surgery) G/GEJC. The study is ongoing, and will be completed in 2025 (<https://clinicaltrials.gov/ct2/show/NCT04592913>).

PANDA (NCT03448835), ML42058(NCT04661150), ICONIC(NCT03399071) and DANTE(NCT03421288) are phase II ongoing studies of atezolizumab(an anti-PD-L1 monoclonal antibody) on neoadjuvant/adjvant immunotherapy in advanced GC. PANDA is a single-centre, phase II study to evaluate the efficacy of neoadjuvant atezolizumab+ chemotherapy(capecitabine, oxaliplatin and docetaxel) in non-metastatic, resectable G/

Table 4
Neoadjuvant/adjvant immunotherapy in resectable G/GEJ cancer.

Study number	Phase	Study design	Disease	Status	Completed date
NCT03488667	II	mFOLFOX6 +Pembrolizumab	patients with potentially resectable G/GEJ	Recruiting	April, 2023
NCT03006705 (Attraction-05)	III	Nivolumab or placebo + S-1 or CapeOX	pStage III G/GEJC after D2 or more extensive lymph node dissection	Recruiting	March, 2023
NCT03221426 (Keynote-585)	III	Pembrolizumab or placebo Plus Chemotherapy (XP or FP)	previously treated advanced G/GEJ with PD-L1 CPS \geq 1	Active, not recruiting	June, 2024
NCT04592913	III	Durvalumab or placebo combined with FLOT chemotherapy	Resectable GC/GEJCancer	Recruiting	February, 2025
NCT 03448835 (PANDA)	II	Atezolizumab+ chemotherapy (capecitabine, oxaliplatin and docetaxel)	Non-metastatic, Resectable Gastric and GE-junction Cancer	Recruiting	January, 2022
NCT04661150 (ML42058)	II	trastuzumab+XELOX with or without atezolizumab	locally advanced HER2-positive G/GEJ adenocarcinoma	Not yet recruiting	April, 2025
NCT03399071 (ICONIC)	II	Atezolizumab+ FLOT	Operable oesophageal and GC	Recruiting	August, 2025
NCT03421288 (DANTE)	II	Atezolizumab+ FLOT vs FLOT alone	locally advanced, operable adenocarcinoma of the stomach or GEJ.	Active, not recruiting	October, 2025
NCT03979131 (WHIO19001)	II	avelumab+FLOT (4 cycles previous to surgery + 4 cycles of adjuvant therapy, avelumab up to one year.	Resectable G/GEJC	Recruiting	June, 2026

CapeOX = Capecitabine plus oxaliplatin.

GEJC(1 cycle of atezolizumab followed by 4 cycles atezolizumab plus chemotherapy). The study is estimated to be completed in 2022 (<https://clinicaltrials.gov/ct2/show/NCT03448835>). NCT04661150 is a phase II, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of perioperative trastuzumab+XELOX with or without atezolizumab in patients with locally advanced HER2-positive G/GEJ adenocarcinoma. Participants will receive trastuzumab + XELOX with or without atezolizumab(1200mg on Day 1,Q3W) for 3 treatment cycles prior to surgery, and 5 further cycles after surgery. The study is estimated to be completed in 2025 (<https://clinicaltrials.gov/ct2/show/NCT04661150>). ICONIC is also a single-centre, phase II study to evaluate the safety and efficacy of avelumab plus cytotoxic FLOT chemotherapy(4 cycles prior to surgery, and 4 further cycles after surgery) for patients with operable oesophageal and GC treated according to a peri-operative protocol. The study is estimated to be completed in 2025 (<https://clinicaltrials.gov/ct2/show/NCT03399071>). NCT03421288 is a multicenter, randomized, controlled, open-label study comparing perioperative atezolizumab(840mg IV Q2W, 4 cycles perioperative with FLOT; 1200mg IV Q3W, 8 additional cycles monotherapy) with FLOT chemotherapy (docetaxel 50mg/m² d1, Oxaliplatin 85 mg/m² d1, Calciumfolinat 200mg/m² d1, 5-Fluorouracil 2600 mg/m² d1, Q2W) versus FLOT alone (4 cycles prior to surgery, and 4 further cycles after surgery) in patients with locally advanced, operable adenocarcinoma of the stomach or GEJ. The study is estimated to be completed in 2025 (<https://clinicaltrials.gov/ct2/show/NCT03421288>).

VHIO19001 (NCT03979131) is an open-label, non-randomized, multicentric phase II clinical trial to evaluate the efficacy of avelumab(up to one year) combined with chemotherapy (FLOT chemotherapy, 4 cycles previous to surgery + 4 cycles of adjuvant therapy) in the peri-operative treatment for patients with resectable G/GEJ cancer. The study is estimated to be completed in 2026 (<https://clinicaltrials.gov/ct2/show/NCT03979131>).

