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Immune checkpoint inhibitors for treatment of advanced Gastric adenocarcinoma

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Abstract
Systemic chemotherapy is the mainstay of therapy in patients with advanced gastric cancer, but has multiple drawbacks including lack of durable efficacy and dose limited toxicities. Recent clinical trials data on the efficacy of immune therapy in this patient group have shed light on its potential as an alternative treatment option. Recently, immunotherapy with antibodies that inhibit the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) interaction has emerged as a new treatment option. Although the toxicity of checkpoint inhibitors is generally unpredictable, they tend to be more manageable and better tolerated than the toxicities of systemic chemotherapy. Results from ongoing phase 3 trials are needed to further evaluate the potential roles of these agents within the continuum of care.

Keywords: immunotherapy, gastric carcinoma, checkpoint inhibitors

1. Introduction
Gastric cancer (GC) represents a major health problem worldwide [1]. Despite a decrease in incidence in past decades, stomach cancer remains the fifth most common type of cancer and the third leading cause of cancer-related mortality worldwide [2].
Because the pathogenesis of gastric cancers involves many different genetic mutations, as well as epigenetic alterations, and the dysfunction of molecular signalling pathways, many efforts have been undertaken in recent years to emphasize the molecular heterogeneity responsible not only for the process of carcinogenesis but also for cancer spread and metastasis. Each of these molecular alterations is involved in a different stage of cancerous disease [3].
Treatments with surgery, chemotherapy, radiation therapy, anti-angiogenic therapy have been the mainstay in the treatment of GC, but over the last decade novel therapeutics with immunotherapies have been evaluated in clinical trials as immunomodulatory strategies for GC.
In recent years, immune checkpoint blockade has emerged as an exciting therapeutic strategy in several malignancies.
The development of monoclonal antibodies that inhibit PD-1, PD-L1 and CTLA-4 have shown dramatic responses and clinical benefit across multiple tumor types.
Recently, some clinical trials have indicated that monoclonal antibodies that target PD-1 or its receptor PD-L1 prevent the inhibitory effects of PD-1/PD-L1 pathway and enhance T cell functions, leading to impressive outcomes in patients with cancers [4, 5]. However, from [6] `the predictive effects of PD-L1 in response to PD-1/PD-L1 antibodies in GC are not conclusive and the indication of PD-L1 expression in tumors remains controversial and needs to be further investigated'.
The remainder of this review focuses on clinical trials of various immune checkpoint inhibitors in GC, including completed or ongoing trials.

2. Materials and Methods
A literature search modality was applied for all English language literature published in the last 10 years, by assessing the PubMed electronic database, EBSCO, Web of Science and Cochrane Library. The keywords used for our research purposes were “gastric cancer”, “stomach neoplasm”, “targeted treatment”, “immunotherapy”, and “checkpoint inhibitors”. The specific search was also performed to identify clinical studies involving novel agents for gastric cancer treatment using the ClinicalTrials.gov database. Furthermore, the search was also performed on different cancer-related Web sites.

3. Results
3.1 Rationale for checkpoint inhibitors in GC
Immune checkpoint inhibitors have revolutionized the treatment of several malignancies, including melanoma and non-small- cell lung cancer. Many patients achieve durable disease control and prolonged survival with less toxicity compared to traditional chemotherapy [7, 8]
The development and progression of tumors are characterized by evasion of immune responses, including tumor escape mediated through immune checkpoint pathways [9, 12].
Key immune checkpoint proteins, including cytotoxic T lymphocyte antigen 4 (CTLA-4), indoleamine 2,3-dioxygenase (IDO), Tcell immunoglobulin and mucin domain-containing protein 3, lymphocyte activation gene 3 protein (LAG-3), and PD-1, are overexpressed on immune cells in patients with GC, suggesting a role for tumor induced T-cell exhaustion in disease progression [13–15]. PD-1 (expressed on immune cells) and its ligand, PD-L1 (expressed on immune and tumor cells), are expressed on up to 50% of GC tumors [16, 17]; expression has been associated with a worse prognosis.
Antibodies that block checkpoint proteins can restore and enhance antitumor activity of T cells by blocking inhibitory signals (Fig. 1) [18, 19]. Furthermore, some GC tumors have a high mutational burden, particularly MSI-high tumors creating tumor neoantigens that can be targeted by immune responses.

