Role of Nivolumab in the Management of First-Line Unresectable Advanced or Recurrent Gastric Cancer in Combination with Chemotherapy: Lessons from the Japanese Experience

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Abstract: Recently, immune checkpoint inhibitor (ICI), such as anti-programmed cell death-1 (PD-1) or programmed cell death ligand-1 (PD-L1) monoclonal antibodies, has provided clinical benefits in various cancer types including advanced gastric cancer (AGC). Nivolumab, a monoclonal anti-PD-1 antibody, firstly showed an improvement in the overall survival (OS) in patients with AGC in the ATTRACTION-2 trial. Recently, chemotherapy plus nivolumab, as a first-line treatment for AGC, showed both OS and progression-free survival (PFS) benefits in patients with PD-L1 combined positive score (CPS) ≥5 in the global CheckMate-649 trial, and demonstrated PFS benefit irrespective of CPS status in the Asian ATTRACTION-4 trial. Based on these results, chemotherapy plus nivolumab in a first-line treatment was approved worldwide. However, the approval requirements and recommendations are different according to the approval agent or country. Thus, this review summarized the clinical trials of chemotherapy plus anti-PD1 antibody as a first-line treatment and focused on the role of nivolumab combined with chemotherapy mainly from the viewpoint of the Japanese experience.

Keywords: immune checkpoint inhibitors, chemotherapy, programmed cell death-1, human epidermal growth factor receptor 2

Introduction

Gastric cancer, including gastro-esophageal junction cancer, is the fifth most reported cancer type and the fourth leading cause of cancer-related deaths worldwide.1 A combination of fluoropyrimidines and platinum agents was the standard first-line treatment for human epidermal growth factor receptor 2 (HER2)-negative advanced gastric cancer (AGC),2–4 and the combination of nivolumab is now added to the standard first-line treatment.5–7 A combination of fluoropyrimidines and platinum agents with trastuzumab is the standard first-line treatment for HER-2-positive AGC,8 with some preliminary evidence to support the combination with pembrolizumab.9 Taxanes, with or without ramucirumab, are recommended in patients with good general status as a second-line treatment.10,11 Third- or later-line treatment options include anti-programmed cell death-1 (PD-1) inhibitors, trifluridine/tipiracil or irinotecan, and trastuzumab deruxtecan (for HER-2-positive AGC).12–15 The prognosis remains poor (median overall survival [OS] of <18 months) despite the recent treatment option development.

Pivotal Trials with Chemotherapy Plus Immune Checkpoint Inhibitor as a First-Line Treatment

Recently, four Phase III trials were reported, including KEYNOTE-062, CheckMate-649, ATTRACTION-4, and ORIENT16, which verified the efficacy of chemotherapy plus anti-PD-1 antibody compared with chemotherapy
alone. The main study designs and results of these trials are summarized in Table 1. In this summary, we focused on chemotherapy plus ICI compared with standard chemotherapy, and the data about chemotherapy-free arm (pembrolizumab arm in KEYNOTE-062 and ipilimumab plus nivolumab arm in CheckMate-649) was not shown. The KEYNOTE-062 trial is a randomized, controlled, and partially blinded interventional Phase 3 trial that was conducted globally to evaluate the antitumor activity of pembrolizumab alone and pembrolizumab plus chemotherapy (XP: capecitabine plus cisplatin, or FP: fluoropyrimidine plus cisplatin) compared with standard chemotherapy (XP/FP) in patients with untreated AGC. This trial enrolled 763 patients who were randomized 1:1:1 to pembrolizumab, pembrolizumab plus chemotherapy, and chemotherapy plus placebo. Pembrolizumab plus chemotherapy was not superior to chemotherapy for OS in patients with either PD-L1 combined positive score (CPS) ≥1 (median, 12.5 vs 11.1 months; hazard ratio [HR]: 0.85; 95% confidence interval [CI]: 0.70–1.03; P = 0.05) or ≥10 (median: 12.3 vs 10.8 months; HR: 0.85; 95% CI: 0.62–1.17; P = 0.16), and for progression-free survival (PFS) in patients with CPS ≥1 (median: 6.9 vs 6.4 months; HR: 0.84; 95% CI: 0.70–1.02; P = 0.04). The subgroup analysis revealed that OS benefit was enriched in patients with microsatellite instability-high (MSI-H) tumors and CPS ≥1 (HR for OS: 0.37). Pembrolizumab was noninferior to chemotherapy for OS in patients with CPS ≥1.