1.5. The exploration of dual immunotherapy in GC

To enhance the response in patients with advanced cancers, researchers also evaluated the efficacy of Dual PD-1/CTLA-4 blockade, and the combination immunotherapy with nivolumab (nivo) and ipilimumab (IPI) has shown encouraging effect in metastatic small-cell lung cancer, and colorectal cancer.^[33] Checkmate-032(NCT01928394), a phase I/II study to assess the safety and efficacy of nivo and nivo plus IPI in western patients with chemotherapy-refractory esophagogastric cancers.^[34] Patients were randomly assigned 1:1:1 to three group: nivo alone, nivo (1 mg/kg) with IPI (3 mg/kg) (N1+I3), or nivo (3 mg/kg) with IPI(1 mg/kg) (N3+I1). Results showed ORR was higher in PD-L1 ≥1% tumors (19% N alone, 40% in N1+I3, 23% in N3+I1) than that of in PD-L1 < 1% tumors (12% N alone, 22% in N1+I3, 0% in N3+I1). PFS was similar in all these groups, (1.4 months in N alone group vs 1.4 months for the N1+I3 group vs 1.6 months in the N3+I1 group). But 12-month PFS was better in combination immunotherapy(8% for the N alone, 17% of N1+I3, and, and 10% in N3+I1 groups). OS was 6.2 versus 6.9 versus 4.8 months, and 12-month OS was 39% versus 35% versus 24% in the N alone, N1+I3 group and N3+I1 group, respectively. The data provide encouraging OS with N1+I3, but grade 3/4 TRAEs was also higher in combination immunotherapy group(17% vs 47% vs 27% for N alone, N1+I3 group and N3+I1 group).^[34,35] So toxicity and drug sensitivity of ICIs

needs to be further optimized, and available therapeutic options are important. Data from Checkmate-649(NCT02872116) to evaluate the efficacy of nivolumab + IPI will show in near future.

FRACTION-GC(NCT02935634) is a phase 2, fast real-time assessment of Combination Therapies in Immuno-ONcology Study to determine whether nivolumab in combination with other therapies is more effective than nivolumab in combination with IPI in treating patients/subjects with advanced GC. The choice treatment consist of Nivolumaband IPI combination, nivo and relatlimab combination, nivo and BMS-986205 combination, Nivo and rucaparib combination, IPI with rucaparib combination and nivo with IPI and rucaparib. The study is estimated to be completed in 2023. Maybe this study will answer the question which combination therapeutic options are available (Table 5).

1.6. The exploration of ICIs plus target therapy in advanced GC

At present, trastuzumab has been approved for first-line treatment of advanced GC patients with HER-2 positive. The vascular endothelial growth factor (VEGF)-targeted drug, ramucirumab, has also been approved for second-line and subsequent therapy for advanced GC. But to date, targeted drugs have no significant efficacy in advanced first-line and second-line therapy, and the HER2-positive rate of advanced GC is only 12–13%. The overall survival rate for GC is only ~20% worldwide. How about the efficacy for ICIs combination with targeted drugs? KEYNOTE-811 and some ongoing clinical trials will answer this question (Table 6).

KEYNOTE-811(NCT03615326) is phase 3 study to evaluate the efficacy and safety of pembrolizumab in combination with trastuzumab and chemotherapy as first-line treatment of patients with advanced/metastatic HER2-positive GC. The study is ongoing, and we expect exciting results.

In recent years, several novel anti-HER2 agents are emerging, trastuzumab deruxtecan is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor, and showed durable antitumor activity in a pretreated patient population with HER2-positive metastatic breast cancer and GC, and is approved for GC in Japan.^[36,37] DESTINY-Gastric03(NCT04379596) is a phase 1b/2 multicenter, Open-label, dose-escalation and dose-expansion study to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary antitumor activity of trastuzumab deruxtecan (T-DXd,) alone or in combination with chemotherapy and/or durvalumab in HER2-positive advanced/metastatic G/ GEJ adenocarcinoma patients. The study will complete in December 2022. Furthermore, margetuximab, a novel FC-engineered anti-HER2 monoclonal antibody, has recently demonstrated to improve PFS compared with trastuzumab, when combined with chemotherapy for pretreated HER2-positive advanced breast cancer.^[38] CP-MGAH22-05(NCT02689284) and MAHOGANY(NCT04082364) are two studies of margetuximab in GC. CP-MGAH22-05 is a single-arm, open-label, phase 1b-2 dose-escalation and cohort expansion study done at 11 academic centers in the USA and Canada and 15 centers in southeast Asia (Korea, Taiwan, and Singapore) to evaluate the safety, tolerability, and antitumor activity of margetuximab plus pembrolizumab in previously treated patients with HER2-positive gastro-oesophageal adenocarcinoma.^[39] 95 patients were enrolled. Median follow-up was 19.9 months (10.7-23.1 months).