Based on genomic profiling, 4 distinct subtypes were described: Ebstein-Barr Virus (EBV)- associated tumors, microsatellite instability (MSI)-associated tumors, genetically-stable tumors, and tumors with chromosomal instability. The MSI subtype is associated with gene promoter hyper-methylations and exhibit high mutational burden including within the major histocompatibility class I genes. Moreover, EBV-associated tumors are characterized by amplification of genes coding for programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1), suggesting responsiveness to immune therapies targeting PD-1/PD-L1 [20].

3.2 Phase 1 and 2 trials of checkpoint inhibitors as 2L or later

The first study of a checkpoint inhibitor in GC/GEJC was a small phase 2 trial of tremelimumab (anti–CTLA-4), performed in 18 patients with metastatic gastric adenocarcinoma. In this study, the objective response rate (ORR) was low (1 of 18 patients [6%]), but the responding patient experienced a durable response and remained on treatment after 32.7 months [21].

The first study of an anti–PD-1 antibody in advanced GC was KEYNOTE-012, a phase 1b study of pembrolizumab in 39 patients with recurrent or metastatic PD-L1+ (≥1% tumor cell cutoff) GC adenocarcinoma; The ORR adjudicated by central review was 22%, based on 8 partial responses, with no significant difference between Asian and non-Asian patients (24% vs 21%, respectively), and the median OS was 11.4 months overall [22].

Following these encouraging results, a large phase 2 trial of pembrolizumab in patients with GC, comprising 3 cohorts, was initiated (KEYNOTE-059) [23]. Cohort 1 represents the largest early-phase trial of a checkpoint inhibitor in GC, enrolling 259 patients who received pembrolizumab monotherapy as 3L or later treatment [61]. The ORR in this cohort was 12%, with a trend for higher ORR in PD-L1+ vs PD-L1−tumors (16% vs 6%, respectively), and median OS was 5.5 months. Results from this cohort led to the accelerated approval of pembrolizumab by the US Food and Drug Administration (FDA) as 3L treatment for patients with advanced PD-L1+ GC [24]. Results from the other 2 cohorts of the KEYNOTE-059 trial are summarized in later sections of this review.

Avelumab, an anti–PD-L1 antibody, have been reported in the JAVELIN

Solid Tumor trial, it was administered to a large phase 1b cohort of patients with locally advanced or metastatic GC unselected for PD-L1 expression [25]. A total of 151 patients were enrolled, including a subgroup of 62 patients who received avelumab as 2L or later treatment. In an interim analysis from this subgroup, the unconfirmed ORR was 10%, and clinical activity was seen irrespective of PD-L1 expression status. OS data were not mature at the time of reporting.

3.3 Phase 1 and 2 trials of checkpoint inhibitors as 1L therapy

In addition to patients with previously treated GC, pembrolizumab monotherapy was also investigated as 1L treatment in cohort 3 of the phase 2 KEYNOTE-059 trial [23]. In the 31 patients enrolled, who all had PD-L1+/HER2− tumors, the ORR was 26%, median OS was 20.7 months.

In cohort 2 of KEYNOTE-059, 25 patients with advanced HER2− GC received 1L treatment with pembrolizumab in combination with 5-FU/cisplatin chemotherapy [23]. The ORR was 60%, and there was a potential association between PD-L1+ tumors and higher ORR (69% and 38% in patients with PD-L1+ vs PD-L1− tumors, respectively). Median OS was 13.8 months.

3.4 Phase 3 trials

JAVELIN Gastric 100 (NCT02625610) is the only phase 3 trial assessing switch-maintenance treatment with immunotherapy. This study is comparing avelumab vs continuation of leucovorin+5- FU+oxaliplatin (FOLFOX) or capecitabine+oxaliplatin (XELOX) in patients with advanced GC and without disease progression after 1L induction chemotherapy. The primary endpoints are PFS and OS, and recruitment is now complete.