The CheckMate-649 trial is a randomized, open-label, and phase 3 trial that was globally conducted to evaluate the antitumor activity of nivolumab plus chemotherapy (CapeOX/FOLFOX) and nivolumab plus ipilimumab compared to standard chemotherapy (CapeOX/FOLFOX) in patients with untreated AGC. A total of 1581 patients were assigned to nivolumab plus chemotherapy or chemotherapy. Nivolumab plus chemotherapy demonstrated significant OS (median: 14.4 vs 11.1 months; HR: 0.71; 98.4% CI: 0.59–0.86; P < 0.0001) and PFS improvements (7.7 vs 6.0 months; HR: 0.68; 98% CI: 0.56–0.81; P < 0.0001) compared with chemotherapy in patients with CPS ≥5. The additional analysis revealed significant OS improvements, accompanied by PFS benefit, in patients with CPS ≥1 and all randomized patients. Grades 3–4 treatment-related adverse events (AEs) occurred in 59% and 44% of the nivolumab plus chemotherapy and chemotherapy groups, respectively. The subgroup analysis revealed that OS benefit was enhanced in patients with MSI-H tumors (HR for OS: 0.38), which result was consistent with subgroup analysis in KEYNOTE-062. Enrolment to the nivolumab plus ipilimumab arm was closed early due to relatively higher incidence of adverse events and early death, and OS in patients with CPS ≥5 treated nivolumab plus ipilimumab did not meet the prespecified boundary for statistical significance compared with chemotherapy.

The ATTRACTION-4 trial is a randomized, double-blinded, placebo-controlled, and Phase 2–3 trial that was conducted in Asian countries to evaluate the antitumor activity of nivolumab plus chemotherapy (CapeOX/FOX) compared with standard chemotherapy (CapeOX/FOX) in patients with untreated AGC. A total of 724 patients were randomly assigned to treatment, including 362 in the nivolumab plus chemotherapy group and 362 in the placebo plus chemotherapy group. The analysis with a median follow-up of 11.6 months revealed a significant PFS improvement with nivolumab plus chemotherapy (median: 10.45 vs 8.34 months; HR: 0.68; 98.5% CI: 0.51–0.90; P = 0.0007). However, significant OS improvement was not demonstrated with a median follow-up of 26.6 months (median: 17.45 vs 17.15 months; HR: 0.90; 95% CI: 0.75–1.08; P = 0.26). Treatment-related serious AEs of any grade occurred in 25% and 14% of the nivolumab plus chemotherapy and placebo plus chemotherapy groups, respectively.

The ORIENT-16 trial is a randomized, double-blinded, and phase 3 trial that was conducted in China to evaluate the antitumor activity of sintilimab (anti-PD-1 antibody) plus chemotherapy (CapeOX) compared with standard chemotherapy (CapeOX) in patients with untreated AGC. A total of 650 patients were randomly assigned to treatment, including 327 in sintilimab plus chemotherapy and 323 in chemotherapy, with 397 patients having CPS ≥5. Sintilimab plus chemotherapy showed significant OS improvements compared with chemotherapy in patients with CPS ≥5 (median: 18.4 vs 12.9 months; HR: 0.660; 95% CI: 0.505–0.864; P = 0.0023) and all patients (median 15.2 vs 12.3 months; HR, 0.766; 95% CI 0.626–0.936; P = 0.0090). Treatment-related AEs with a grade of ≥3 occurred in 59.8% and 52.5% of the sintilimab plus chemotherapy and chemotherapy groups, respectively.