Table 5**Dual immunotherapy in advanced G/GEJ cancer.**

Study number	Phase	Study design	Disease	Status	Effect or completed date
NCT01928394 (Checkmate-032)	I/II	Nivolumab(nivo) alone or nivo (1 mg/kg) + ipilimumab (ipi, 3 mg/kg) (N1+I3), or nivo (3 mg/kg) + ipi (1 mg/kg) (N3+I1).	Western patients with chemotherapy-refractory esophagogastric cancers	completed	N vs N1 +I3 vs N3 +I1: ORR: PD-L1 \geq 1%:19% vs 40 vs 23% PD-L1 <1%:12% vs 22% vs 0%. PFS:1.4 vs 1.4 vs1.6 mo 12-moPFS: 8%vs 17% vs 10% OS: 6.2 vs 6.9 vs 4.8 mo 12-mo OS: 39%vs35% vs 24% October, 2022
NCT02872116 (Checkmate-649)	III	Nivo + Ipi vs XELOX vs FOLFOX vs Nivo+ XELOX vs Nivo + FOLFOX	Previously Untreated Advanced or Metastatic G/GEJC	Active, not recruiting	October, 2022
NCT02935634	II	nivo+ Ipi vs nivo+relatlimab vs nivo + BMS-986205 vs Nivo +rucaparib vs Ipi + rucaparib vs nivo+ ipi + rucaparib	advanced GC	recruiting	May, 2023

Table 6**Studies of ICIs combined with target therapy in advanced GC.**

Study number	Phase	Study design	Disease	Status	Effect or completed date
NCT03406871 (REGONIVO)	Ib	regorafenib plus nivolumab	Advanced GC or Colorectal cancer	Active, not recruiting; completed in part	Regorafenib 80mg was the safety. Median PFS was 5.6 in patients with GC, and ORR was 44%. completed date: April, 2022
NCT02689284 (CP-MGAH22-05)	Ib/II	margetuximab plus pembrolizumab	previously treated HER2-positive gastro-oesophageal adenocarcinoma.	completed	ORR was 18.48%. No dose-limiting toxicities in the dose-escalation phase. 9% was serious TRAEs. No treatment-related deaths were reported.
NCT02443324 (Keynote-098)	Ia/b	ramucirumab plus pembrolizumab	advanced and unresectable or metastatic G/GEJ adenocarcinoma	Active, not recruiting	ORR was 7%(3/41). phase 1a safety, one patient died related to PD. For patients with no prior chemotherapy, ORR was 25% (32 for PD-L1-positive, and 40% for CPS \geq 10; 17% for PD-L1-negative) with duration of response not reached. PFS was 5.6 mo, and OS 14.6 mo.
NCT02999295	I/II	ramucirumab plus nivolumab	advanced or recurrent unresectable gastric or GEJ cancer	completed	Results are expected in the near future.
NCT03321630	II	lenvatinib and pemrolizumab	metastatic gastroesophageal cancer	recruiting	November, 2020
NCT04379596 (DESTINY-Gastric03)	1b/2	trastuzumab deruxtecan (T-DXd,) alone or + chemotherapy and/or durvalumab	HER2-positive advanced/ metastatic G/ GEJ adenocarcinoma	recruiting	December, 2022
NCT04609176	II	Cohort 1:camrelizumab and apatinib+SOX(as first line therapy) Cohort 2:camrelizumab and apatinib(\geq 1 line)	unresectable recurrent or metastatic Alpha-fetoprotein (AFP)-Producing G/GEJC	recruiting	March, 2023
NCT04082364 (MAHOGANY)	II/III	Margetuximab+INCMGA00012 vs Margetuximab + INCMGA00012+chemo vs Margetuximab +MGD013 +chemo vs Margetuximab +chemo vs Trastuzumab +XELOX or mFOLFOX-6	Metastatic or Locally Advanced, Treatment-naïve, HER2-Positive G/ GEJC	recruiting	May, 2026

TRAEs = treatment-related adverse events.

