Abstract

Background: Gastric cancer is a major global health concern with poor prognosis for patients with advanced disease. Pembrolizumab, a programmed cell death-1 (PD-1) inhibitor, has shown promise in the treatment of advanced gastric cancer. The KEYNOTE-659 study evaluated the efficacy and safety of pembrolizumab in combination with standard-of-care chemotherapy regimens as first-line therapy for Japanese patients with advanced gastric/gastroesophageal junction (G/GEJ) adenocarcinoma.

Methods: The KEYNOTE-659 study included two cohorts: cohort 1 evaluated pembrolizumab plus S-1 and oxaliplatin (SOX), and cohort 2 evaluated pembrolizumab plus S-1 and cisplatin (SP). The primary endpoint was objective response rate (ORR) assessed by central review. Secondary endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.

Results: In cohort 1 (n=54), the ORR was 72.2%, the median DOR was 10.6 months, the median PFS was 9.4 months, and the median OS was 16.9 months. In cohort 2 (n=46), the ORR was 80.4%, the median DOR was 9.5 months, the median PFS was 8.3 months, and the median OS was 17.1 months. The safety profile was manageable, with the most common treatment-related adverse events (TRAE) being neutropenia, decreased appetite, and nausea.

Conclusions: Pembrolizumab in combination with SOX or SP demonstrated favorable efficacy and a manageable safety profile as first-line treatment for Japanese patients with advanced G/GEJ adenocarcinoma. These results suggest that pembrolizumab-containing regimens may be a promising treatment option for this patient population.

Introduction

Gastric cancer is a significant global health concern, with a high incidence and mortality rate worldwide [1,2]. Despite advancements in treatment modalities, the prognosis for patients with advanced gastric cancer remains poor, with a 5-year survival rate of less than 30% [3,4]. Consequently, there is an urgent need to explore novel therapeutic approaches to improve clinical outcomes for this patient population.

Pembrolizumab, a programmed cell death-1 (PD-1) inhibitor, has emerged as a promising treatment option for various malignancies, including gastric cancer [5,6]. Pembrolizumab's mechanism of action involves blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby enhancing the immune system's ability to recognize and destroy cancer cells [7,8]. The clinical utility of pembrolizumab in gastric cancer has been investigated in several studies, with a particular focus on the Combined Positive Score (CPS) system, which measures the expression of PD-L1 on tumor cells and tumor-infiltrating immune cells [9,10].

The KEYNOTE-059 study, a phase 2 trial, evaluated the efficacy and safety of pembrolizumab as a monotherapy in patients with advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma who had received at least two prior lines of therapy [5]. The study demonstrated that pembrolizumab monotherapy resulted in an objective response rate (ORR) of 11.6% in the overall population, with higher ORRs observed in patients with a CPS $\geq$ 1 (15.5%) and CPS $\geq$ 10 (23.4%) [5]. These findings suggested that the CPS score could be a useful biomarker for predicting response to pembrolizumab in patients with advanced gastric cancer.

Building on the promising results of KEYNOTE-059, the KEYNOTE-062 study, a phase 3 trial, investigated the efficacy and safety of pembrolizumab as a first-line treatment for patients with advanced G/GEJ adenocarcinoma [11]. The study compared pembrolizumab monotherapy, pembrolizumab plus chemotherapy (cisplatin plus 5-fluorouracil or capecitabine), and chemotherapy alone. The results showed that pembrolizumab monotherapy was non-inferior to chemotherapy in terms of overall survival (OS) in patients with a CPS $\geq$ 1, and that the combination of pembrolizumab and chemotherapy did not improve OS compared to chemotherapy alone [11].

The KEYNOTE-659 study, the focus of the current investigation, was designed to further explore the efficacy and safety of pembrolizumab in combination with standard-of-care chemotherapy regimens in Japanese patients with advanced G/GEJ adenocarcinoma [12]. Specifically, the study evaluated the combination of pembrolizumab with S-1 (tegafur-gimeracil-oteracil potassium) and oxaliplatin (cohort 1) or S-1 and cisplatin (cohort 2) as first-line therapy. The results from cohort 1 have been previously reported, and this article presents the updated findings from cohort 1 as well as the efficacy and safety results for cohort 2 [12].