In summary, chemotherapy (fluoropyrimidines and platinum agents) plus anti-PD1 antibody, as a first-line treatment, showed significant OS benefit (HR: 0.66–0.77) in CheckMate-649 and ORIENT-16 and demonstrated significant PFS benefit (HR: 0.63–0.68) in CheckMate-649, ORIENT-16, and ATTRACTION-4. Only the KEYNOTE-062 did not show either OS or PFS benefit with anti-PD1 antibody plus chemotherapy. The response rates increased by approximately 10% (9–15%) with the addition of anti-PD1 antibody, while grade 3- AEs also increased by approximately 10% (3–14%), which
| Table 1 Summary of Pivotal Trials with Anti-PD1 Antibody Plus Chemotherapy for HER2-Negative AGC |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Design** | **KEYNOTE062** | **CheckMate649** | **ATTRACTION-4** | **ORIENT16** |
| **Phase** | P3 / blinded | P3 / open | P3 / blinded | P3 / blinded |
| **Region** | Global | Global | Asia (Japan, Korea, Taiwan) | China |
| **Eligibility** | GC / GEJ, HER2-neg | GC / GEJ, HER2-neg | GC / GEJ, HER2-neg | GC / GEJ, HER2-neg |
| **Chemo** | XP / FP | CapeOX / FOLFOX | CapeOX / SOX | CapeOX |
| **Anti-PD1** | Pembrolizumab | Nivolumab | Nivolumab | Sintilimab |
| **Primary endpoint** | OS and PFS | OS and PFS | OS and PFS | OS and PFS |
| **Primary cohort** | CPS ≥ 1 and CPS ≥ 10 | CPS ≥ 5 | All | CPS ≥ 5 and all |
| **Patients** | | | | |
| **Age (median)** | 62 | 63 | 64 | 62 |
| **Male** | 76% | 70% | 70% | 77% |
| **PS 0/1** | 46% / 54% | 41% / 59% | 54% / 46% | 27% / 73% |
| **Overall** | 25% | 25% | 100% | 100% |
| **Tumor status** | GC/EGJ/EC | 67% / 33% / 0% | 70% / 18% / 12% | 65% / 8% / 0% (NA 27%) |
| **Liver/ Peritoneal metastasis** | NR | 40% / 21% | 36% / 48% | 39% / NR |
| **TPS≥1** | NR | 23% | 16% | NR |
| **MSI-H** | 6.60% | 4% | NR | NR |
| **Results** | | | | |
| **Cohort** | CPS ≥ 1** | CPS ≥ 10*** | CPS ≥ 5** | CPS < 5 | All | All** | CPS ≥ 5** | All** |
| **mOS** | 12.5m vs 11.1m | 14.4m vs 11.1m | 12.4m vs 11.3m | 13.8m vs 11.6m | 17.5m vs 17.2m | 15.2m vs 12.9m | 18.4m vs 15.2m | 81% / 19% / 0% |
| **mPFS** | 6.9m vs 6.4m | 7.7m vs 6.0m | NR | NR | 10.5m vs 8.3m | 7.7m vs 5.8m | 7.1m vs 16.9m | 81% / 19% / 0% |
| **ORR** | 52.5% vs 55% | 60% vs 55% | 58% vs 58% | 57.5% vs 47.8% | 58.2% vs 48.4% | 58.2% vs 48.4% | 58.2% vs 48.4% | 58.2% vs 48.4% |
| **Grade 3–4 AE** | 52.5% vs 55% | 60% vs 55% | 58% vs 58% | 57.5% vs 47.8% | 58.2% vs 48.4% | 58.2% vs 48.4% | 58.2% vs 48.4% | 58.2% vs 48.4% |
| **Post treatment in control arm (Any / ICIIs)** | 54% / 14% | NR | NR | NR | 44% / 9% | 73% / 25% | NR | NR |

**Notes:** *Data in experimental cohort, **Primary cohort.

**Abbreviations:** AGC, advanced gastric cancer; XP, capecitabine plus cisplatin; FP, fluoropyrimidine plus cisplatin; PS, performance status; TPS, tumor proportion score; MSI-H, microsatellite instability-high; mOS, median overall survival; mPFS, median progression survival; m, months; AE, adverse event; ICIIs, immune checkpoint inhibitors; NA, not available; NR, not released.
were almost common in the trials. The subgroup analyses in CheckMate-649 and KEYNOTE-062 showed a greater survival benefit of immune checkpoint inhibitor (ICI) plus chemotherapy in patients with MSI-H tumors. Nivolumab plus chemotherapy should be aggressively considered for patients with MSI-H (or MMR deficient) tumors even if CPS is <5, considering that MSI-H tumors showed a higher response rate to ICI regardless of CPS status from previous studies.