ORR was 18.48% of 92 evaluable patients. There were no dose-limiting toxicities in the dose-escalation phase. 9% was serious TRAEs. The most common grade 3-4 TRAEs were anaemia (4%) and infusion-related reactions (3%). No treatment-related deaths were reported. The combination therapy showed acceptable safety and tolerability. MAHOGANY (NCT04082364) is a phase 2/3, randomized, open-label study for the treatment of patients with HER2-positive G/GEJC to determine the efficacy of margetuximab combined with INCMGA00012 (also known as MGA012, anti-PD-1 checkpoint inhibitor) and margetuximab combined with INCMGA00012 or MGD013 and chemotherapy compared to trastuzumab combined with chemotherapy. There are 2 cohorts. Cohort A is a single-arm cohort to evaluate safety and efficacy of margetuximab plus INCMGA00012. Cohort B Part 1 is a randomized, 4-arm segment to evaluate margetuximab plus INCMGA00012 plus chemotherapy, margetuximab plus MGD013 plus chemotherapy, margetuximab plus chemotherapy, vs trastuzumab plus chemotherapy. Cohort B Part 2 is a randomized, 2-arm segment to evaluate margetuximab plus the selected checkpoint inhibitor from Part 1, plus chemotherapy vs. trastuzumab plus chemotherapy. The study will complete in 2026. Ramucirumab is approved as single agent or combined with paclitaxel as second-line treatment for advanced/metastatic GC.^[40-42] ICIs combined with VEGF-targeted drug may improve the efficacy. In keynote-098(NCT02443324), which is a phase 1a/b study to evaluate the safety and preliminary efficacy of ramucirumab plus pembrolizumab in patients with locally advanced and unresectable or metastatic G/GEJ adenocarcinoma, NSCLC, transitional cell carcinoma of the urothelium and so on.^[43] In G/GEJ adenocarcinoma cohort, 41 patients were enrolled, median follow-up was 32.8 months. ORR was 7% (3/41). During the first cycle of treatment (phase 1a safety), one patient who received the 8 mg/kg dose of ramucirumab was died, but the death was deemed related to progressive disease (PD). In phase 1b, the most common treatment-related serious adverse events were abdominal pain, only about 7% (3/41). It seems that ramucirumab in combination with pembrolizumab had a manageable safety profile. For 28 patients with no prior systemic chemotherapy, ORR was 25% (32 for PD-L1-positive, and 40% for CPS \geq 10; 17% for PD-L1-negative) with duration of response not reached. PFS was 5.6 months (PD-L1-positive, 8.6 months; PD-L1-negative, 4.3 months), and OS was 14.6 months (17.3 months for PD-L1-positive, and 24.7 months for CPS \geq 10; 11.3 months for PD-L1-negative), 12-month OS rates were numerically higher in the subset of patients with PD-L1-positive tumors and CPS \geq 10 compared to PD-L1-negative (66.7% vs. 80.0% vs. 41.7%, respectively).^[44] Ramucirumab plus pembrolizumab showed encouraging durable clinical activity, especially in patients with PD-L1-positive tumors. Another study, called NCT02999295, is to evaluate the safety and efficacy of ramucirumab plus nivolumab in patients with advanced or recurrent unresectable G/GEJ cancer. The study is completed, and the results are expected in the near future.

Regorafenib, an oral tyrosine kinase inhibitor targets VEGFR1-3, FGFR, etc, is approved for the treatment of refractory metastatic CRC, unresectable hepatocellular carcinoma following progression on sorafenib, and so on.^[45] REGONIVO (NCT03406871) is a phase Ib trial of regorafenib plus nivolumab for gastric and colorectal cancer.^[46] Results showed regorafenib 80mg was the safety. Median PFS was 5.6 in patients with GC, and objective tumor response was 44%. The common grade \geq 3 TRAEs were rash (12%), proteinuria (12%),

and palmar-plantar erythrodysesthesia (10%). The combination of regorafenib 80mg plus nivolumab had a manageable safety profile and encouraging antitumor activity in patients with gastric and colorectal cancer, which warrants additional investigations in larger cohorts.

Apatinib, a novel, small molecule, selective VEGFR-2 tyrosine kinase inhibitor, is the second anti-angiogenic drug to be approved in China for the treatment of advanced or metastatic GC.^[47] NCT04609176 is a prospective, phase II ongoing study to evaluate the efficacy of camrelizumab plus apatinib in G/GEJ cancer, which has 2 cohorts. In cohort 1, participants who have not received any previous therapy will receive camrelizumab and apatinib in combination with oxaliplatin and S-1. In cohort 2, camrelizumab combined with apatinib will also be evaluated in participants who have had \geq 1 line of previous treatment. The primary endpoint is the ORR. The study will complete in 2023. NCT03321630 is an open label, single arm phase II study, to determine the ORR for the combination of lenvatinib (a Multi-targeted Tyrosine Kinase Inhibitor) and pemrolizumab in patients with metastatic gastroesophageal cancer who have progressed on first or subsequent line therapies.

1.7. The biomarkers in the treatment of ICIs in advanced GC

Although PD-1/PD-L1 inhibitors have made significant progress in advanced GC. Noteworthy, not all patients could get benefit, and immunobiological markers can help to correctly screen suitable patients for PD-1/PD-L1 inhibitor therapy. Up to now, some biomarkers including PD-L1, MSI-H, Epstein Barr virus (EBV) and TMB status were reported to evaluate the efficacy of ICIs in GC (Fig. 1).

Evidence suggests that the PD-L1 status is related to the clinical outcomes of pembrolizumab.^[48] In a study, authors detected the PD1, PD-L1 and PD-L2 expression in 1,014 GC specimens.^[49] Results showed that 37.8% of the cases showed membranous PD-L1 expression in tumor cells and 74.9% in infiltrating immune cells, GC patients with higher T cell infiltration showed elevated PD-L1, PD-L2 and PD1 expression. These results highlight the need to assess both PD-L1 expression in all tumor context. So PD-L1 CPS is better for evaluating the efficacy of immunotherapy.