The current study builds upon the existing evidence on the use of pembrolizumab in the treatment of advanced gastric cancer. The KEYNOTE-059 and KEYNOTE-062 studies have demonstrated the potential of pembrolizumab, both as a monotherapy and in combination with chemotherapy, in this patient population [5,11]. The KEYNOTE-659 study aims to further elucidate the role of pembrolizumab in combination with different chemotherapy regimens, specifically in a Japanese cohort, which may provide valuable insights into the optimal treatment approach for patients with advanced G/GEJ adenocarcinoma.

Results

Baseline Characteristics

The baseline demographic and clinical characteristics of the study population are presented in Table 1. The median age was 66.0 years (range, 32-75 years) in cohort 1 and 65.0 years (range, 30-75 years) in cohort 2. The majority of patients were male (79.6% in cohort 1 and 60.9% in cohort 2). Most patients had an ECOG performance status of 0 (85.2% in cohort 1 and 76.1% in cohort 2). The majority of patients had metastatic disease at initial diagnosis (90.7% in cohort 1 and 84.8% in cohort 2). The primary tumor location was gastric in 85.2% and 87.0% of patients in cohorts 1 and 2, respectively. Diffuse-type histology was the most common (59.3% in cohort 1 and 52.2% in cohort 2). Most patients had less than 3 metastatic sites (68.5% in cohort 1 and 71.7% in cohort 2). The majority of patients had a CPS ≥10 (57.4% in cohort 1 and 58.7% in cohort 2).

Dose Intensity

The cumulative dose and dose intensity for each drug are summarized in Table 2. The median cumulative dose of pembrolizumab was 1700.0 mg (range, 400-7000 mg) in cohort 1 and 1600.0 mg (range, 400-7000 mg) in cohort 2. The mean actual dose intensity of pembrolizumab was 57.8 mg/week (SD, 9.1) in cohort 1 and 55.7 mg/week (SD, 10.8) in cohort 2, with a median relative dose intensity of 89.7% and 86.1%, respectively. For S-1, the median cumulative dose was 11,130.0 mg (range, 2,180-55,380 mg) in cohort 1 and 9,940.0 mg (range, 1,500-40,460 mg) in cohort 2, with a mean actual dose intensity of 234.5 mg/m2/week (SD, 51.6) and 223.7 mg/m2/week (SD, 72.4), respectively, and a median relative dose intensity of 72.2% and 68.4%. The median cumulative dose of oxaliplatin in cohort 1 was 688.6 mg/m2 (range, 230-1,633 mg/m2), with a mean actual dose intensity of 24.2 mg/m2/week (SD, 10.5) and a median relative dose intensity of 59.6%. In cohort 2, the median cumulative dose of cisplatin was 289.5 mg/m2 (range, 109-719 mg/m2), with a mean actual dose intensity of 11.2 mg/m2/week (SD, 5.4) and a median relative dose intensity of 57.0%.

Efficacy Outcomes

The best overall response and survival results are presented in Table 3. The ORR assessed by central review was 72.2% (95% CI, 58.4%-83.5%) in cohort 1 and 80.4% (95% CI, 66.1%-90.6%) in cohort 2. The disease control rate (DCR) was 96.3% (95% CI, 87.3%-99.5%) in cohort 1 and 97.8% (95% CI, 88.5%-99.9%) in cohort 2. The median PFS was 9.4 months (95% CI, 6.6-12.6 months) in cohort 1 and 8.3 months (95% CI, 5.8-15.3 months) in cohort 2. The median OS was 16.9 months (95% CI, 13.4-20.0 months) in cohort 1 and 17.1 months (95% CI, 12.6-23.1 months) in cohort 2. The median time to response was 1.5 months in both cohorts, and the median duration of response (DOR) was 10.6 months (95% CI, 5.6-not estimable) in cohort 1 and 9.5 months (95% CI, 4.7-15.3 months) in cohort 2.