Regarding the differences in characteristics among the trials, KEYNOTE-062 and CheckMate-649 were conducted globally, whereas ATTRACTION-4 and ORIENT-16 were conducted in Asia. Additionally, biomarker selection of the primary cohort was also different among the trials; KEYNOTE-062 with CPS ≥1 and ≥10; CheckMate-649 with CPS ≥5; ATTRACTION-4 with all patients; ORIENT-16 with CPS ≥5 and all patients. The population rate receiving post-study treatment, including ICIs in the control arm, was also different among the trials. The proportion receiving post-study ICIs was higher (28%) in ATTRACTION-4, which may have confounded the negative OS results. Further, backbone chemotherapy differs among the trials. Oxaliplatin was used as a platinum agent in the trials except for KEYNOTE-062. Oxaliplatin is reported to promote tumor-directed CD8+ cytotoxic T cell activation by inducing immunogenic cell death. This suggests the possibility of showing a synergistic effect with ICI, which might be one of the possible reasons for the positive results in CheckMate-649, ATTRACTION-4, and ORIENT-16. However, the Phase IIb study of pembrolizumab combined with S-1 plus oxaliplatin or S-1 plus cisplatin as a first-line treatment showed no obvious differences in efficacy according to backbone platinum agents, although this was not a direct comparison. Additionally, cisplatin with ICI also demonstrated clinical benefits in other trials for different tumor types, such as KEYNOTE-590 and CheckMate-648 for esophageal cancers. Therefore, further investigations are needed about backbone chemotherapy with ICIs. Statistical assumption and antiemetic corticosteroid usage (cisplatin regimen might be higher) may have affected the difference in the primary results besides these differences among the trials (region, patient selection according to CPS status, post-study treatment, and backbone chemotherapy).

### Asian or Japanese Subgroup

CheckMate-649 included Asian patients in approximately 23%. The OS benefits in the cohort of Asian patients with CPS ≥5 and all patients were similar to those of the whole cohort (HR for OS: 0.64 in CPS ≥5 and 0.80 overall). Conversely, obvious OS benefit was not seen in the Japanese cohort (median OS in experimental and control arm: 16.2 vs 16.1 months; HR: 1.26 in CPS ≥5; 17.0 vs 17.1 months; HR: 1.08 in all patients), although Japanese patients were too few to compare the two treatments (4.8% of the whole cohort). Similarly, OS benefit in Japanese patients was relatively small in ATTRACTION-4 (including Japanese in 54.8%) (median OS in experimental and control arm: 16.5 vs 19.1 months; HR: 1.04; 95% CI: 0.81–1.32). The OS in the control arm of Japanese was longer compared with that of the whole cohort of ATTRACTION-4 and CheckMate649, which may have been caused by the high rate of post-study treatment, including ICI (post-study chemotherapy/ICI, 79%/42% vs 73%/27% in ATTRACTION-4; 67%/32% vs 39%/8% in CheckMate649). Possible reasons for the higher rate of post-study treatment in Japan are based on the support of the national insurance system. Previous trials of the first-line and second-line treatment showed better survival outcomes in Asian/Japanese patients compared with Western patients, which is also consistent with the better OS in the control arm of trials with ICI.

The difference in tumor immunity in AGC between Asians and non-Asians has been reported, wherein AGC of non-Asians significantly showed higher expression of T-cell markers (CD3, CD45R0, and CD8) and lower expression of immunosuppressive T-regulatory cell marker (FOXP3) compared with Asian. However, clinical data showed no obvious differences in the efficacy of anti-PD1 antibody monotherapy between non-Asian and Asian patients; for example, the objective response rates of anti-PD1 antibody were almost the same (approximately 11–16%) in the Asian ATTRACTION-2 trial and the mainly non-Asian KEYNOTE-059 or KENOTE-061 trials. Additionally, genomic analysis of patients in KEYNOTE-059 and KEYNOTE-061 revealed no significant differences in genomic features including MSI-H between Asians and Whites. Overall, anti-PD1 antibody sensitivity is not different between Asians and non-Asians, and the difference in OS may come from the different rates of post-treatment.

The subgroup analyses of Japanese patients in CheckMate-649 and ATTRACTION-4 revealed that chemotherapy plus nivolumab did not improve OS because of the better survival of control arms in CheckMate-649 and ATTRACTION-4, but they are just results of subgroup analyses with caution.
Regulatory Approval and Guideline

Regulatory approvals of each region regarding first-line chemotherapy plus nivolumab and the recommendations of each guideline are summarized in Table 2. In Europe, the European Medicines Agency (EMA) has approved chemotherapy plus nivolumab as a first-line treatment in patients with a CPS ≥5. Conversely, the United States Food and Drug Administration (FDA) and Japan Ministry of Health, Labor, and Welfare approved the same regardless of CPS status. The viewpoints of each stance are summarized in Table 3.