KEYNOTE-059 cohort 1, pembrolizumab monotherapy in patients with PD-L1 CPS \geq 1 demonstrated promising antitumor activity, and FDA recommended it for third-line or subsequent therapy for GC with PD-L1 levels by CPS of \geq 1. But in subgroup analysis of KEYNOTE-061 and KEYNOTE-062, PD-L CPS \geq 5 and/or \geq 10 showed better efficacy in patients treated with pabrolizumab. In comprehensive analysis, authors analyzed the efficacy of pembrolizumab in PD-L1-positive (CPS \geq 10) advanced G/GEJ cancer, including the first-, second-, and third-line setting in the above three studies.^[50] In KEYNOTE-059, the confirmed ORR was 17%, and median DOR was 21 months. Median OS was 8 months. In KEYNOTE-061, median OS prolonged 2 months pembrolizumab group compared with chemotherapy (10 vs 8 months), confirmed ORR with pembrolizumab was nearly 3 fold high than chemotherapy group (25% vs 9%). In KEYNOTE-062, median OS for pembrolizumab-treated patients improved 6 months compared with chemotherapy-treated patients (17 vs 11 months). All of the above data showed increasing the CPS cutoff to CPS \geq 10 in patients with

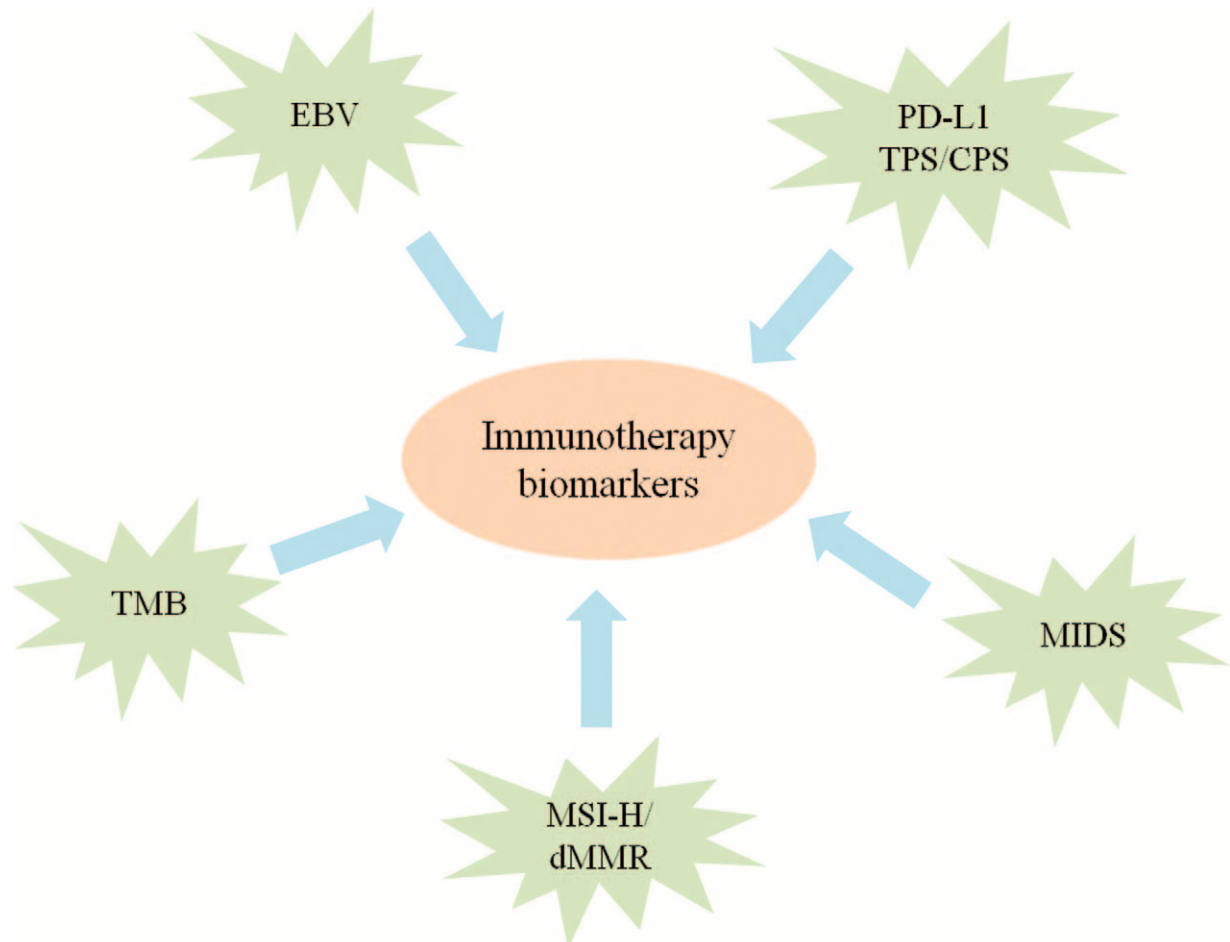


Figure 1. the potential biomarkers for ICIs in advanced GC.

G/GEJC may provide more favorable clinical outcomes for patients to receive pembrolizumab monotherapy.