The investigator-assessed efficacy outcomes are presented in Table 4. The ORR was 72.2% (95% CI, 58.4%-83.5%) in cohort 1 and 63.0% (95% CI, 47.5%-76.8%) in cohort 2. The DCR was 94.4% (95% CI, 84.6%-98.8%) in cohort 1 and 97.8% (95% CI, 88.5%-99.9%) in cohort 2. The median PFS was 6.9 months (95% CI, 5.6-8.3 months) in cohort 1 and 6.7 months (95% CI, 5.3-8.4 months) in cohort 2. The median OS was 16.9 months (95% CI, 13.4-20.0 months) in cohort 1 and 17.1 months (95% CI, 12.6-23.1 months) in cohort 2.

The overall tumor response assessed by central review according to RECIST version 1.1 is shown in Figure 1. The best change from baseline in the sum of the longest target lesion diameter per patient by CPS is also presented in this figure.

The Kaplan-Meier estimates of PFS assessed by central review are shown in Figure 2. The median PFS was 9.4 months (95% CI, 6.6-12.6 months) in cohort 1 and 8.3 months (95% CI, 5.8-15.3 months) in cohort 2.

The Kaplan-Meier estimates of OS are presented in Figure 3. The median OS was 16.9 months (95% CI, 13.4-20.0 months) in cohort 1 and 17.1 months (95% CI, 12.6-23.1 months) in cohort 2.

The Kaplan-Meier estimates of PFS and OS by CPS are shown in Figures 4 and 5, respectively. In cohort 1, the median PFS was 9.4 months (95% CI, 6.6-12.6 months) for CPS ≥10 and 9.4 months (95% CI, 5.6-12.6 months) for CPS 1-9. The median OS was 16.9 months (95% CI, 13.4-20.0 months) for CPS ≥10 and 16.9 months (95% CI, 12.6-20.0 months) for CPS 1-9. In cohort 2, the median PFS was 15.3 months (95% CI, 5.8-not estimable) for CPS ≥10 and 6.7 months (95% CI, 5.3-8.4 months) for CPS 1-9. The median OS was 23.1 months (95% CI, 12.6-not estimable) for CPS ≥10 and 12.6 months (95% CI, 9.2-17.1 months) for CPS 1-9.

Safety

The incidence of TRAEs is summarized in Table 5. All patients in both cohorts experienced at least one TRAE. The most common TRAEs (≥10% in either cohort) included neutrophil count decreased, decreased appetite, nausea, constipation, diarrhea, anemia, stomatitis, dysgeusia, malaise, peripheral sensory neuropathy, platelet count decreased, fatigue, vomiting, and white blood cell count decreased. Grade ≥3 TRAEs occurred in 59.3% and 78.3% of patients in cohorts 1 and 2, respectively.

The incidence of TRAEs of interest, including adrenal insufficiency, hypothyroidism, hyperthyroidism, colitis, pneumonitis, and type 1 diabetes mellitus, is also reported in Table 5. Adrenal insufficiency occurred in 5.6% and 6.5% of patients in cohorts 1 and 2, respectively, with grade ≥3 events in 5.6% and 4.3% of patients. Hypothyroidism was reported in 9.3% of patients in cohort 1 and 6.5% in cohort 2, with no grade ≥3 events. Hyperthyroidism was reported in 3.7% and 4.3% of patients in cohorts 1 and 2, respectively, with no grade ≥3 events. Colitis occurred in 11.1% of patients in cohort 1, with 7.4% experiencing grade ≥3 events, compared to 2.2% in cohort 2 with no grade ≥3 events. Pneumonitis was reported in 7.4% of patients in cohort 1, with 1.9% experiencing grade ≥3 events, and in 2.2% of patients in cohort 2 with no grade ≥3 events. Type 1 diabetes mellitus was reported in 1.9% of patients in cohort 1 and 2.2% in cohort 2, with grade ≥3 events in 1.9% and 2.2% of patients, respectively.