Two phase 3 trials were designed to compare 2L pembrolizumab monotherapy vs paclitaxel in non-Asian (KEYNOTE-061; NCT02370498) or Asian (KEYNOTE-063; NCT03019588) patients with advanced PD-L1+ GC that progressed after 1L platinum/fluoropyrimidine doublet therapy. KEYNOTE-061 did not meet its primary endpoints of superior OS and PFS for pembrolizumab vs paclitaxel [26]; data for KEYNOTE-063, which has completed enrollment, are expected.

ATTRACTION- 02 (ONO-4538-12; NCT02267343) is a completed phase 3 trial of 3L or later nivolumab vs placebo in 493 Asian patients with unresectable advanced or recurrent GC [27]. Median OS (primary endpoint) was 5.3 vs 4.1 months (HR=0.63; $p < 0.0001$), and ORR was 11% vs 0% ($P < 0.0001$). Nivolumab efficacy was seen irrespective of PD-L1 status.

Based on this trial, the Japanese Ministry of Health, Labour, and Welfare approved nivolumab in September 2017 for the treatment of unresectable advanced or recurrent GC progressed after chemotherapy [28].

JAVELIN Gastric 300 (NCT02625623) is a global randomized trial of 3L avelumab compared with investigator choice of chemotherapy (either paclitaxel or irinotecan) performed in 371 patients with advanced GC progressed or relapsed after 2 prior lines of treatment, unselected for PD-L1 expression and stratified by region (Asia vs non-Asia), with all patients receiving BSC as background therapy. It has been reported in a press release that the trial did not meet its primary endpoint of superior OS for avelumab vs chemotherapy [29].

Ongoing phase 3 trials assessing checkpoint inhibitor–based combination therapy in the 1L setting are KEYNOTE-062 (NCT02494583), a trial of pembrolizumab alone or in combination with cisplatin/5-FU vs cisplatin/5-FU alone in patients with PD-L1+/HER2− advanced GC, and CheckMate 649 (NCT02872116), a 3-arm trial of nivolumab plus ipilimumab, nivolumab plus investigator choice of chemotherapy (XELOX or FOLFOX), or XELOX/FOLFOX alone in patients with previously untreated advanced or metastatic GC. The primary endpoint in both studies is OS in patients with PD-L1+ tumors. Enrollment in KEYNOTE-062 is complete.

3.5 Safety profile of checkpoint inhibitors in patients with GC

Checkpoint inhibitors are generally better tolerated than chemotherapy regimens administered to patients with GC. The profile of side effects that occur with different anti–PD-

1/PD-L1 inhibitors are broadly similar (Table 2) [22, 27]. The most common TRAEs of any grade across the different agents include fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, and rash. In addition, infusion-related reactions occur in approximately 13% of patients treated with avelumab; these reactions are typically low grade and occur during the first 1 to 2 infusions [25].

The incidence of grade ≥3 TRAEs with anti–PD-1/PD-L1 monotherapy in patients with GC ranges from approximately 10% to 20%, with the most common events including fatigue, anemia, and elevated alanine and aspartate aminotransferase levels (Table 2). Checkpoint inhibitor therapy is also associated with immune-related AEs (irAEs) that may affect rheumatic, gastrointestinal, skin, pulmonary, endocrine, neurological, hepatic, cardiac, and renal tissues [30].

Although AEs with checkpoint inhibitors are manageable in most cases through treatment interruption and corticosteroid treatment, long-term sequelae and deaths due to irAEs have been reported in a small proportion of patients highlighting the need for education of healthcare professionals and patients, close monitoring, and multidisciplinary collaboration to effectively manage these AEs.