Some valid reasons support the approval or its use in patients with CPS ≥5 only. Firstly, the primary endpoints in CheckMate-649, which showed significant improvements based on predefined statistical analyses, were OS and PFS in patients with CPS ≥5. The additional report of exploratory subgroup analysis did not reveal OS and PFS benefits in patients with CPS <5 (HR for OS: 0.95, 95% CI: 0.74–1.20, p = 0.678; HR for PFS: 0.95, 95% CI: 0.74–1.23, P = 0.743). The primary endpoints in ATTRACTION-4 were OS and PFS in all patients (regardless of CPS status); the OS result was negative without patients’ enrichment by CPS. Therefore, the OS benefit of additional nivolumab in first-line treatment was mainly driven by patients’ cohort with CPS ≥5. As previously mentioned, the objective response rate (ORR) increased by approximately 10% with additional nivolumab use even in CPS <5. However, no data showed the quality of life improvement from chemotherapy plus nivolumab in patients with CPS <5, although this was shown in patients with CPS ≥5 in CheckMate-649. Additionally, anti-PD1 antibody, in combination with chemotherapy in first-line treatment, increased AEs of grades 3–4 by 3–14%, which also increase inpatient treatment due to severe AEs (+4–10%) or treatment discontinuation (+1.4–13%). The additional nivolumab use in patients with CPS <5 is not reasonable considering the unproven effect on OS and increased toxicity from the viewpoint of risk and benefit ratio. Notably, examining both CPS and MSI status is necessary because MSI-H will be overlooked by approximately 25% in limited use to CPS ≥5.

Conversely, several acceptable reasons support the approval regardless of CPS status. First, CPS evaluation has some limitations. CPS status is unusually assessed using primary tumor biopsy in most patients with metastatic disease, but it might not accurately reflect the PD-L1 status of the entire tumor or metastatic disease because of tumor heterogeneity. Concordances of CPS status between single and multiple biopsies and between primary and metastatic tumors are

| Table 2 Regulatory Approval and Recommendation of Each Region About First-Line Chemotherapy Plus Nivolumab |
|--------------------------------------------------------------------------------------------------|
| **US/FDA** | **EU/EMA** | **Japan** |
| 1st line nivolumab indication | All comer | CPS ≥ 5 | All comer |
| Guideline | NCCN guideline 2022 ver2 | ESMO-MCBS ver1.1 (ESMO guideline) | JGCA |
| Recommendation | CPS ≥ 5 | Preferred (Category 1) | ESMO-MCBS: 4 | Recommended |
| | CPS < 5 | Useful in certain circumstance (Category 2B) | ESMO-MCBS: 3 | Need to carefully select chemotherapy or nivolumab plus chemotherapy |
| | All | – | ESMO-MCBS: 2 | – |
| Other G/GEJ AC indication | Pembrolizumab: 1st line HER2+ ≥ 2nd line MSI-H ≥ 2nd line TMB-H | None | Nivolumab: ≥3rd line all comer Pembrolizumab: ≥ 2nd line MSI-H |

**Notes:** Category 1, there is uniform NCCN consensus that the intervention is appropriate based upon high-level evidence; Category 2B, there is uniform NCCN consensus that intervention is appropriate based upon lower-level evidence; ESMO-MCBS, ESMO-magnitude of Clinical Benefit Scale of ≥4 indicate a substance magnitude of clinical benefit.

**Abbreviations:** CPS, PD-L1 combined positive score; G, gastric; GEJ, gastroesophageal junctional; AC, adenocarcinoma; FDA, US Food and Drug Administration; EMA, European Medicines Agency; JGCA, Japanese gastric Cancer Association.
relatively low (64.4% and 61%, respectively). Additionally, CPS is affected by immunohistochemistry assay or tumor specimen age (time from biopsy to immunohistochemistry). Secondly, additional nivolumab use in first-line treatment might show clinical benefit in some patients even in CPS <5, considering the viewpoint not to miss the opportunity of anti-PD1 antibody use. The use rates of anti-PD1 antibodies in later-line settings were low (8–28% in phase III trials), and anti-PD1 antibodies cannot be used in later-line in some countries unless MSI-H or high tumor mutational burden (TMB-H). Moreover, the addition of an anti-PD1 antibody in first-line treatment increased the ORR by approximately 10% even in CPS <5 (Table 1). Therefore, additional nivolumab use might be considered particularly for patients with high tumor volume or with symptoms caused by the tumor, even in CPS <5.