And in a phase 1b trial, KEYNOTE-012 study (NCT01848834), researchers assessed the activity of pembrolizumab in patients with PD-L1–positive recurrent or metastatic adenocarcinoma of the stomach or GEJ.^[51] PD-L1 expression was measured with available biopsy samples at baseline using tumor proportion score (TPS) and mononuclear inflammatory cell density score (MIDS). Results failed to demonstrate an association between ORR and high PD-L1 expression using TPS, (24% for patients with TPS 0%, 0% for patients with TPS 1% to 49%, and 33% for patients with TPS \geq 50%), but showed ORR maybe related to MIDS (ORR was 0% for MIDS 0, 25% for MIDS 1, 12% for MIDS 2, 44% for MIDS 3, and 0% for MIDS 4). This suggests that measuring PD-L1 expression in immune cells maybe important.

To date, clinical trials have been proved that patients with microsatellite-unstable/instability (MSI) or dMMR status in advanced colorectal cancer showed a specific and highly immunosensitive population. And ICIs are recommended only for advanced colorectal cancer patients with MSI-H/dMMR type in NCCN and CSCO guidelines. How about in advanced GC? It was reported that MSI GCs seem responsive to immunotherapy drugs.^[52] In a meta analysis, which included KEYNOTE-062, CheckMate-649, JAVELIN Gastric 100 and

KEYNOTE-061 trials, 123 (4.8%) of 2545 patients had MSI-high cancers.^[53] The HR for OS benefit with anti-PD-1-based regimens was 0.34 (95% CI: 0.21–0.54) for MSI-high cancers compared with 0.85 (95% CI: 0.71–1.00) for mutation and microsatellite stable. The treatment effect was significantly different in the two subgroups ($P=.003$). In the MSI-high subgroup, the HR for PFS was 0.57 (95% CI: 0.33–0.97; $P=.04$) and the odds ratio for response was 1.76 (95% CI: 1.10–2.83; $P=.02$). It suggests that patients with MSI-high showed highly immunosensitive to PD-1/PD-L1-targeted immunotherapy.

It is reported that approximately 10% of GC patients showed EBV positive, and abundant PD-L1 expression was found in EBV positive GC.^[54,55] This makes EBV has a better response to immunotherapy and better survival in patients with EBV-positive GC.^[56,57] In a prospective observational study, all of 9 patients who were diagnosed with stage-IV EBV-associated GC, were treated by ICIs. Results showed 33 (33.3%) and 5 (55.6%) patients showed PR and stable disease after immunotherapy, respectively. The longest duration of response was 18 months by the time of the last follow-up.^[58] It was similar to Kim et al' report whose report that all of 6 recruited EBV-associated GC patients exhibited a PR after immunotherapy.^[59] All of above suggest that EBV-positive status may be a potential biomarker for GC immunotherapy.

TMB can also be a biomarker for the outcome of immunotherapy. NCT02915432 is a phase Ib/II study, to evaluate anti-tumor activity of toripalimab in advanced GC, and the predictive survival benefit of TMB and PD-L1.^[19] Results showed that the TMB-H group showed significant superior OS than the TMB-L group (14.6 vs 4.0 months, HR = 0.48, 96% CI 0.24–0.96, $P = .038$), while PD-L1 overexpression seemed no correlation with significant survival benefit. High TMB may be a predictive outcome marker for GC patients receiving ICIs.

2. Conclusion

In conclusion, ICIs have shown encouraging treatment efficacy and manageable safety profile in GC. To date, ICIs as the standard therapy are mainly recommended for the later line treatment (third line and/or later) of advanced GC in some guidelines including NCCN and CSCO, and nivolumab plus chemotherapy has been recommended as the first line treatment in advanced GC in CSCO guideline in 2021. But the exploration trials on the combination of immunization in the late second-line treatment has not made breakthrough progress, and the effective and suitable population is still worth exploring. PD-L1, MSI-H, EBV and TMB status maybe potential biomarkers for response to clinical outcomes for ICIs in GC.