3.6 Further Considerations in Immune Therapy Research

Currently, biomarkers predicting response to immune therapy for clinical use are remarkably underdeveloped. PD-L1 has proven to be effective in predicting response to anti-PD-1 therapy in non-squamous non-small cell lung cancer patients and is part of routine testing in these patient populations [31]

However, the predictability of this biomarker is poor in squamous non-small cell lung cancer patients and highly variable for combination immune therapies [32, 36]. Several other biomarkers including the presence or absence of tumorinfiltrating lymphocytes (TIL) are under evaluation. A recent study has proposed the use of criteria that rely on PD-L1 expression and TILs to classify tumors on the likelihood of responding to anti-PD-1/PD-L1 therapy [37]. The criteria seem to have some value in predicting response in melanoma.

However, further studies will be necessary to validate such criteria and other putative biomarkers in other types of cancers including EC and GC.

The dynamics of response to immune therapy are distinct from that of conventional chemotherapy. Treatment response seems to take a longer time to manifest for immune therapy than for conventional chemotherapy. Furthermore, immune therapy is associated with 'pseudoprogression' which refers to the initial increase in the size of cancer-associated lesions before decreasing in size to reflect treatment response [38-40]. Because of this reason, measurement of the response via criteria established for conventional chemotherapy such as RECIST 1.1 or WHO criteria are not optimal for immune therapy and thus the immune-related response criteria (irRC) have been established and are already in widespread use for objectively evaluating immune therapeutics [38]. Accurate evaluation of tumor responses to immune therapy will depend on fine-tuning of evaluation criteria that take into account the dynamics underlying innate and adaptive immune responses.

4. Conclusion

Recent advances in immune therapy have led to remarkable improvements in the management of advanced gastric cancer. The optimal strategy for incorporating checkpoint inhibitors in the continuum of care for patients with advanced GC is unknown, and a range of other strategies is being assessed in phase 3 trials, including monotherapy, maintenance therapy, and combination therapy in earlier lines. The role of checkpoint inhibitors in the premetastatic setting must also be evaluated, and trials are ongoing. Areas for further study include the development and validation of novel biomarkers to identify patients most likely to respond to treatment and characterization of outcomes with checkpoint inhibitors in different genomically defined disease subgroups. Future developments are eagerly awaited.

The future direction of immune therapeutic research should address the development of immune therapeutic biomarkers and improveing the evaluation of responses to immune therapy.

5. Tables and Figures

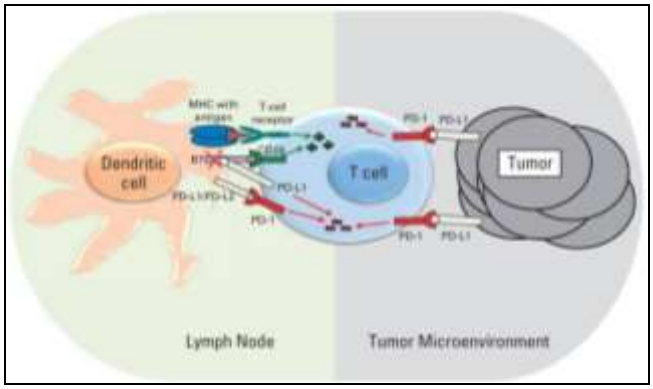

Fig 1: Overview of immune pathways and actions of checkpoint inhibitors.

Table 2: Treatment-related adverse events associated with checkpoint inhibitors in GC

Treatment	Any TRAE, %	Grade≥3 TRAEs	Grade≥3 TRAEs
Pembrolizumab	77	Anemia, fatigueNeutropenia, diffuse uveal melanocytic proliferation, colitis, bile duct obstruction, decreased neutrophils, dehydration, hyponatremia, rash	Pneumonitis, Hyperthyroidism Colitis, pneumonitis
Nivolumab	69	Nivolumab: decreased appetite, diarrhea, elevated AST, fatigue	Not reported
Avelumab	59	Anemia, asthenia, decreased platelet count, elevated GGT, fatigue	Colitis, adrenal insufficiency
Tremelimumab	83	Atrial fibrillation, elevated AST, diarrhea	Not reported
Ipilimumab	72	Ipilimumab: diarrhea, fatigue, asthenia, hypothyroidism	Not reported

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