The approval of chemotherapy plus nivolumab in first-line treatment might depend on the attitudes of each regulatory agency toward evidence of clinical benefits, AEs, or cost-effectiveness. Careful discussions of each case about the addition of nivolumab are important, considering the risks and benefits. Additionally, further investigations are needed to optimize the treatment, such as biomarker exploration other than CPS.

### Experience During Pivotal Clinical Trials

The results of CheckMate-649 and ATTRACTION-4 have led to the approval of nivolumab plus chemotherapy combination for first-line treatment of AGC, but considering treatment adaptation in clinical practice is necessary. Generally, randomized clinical trials (RCTs) include only fit patients and exclude vulnerable patients, including older age, poor performance status (PS), organ dysfunction, or severe comorbidity. The PD-L1 expression status was examined by the central laboratory before randomization, which needed a certain screening period, in the recent RCTs of ICI plus chemotherapy (ICI-RCTs: CheckMate-649, KEYNOTE-062, and ATTRACTION-4). Therefore, patients who experienced deterioration in physical condition during the screening period could not wait to participate in RCTs. Hence, these trials may have enrolled more selected patients.

We retrospectively compared the characteristics and clinical outcomes of patients with AGC who received first-line chemotherapy in the control arm of ICI-RCTs (control group) or clinical practice (practice group) at our institution from February 2016 to April 2019, during which these ICI-RCTs were conducted. A total of 509 patients received primary treatment for AGC in our hospital. Excluding patients with positive HER2, 48 patients were treated in the control arm (control group) and 251 in clinical practice (practice group). Among the patients in the practice group, 28 were screened for ICI-RCTs but had become ineligible mainly because of deteriorating conditions during the screening period. The results showed that the control group included patients with better baseline Eastern Cooperative Oncology Group (ECOG) PS (0, 81.2% vs 51.4%; P < 0.001) and a longer interval from the first visit to first-line chemotherapy initiation (median: 19 days vs 9 days; P < 0.001) than the practice group. More patients in the control group were treated with...
subsequent chemotherapy than those in the practice group (87.5% vs 73.7%; \( P = 0.043 \)), including ICIs (50% vs 32.3%; \( P = 0.021 \)). Participation in additional clinical trials was also more common in the control group than in the practice group (37.5% vs 13.1%; \( P = 0.001 \)). The control group had the tendency of better survival benefits than the practice group with >4 months difference although not significant (median: 20.3 months vs 15.7 months; HR: 0.71; \( P = 0.062 \)). These results suggested that patients in the control group had better PS or a higher chance to receive subsequent chemotherapy, which resulted in a better prognosis than patients in the practice group. Particularly, the efficacy and safety of the ICI plus chemotherapy for patients, such as our practice group, remain unclear. This experience should be considered when interpreting the results of ICI-RCTs and their application into clinical practice.

**Single Institutional Experience After Nivolumab Approval/ Practical Consideration**

In November 2021, nivolumab plus chemotherapy was approved as the first-line treatment of AGC in Japan. Here, we introduce the current practical consideration of first-line chemotherapy in our institution. We usually perform immunohistochemistry (IHC) for HER2, PD-L1 CPS, and IHC for mismatch repair (MMR) protein (MLH1, MSH2, MSH6, and PMS2). Additionally, we have tested additional biomarkers, including *in-situ* hybridization for Epstein-Barr virus-encoded small RNA, IHC for FGFR2, EGFR, CLDN18,2, and MET, for research purposes to consider eligibility for ongoing clinical trials. The early introduction of chemotherapy before confirmation of biomarker results may be considered depending on the patient’s condition. Combination treatment with trastuzumab is considered for patients with positive HER2. Conversely, we consider the introduction of nivolumab combined with chemotherapy based on CPS and MMR status for patients with negative HER2. We would fundamentally consider nivolumab plus chemotherapy combination for patients with CPS ≥5 or MMR-D. However, vulnerable patients (elderly, poor PS, organ dysfunction, or severe comorbidity) or patients who are not indicated for ICI, such as concomitant autoimmune disease or interstitial pneumonia, were considered with chemotherapy alone even with CPS ≥5.