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References

- [1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209–49.
- [2] Chen W, Sun K, Zheng R, et al. Cancer incidence and mortality in China, 2014. *Chin J Cancer Res* 2018;30:1–12.
- [3] Smyth EC, Nilsson M, Grabsch HI, et al. Gastric cancer. *Lancet* 2020;396:635–48.
- [4] Pellino A, Riello E, Nappo F, et al. Targeted therapies in metastatic gastric cancer: current knowledge and future perspectives. *World J Gastroenterol* 2019;25:5773–88.
- [5] Herrscher H, Robert C. Immune checkpoint inhibitors in melanoma in the metastatic, neoadjuvant, and adjuvant setting. *Curr Opin Oncol* 2020;32:106–13.
- [6] Onoi K, Chihara Y, Uchino J, et al. Immune Checkpoint Inhibitors for Lung Cancer Treatment: A Review. *J CLIN MED* 2020;9:1362.
- [7] Jacome AA, Eng C. Role of immune checkpoint inhibitors in the treatment of colorectal cancer: focus on nivolumab. *Expert Opin Biol Ther* 2019;19:1247–63.
- [8] Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;390:2461–71.
- [9] Chen LT, Satoh T, Ryu MH, et al. A phase 3 study of nivolumab in previously treated advanced gastric or gastroesophageal junction cancer (ATTRACTION-2): 2-year update data. *Gastric Cancer* 2020;23:510–9.
- [10] Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *Jama Oncol* 2018;4:e180013.
- [11] Fashoyin-Aje L, Donoghue M, Chen H, et al. FDA approval summary: pembrolizumab for recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma expressing PD-L1. *Oncologist* 2019;24:103–9.
- [12] Chung HC, Arkenau HT, Lee J, et al. Avelumab (anti-PD-L1) as first-line switch-maintenance or second-line therapy in patients with advanced gastric or gastroesophageal junction cancer: phase 1b results from the JAVELIN Solid Tumor trial. *J Immunother Cancer* 2019;7:30.
- [13] Bang YJ, Ruiz EY, Van Cutsem E, et al. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. *Ann Oncol* 2018;29:2052–60.
- [14] Bang YJ, Kang YK, Catenacci DV, et al. Pembrolizumab alone or in combination with chemotherapy as first-line therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: results from the phase II nonrandomized KEYNOTE-059 study. *Gastric Cancer* 2019;22:828–37.
- [15] Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. *JAMA ONCOL* 2020;6:1571–80.
- [16] Moehler M, Shitara K, Garrido M, et al. Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): first results of the CheckMate 649 study. *Ann Oncol* 2020;31:191.
- [17] Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021;398:27–40.
- [18] Boku N, Ryu MH, Kato K, et al. Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4). *Ann Oncol* 2019;30:250–8.
- [19] Wang F, Wei XL, Wang FH, et al. Safety, efficacy and tumor mutational burden as a biomarker of overall survival benefit in chemo-refractory gastric cancer treated with toripalimab, a PD-1 antibody in phase Ib/II clinical trial NCT02915432. *Ann Oncol* 2019;30:1479–86.
- [20] Kawazoe A, Yamaguchi K, Yasui H, et al. Safety and efficacy of pembrolizumab in combination with S-1 plus oxaliplatin as a first-line treatment in patients with advanced gastric/gastroesophageal junction cancer: cohort 1 data from the KEYNOTE-659 phase IIb study. *Eur J Cancer* 2020;129:97–106.
- [21] Chung HC, Bang YJ, S FC, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. *Future Oncol* 2021;17:491–501.
- [22] Taberner J, Bang YJ, Van Cutsem E, et al. KEYNOTE-859: a Phase III study of pembrolizumab plus chemotherapy in gastric/gastroesophageal junction adenocarcinoma. *Future Oncol* 2021;17:2847–55.
- [23] Yu X, Huang X, Chen X, et al. Characterization of a novel anti-human lymphocyte activation gene 3 (LAG-3) antibody for cancer immunotherapy. *MABS-AUSTIN* 2019;11:1139–48.
- [24] Moehler M, Ryu MH, Dvorkin M, et al. Maintenance avelumab versus continuation of first-line chemotherapy in gastric cancer: JAVELIN Gastric 100 study design. *Future Oncol* 2019;15:567–77.
- [25] Moehler M, Dvorkin M, Boku N, et al. Phase III Trial of avelumab maintenance after first-line induction chemotherapy versus continuation of chemotherapy in patients with gastric cancers: results From JAVELIN Gastric 100. *J Clin Oncol* 2020;O2000892.
- [26] Shitara K, Ozguroglu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2018;392:123–33.
- [27] Evrard C, Louvet C, Hajbi FE, et al. PRODIGE 59-DURIGAST trial: A randomised phase II study evaluating FOLFIRI+Durvalumab +/- Tremelimumab in second-line of patients with advanced gastric cancer. *Dig Liver Dis* 2020.
- [28] Marquez-Rodas I, Longo F, Rodriguez-Ruiz ME, et al. Intratumoral nanoplexed poly I:C BO-112 in combination with systemic anti-PD-1 for patients with anti-PD-1-refractory tumors. *Sci Transl Med* 2020;12.
- [29] Miao ZF, Liu XY, Wang ZN, et al. Effect of neoadjuvant chemotherapy in patients with gastric cancer: a PRISMA-compliant systematic review and meta-analysis. *BMC CANCER* 2018;18:118.
- [30] Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. *SCIENCE* 2020;367:eaax0182.