Discussion

The present study evaluated the efficacy and safety of pembrolizumab in combination with SOX or SP as a first-line treatment in patients with advanced G/GEJ adenocarcinoma with PD-L1 expression. The primary endpoint was the ORR, and other endpoints included DOR, DCR, PFS, OS, and safety.

The results of our study showed a favorable efficacy profile for the pembrolizumab-containing regimens. In cohort 1 (pembrolizumab + SOX), the ORR was 61.5%, with a median DOR of 7.4 months, a median PFS of 8.3 months, and a median OS of 16.4 months [13]. In cohort 2 (pembrolizumab + SP), the ORR was 55.0%, with a median DOR of 7.4 months, a median PFS of 7.5 months, and a median OS of 13.1 months [13]. These findings are consistent with the results reported in the KEYNOTE-659 study, which evaluated the safety and efficacy of pembrolizumab in combination with SOX as a first-line treatment for advanced G/GEJ adenocarcinoma [14]. In that study, the ORR was 60.0%, the median PFS was 8.3 months, and the median OS was 16.4 months [14].

The safety profile of the pembrolizumab-containing regimens in our study was also favorable. TRAEs occurred in all patients, with the most common being peripheral sensory neuropathy, decreased neutrophil count, nausea, and decreased appetite [13]. Grade 3 or higher TRAEs were reported, including decreased platelet count (cohort 1) and decreased neutrophil count (cohort 2) [13]. These findings are consistent with the safety profile reported in the KEYNOTE-061 study, which evaluated pembrolizumab versus paclitaxel in patients with previously treated, advanced G/GEJ cancer [6]. In that study, TRAEs were reported in 99.7% of patients receiving pembrolizumab, with the most common being fatigue, decreased appetite, and nausea [6].

The administration of pembrolizumab every three weeks and the high doses used in our study did not create any additional safety issues. This is in line with the findings from other studies that have evaluated pembrolizumab in combination with chemotherapy regimens for the treatment of advanced G/GEJ cancer [15,10]. For example, the KEYNOTE-062 study, which evaluated pembrolizumab with or without chemotherapy as a first-line treatment for advanced G/GEJ cancer, reported a similar safety profile for the pembrolizumab-containing regimens, with no unexpected toxicities [15].

When compared to other studies that have evaluated the use of pembrolizumab in combination with chemotherapy for the treatment of advanced G/GEJ cancer, our study appears to have superior outcomes. For instance, the KEYNOTE-062 study reported an ORR of 27.3% and a median PFS of 6.9 months for the pembrolizumab plus chemotherapy arm [15], which are lower than the results reported in our study. Similarly, the KEYNOTE-061 study, which evaluated pembrolizumab versus paclitaxel in previously treated, advanced G/GEJ cancer, reported a median PFS of 1.5 months and a median OS of 9.1 months for the pembrolizumab arm [6], which are also lower than the results reported in our study.

One potential explanation for the superior outcomes observed in our study may be the use of a different chemotherapy backbone (SOX or SP) in combination with pembrolizumab. The KEYNOTE-062 study used a platinum-based chemotherapy regimen (cisplatin plus 5-fluorouracil or capecitabine) [15], while the KEYNOTE-061 study used paclitaxel [6]. The combination of pembrolizumab with SOX or SP may have resulted in a more favorable synergistic effect, leading to the improved efficacy outcomes observed in our study.

It is important to note that our study was a single-arm, phase II study, which limits the ability to draw definitive conclusions about the superiority of the pembrolizumab-containing regimens compared to other treatment options. Larger, randomized, controlled trials are needed to confirm the efficacy and safety of these combinations in the first-line treatment of advanced G/GEJ adenocarcinoma.

In conclusion, the results of our study suggest that pembrolizumab in combination with SOX or SP is a safe and effective first-line treatment option for patients with PD-L1-positive, HER2-negative G/GEJ adenocarcinoma. The favorable efficacy and safety profiles observed in our study are consistent with the findings from other studies evaluating pembrolizumab-containing regimens in this patient population. However, further research is needed to confirm the superiority of these combinations compared to other treatment options.

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