From November 2021 to June 2022, 110 patients with AGC received first-line chemotherapy in our hospital, of which 44 participated in clinical trials and 66 were treated in clinical practice (Figure 1). Of the patients treated in clinical practice, 11 were HER2-positive and 55 were HER2-negative. There were 23 patients with CPS ≥5 in the HER2-negative cohort, of which 18 patients were treated with nivolumab plus chemotherapy combination and 5 were treated with chemotherapy alone. The reasons to select chemotherapy alone regardless of CPS ≥5 were PS of ≥2 and comorbidity, such as dementia or pre-existing interstitial pneumonitis. Meanwhile, of the 32 patients with CPS <5 in the HER2-negative cohort, 30 were treated with chemotherapy alone and 2 were treated with nivolumab plus chemotherapy combination.
combination, of which 1 presented with MMR-D tumor. Most patients with CPS <5 received chemotherapy alone based on shared decision process between physicians and patients after explaining limited survival benefit of adding nivolumab despite increased AEs. Of the 20 patients who received nivolumab plus chemotherapy, 7 received chemotherapy alone before the nivolumab combination to start treatment earlier than biomarker confirmation or ensure the tolerability of chemotherapy alone due to poor conditions.

**Case Presentation**

We present two cases who received chemotherapy plus nivolumab as a first-line treatment in clinical practice. The two patients provided written informed consent for case presentation including publication of images and our hospital also approved for the case publication.

**Case 1**

A 62-year-old female patient was referred to our hospital with a diagnosis of gastric cancer with metastases of multiple lymph nodes, liver, peritoneum, and ovary (Figure 2A). The pathological examination showed well-differentiated tubular adenocarcinoma with HER2-negative and CPS of 5. She had difficulty in joining clinical trials due to severe anemia with hemoglobin of 4.3 g/dl. SOX regimen with 80% dose combined with nivolumab was started after sufficient red blood cell transfusion because this case presented CPS ≥5. After the third course, computed tomography (CT) showed marked primary and metastatic site shrinkage (Figure 2B). No major AEs were observed other than grade 1 pruritus. Partial response is maintained after the fifth course, and she remains on treatment.

As aforementioned, the evidence for nivolumab plus chemotherapy is based on RCTs in selected patient populations with good general conditions and prognosis; therefore, the efficacy and safety in patients with the impaired general condition remain unclear. Patients with severe anemia, such as this case, would be excluded from RCTs. Considering the risk of AEs and treating with more caution would be important when applying nivolumab plus chemotherapy combination to patients who could be excluded from pivotal trials, thereby reducing chemotherapy dose if applicable.

![Figure 2 CT scan in case 1. (A) Before the start of nivolumab plus SOX, (B) After the third course of nivolumab plus SOX. Explanations: Arrows in upper pictures show liver metastasis; Arrows in lower pictures show bilateral ovarian metastasis. Abbreviations: CT, computed tomography; SOX, S-1+oxaliplatin.](https://doi.org/10.2147/CMAR.S351791)
Case 2

A 59-year-old male patient with ECOG PS of 0 was diagnosed with AGC by upper gastrointestinal endoscopy (Figure 3A) with poorly differentiated adenocarcinoma by pathological examination. CT scan revealed metastases of multiple lymph nodes and liver, as well as interstitial infiltration, which suggested interstitial pneumonitis (IP) (Figure 3B and C). He had been treated for IP for 2 years, with prednisolone at dosage increased to 20 mg per day recently. This case presented a high CPS of 50 and MMR-D tumor, but SOX alone without nivolumab was selected because of his IP and anti-PD1 therapy in later-line with limited treatment options. CT showed a good response after two courses, but disease progression was suggested in liver metastasis after the fourth course of SOX. Pembrolizumab was given after careful discussion with the patient about the risk for flared IP. He presented dyspnea due to mediastinal and subcutaneous emphysema just after the second course of pembrolizumab (Figure 3D and E). CT showed that the metastatic lesions had maintained shrinkage (Figure 3F). The exacerbation of IP was not evident on CT, an increased dose of corticosteroid was administered, and his respiratory condition improved thereafter.