- [31] Pelster MS, Amaria RN. Neoadjuvant immunotherapy for locally advanced melanoma. *Curr Treat Options Oncol* 2020;21:10.
- [32] Bang YJ, Van Cutsem E, Fuchs CS, et al. KEYNOTE-585: phase III study of perioperative chemotherapy with or without pembrolizumab for gastric cancer. *FUTURE ONCOL* 2019;15:943–52.
- [33] Overman MJ, Lonardi S, Wong K, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA Mismatch Repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol* 2018;36:773–9.
- [34] Janjigian YY, Bendell J, Calvo E, et al. CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer. *J Clin Oncol* 2018;36:2836–44.
- [35] Sun S, Kim JJ, Ko YH. CheckMate-032 Study: promising efficacy with nivolumab-based immunotherapy in pretreated esophagogastric cancer. *J Thorac Dis* 2019;11(Suppl 3):S394–5.
- [36] Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med* 2020;382:610–21.
- [37] Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med* 2020;382:2419–30.
- [38] Tarantino P, Morganti S, Uliano J, et al. Margetuximab for the treatment of HER2-positive metastatic breast cancer. *Expert Opin Biol Ther* 2021;21:127–33.
- [39] Catenacci DVT KYPH, Knutson KL, Yen J, et al. Margetuximab plus pembrolizumab in patients with previously treated, HER2-positive gastro-oesophageal adenocarcinoma (CP-MGAH22-05): a single-arm, phase 1b-2 trial. *LANCET ONCOL* 2020;21:1066–76.
- [40] Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *LANCET* 2014;383:31–9.
- [41] De Vita F, Borg C, Farina G, et al. Ramucirumab and paclitaxel in patients with gastric cancer and prior trastuzumab: subgroup analysis from RAINBOW study. *Future Oncol* 2019;15:2723–31.
- [42] Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–35.
- [43] Herbst RS, Arkenau HT, Santana-Davila R, et al. Ramucirumab plus pembrolizumab in patients with previously treated advanced non-small-cell lung cancer, gastro-oesophageal cancer, or urothelial carcinomas (JVDF): a multicohort, non-randomised, open-label, phase 1a/b trial. *Lancet Oncol* 2019;20:1109–23.
- [44] Chau I, Penel N, Soriano AO, et al. Ramucirumab in Combination with pembrolizumab in treatment-naïve advanced gastric or GEJ adenocarcinoma: safety and antitumor activity from the phase 1a/b JVDF Trial. *Cancers (Basel)* 2020;12:2985.
- [45] Grothey A, Blay JY, Pavlakis N, et al. Evolving role of regorafenib for the treatment of advanced cancers. *CANCER TREAT REV* 2020;86:101993.
- [46] Fukuoka S, Hara H, Takahashi N, et al. Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer: an open-label, dose-escalation, and dose-expansion phase 1b trial (REGONIVO, EPOC1603). *J Clin Oncol* 2020;38:2053–61.
- [47] Scott LJ. Apatinib: a review in advanced gastric cancer and other advanced cancers. *DRUGS* 2018;78:747–58.
- [48] Wainberg ZA, Fuchs CS, Taberero J, et al. Efficacy of pembrolizumab monotherapy for advanced gastric/gastroesophageal junction cancer with programmed death ligand 1 combined positive score [greater than or equal to]10. *Clin Cancer Res* 2021;27:1923–31.
- [49] Xing X, Guo J, Ding G, et al. Analysis of PD1, PDL1, PDL2 expression and T cells infiltration in 1014 gastric cancer patients. *Oncoimmunology* 2018;7:e1356144.
- [50] Liu X, Guo CY, Tou FF, et al. Association of PD-L1 expression status with the efficacy of PD-1/PD-L1 inhibitors and overall survival in solid tumours: a systematic review and meta-analysis. *INT J CANCER* 2020;147:116–27.
- [51] Muro K, Chung HC, Shankaran V, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2016;17:717–26.
- [52] Rodriquenz MG, Roviello G, D'Angelo A, et al. MSI and EBV positive gastric cancer's subgroups and their link with novel immunotherapy. *J Clin Med* 2020;9:1427.
- [53] Pietrantonio F, Randon G, Di Bartolomeo M, et al. Predictive role of microsatellite instability for PD-1 blockade in patients with advanced gastric cancer: a meta-analysis of randomized clinical trials. *ESMO Open* 2021;6:100036.
- [54] Murphy G, Pfeiffer R, Camargo MC, Rabkin CS. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. *Gastroenterology* 2009;137:824–33.
- [55] Derks S, Liao X, Chiaravalli AM, et al. Abundant PD-L1 expression in Epstein-Barr Virus-infected gastric cancers. *Oncotarget* 2016;7:32925–32.
- [56] Kim SY, Park C, Kim HJ, et al. Deregulation of immune response genes in patients with Epstein-Barr virus-associated gastric cancer and outcomes. *Gastroenterology* 2015;148:137–47.
- [57] Sun K, Jia K, Lv H, et al. EBV-positive gastric cancer: current knowledge and future perspectives. *FRONT ONCOL* 2020;10:583463.
- [58] Xie T, Liu Y, Zhang Z, et al. Positive status of Epstein-Barr virus as a biomarker for gastric cancer immunotherapy: a prospective observational study. *J Immunother* 2020;43:139–44.
- [59] Kim ST, Cristescu R, Bass AJ, et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *NAT MED* 2018;24:1449–58.