MSI-H is a good predictor of ICI responses. However, flaring of interstitial lung disease (ILD) could be expected. Additionally, the corticosteroid use of ≥10 mg was reported to attenuate the effect of PD-1 antibody in patients with non-small–cell lung cancer.\(^\text{38}\) Generally, most clinical trials of ICIs exclude patients with active acquired immunodeficiency and IP. Pre-existing ILD is reported as one of the risk factors for nivolumab-induced pneumonitis, not only in small cell lung cancer but also in solid tumors (odds ratio: 5.92, \(P = 0.0008\)).\(^\text{39}\) Furthermore, pneumonitis occurred in 5 of 17 (29.4%) patients, of which 1 was fatal, in the Phase II study investigating the safety and efficacy of atezolizumab monotherapy in patients with advanced or recurrent non–small cell lung cancer (NSCLC) with comorbid idiopathies.\(^\text{40}\) Thus, treatment selection should be carefully discussed with patients in terms of benefits and risk ratios.

Future Perspective

The nivolumab plus chemotherapy combination has changed the first-line treatment of AGC, wherein ICI is expected to play an important role in various combinations.

The vascular endothelial growth factor (VEGF) pathway inhibition was reported to effectively control tumor growth and inhibited the infiltration of immune suppressive cells while increasing the mature dendritic cell fraction.\(^\text{41}\) The phase Ib trial of regorafenib plus nivolumab and the Japanese phase II trial of lenvatinib plus pembrolizumab showed favorable results.\(^\text{42}\) A subsequent phase III LEAP-015 trial, evaluating lenvatinib plus pembrolizumab plus chemotherapy compared with chemotherapy (NCT04662710), is ongoing. Additionally, an anti-CTLA-4 antibody is expected to have
a synergistic effect with an anti-PD-1 antibody. The cohort of 1 mg/kg of nivolumab plus 3 mg/kg of ipilimumab was closed earlier than other cohorts in Checkmate-649, and nivolumab plus ipilimumab did not improve the OS compared with chemotherapy in patients with CPS $\geq 5$. Currently, a phase III trial (ATTRACTION-6) is ongoing in Asian countries, which investigates the efficacy and safety of nivolumab plus 1 mg/kg of ipilimumab plus chemotherapy. Including these trials, ICI development for first-line treatment in HER2-negative AGC is currently underway and results are expected (Table 4).

**Conclusion**

Nivolumab plus chemotherapy in the first-line setting has demonstrated clinical efficacy in patients with HER2-negative AGC. In Japan, nivolumab plus chemotherapy can be used for all patients irrespective of CPS status, the same as the United States. However, considering the limited survival benefits in patients with CPS <5 and increased AEs when nivolumab is combined, it is important to carefully decide whether to use chemotherapy plus nivolumab according to individual cases, considering CPS status, MSI status, and other clinical factors such as age, ECOG PS, or commodities. In Japan, nivolumab monotherapy can also be used for all patients in third or later line, and it might be also important not to miss the opportunity to use nivolumab in AGC. Further examinations are needed to optimize the combination or sequential treatment strategy in a first-line treatment.

**Disclosure**

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**Table 4 Overview of Ongoing Pivotal Clinical Trials, Including ICI as a First-Line Treatment in HER2-Negative AGC**

| Trial             | Phase | Patients | Target Structure | Arm                                     |
|-------------------|-------|----------|------------------|-----------------------------------------|
| KEYNOTE-859       | III   | All comer| PD-1             | CapeOX/ FP + Pembrolizumab              |
| (NCT03675737)     |       |          |                  | CapeOX / FP                            |
| BGB-A317-305      | III   | All comer| PD-1             | CapeOX + Tislelizumab                   |
| (NCT03777657)     |       |          |                  | CapeOX                                  |
| ATTRACTION-6      | III   | All comer| PD-1 + CTLA4     | SOX / CapeOX + Nivolumab + Ipilimumab   |
| (NCT029999295)    |       |          |                  | SOX / CapeOX                            |
| LEAP-15           | III   | All comer| PD-1 + VEGF, etc | CapeOX / FOLFOX + Lenvatinib + Pembrolizumab |
| (NCT04662710)     |       |          |                  | CapeOX / FOLFOX                         |
| SHR-1210          | III   | All comer| PD-1 + VEGF, etc | CapeOX + SHR-1210 (Anti-PD1) Maintenance: SHR-1210 ± Apatinib |
| (NCT03813784)     |       |          |                  | CapeOX                                  |

**Abbreviation:** FP, fluoropyrimidine + platinum.
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