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ORIGINAL ARTICLE

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

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Background: High tumor mutational burden (TMB-H) is correlated with enhanced objective response rate (ORR) and progression-free survival (PFS) for certain cancers receiving immunotherapy. This study aimed to investigate the safety and efficacy of toripalimab, a humanized programmed death-1 (PD-1) antibody, in advanced gastric cancer (AGC), and the predictive survival benefit of TMB and PD-L1.

Patients and methods: We reported on the AGC cohort of phase Ib/II trial evaluating the safety and activity of toripalimab in patients with AGC, oesophageal squamous cell carcinoma, nasopharyngeal carcinoma and head and neck squamous cell carcinoma. In cohort 1, 58 chemo-refractory AGC patients received toripalimab (3 mg/kg d1, Q2W) as a monotherapy. In cohort 2, 18 chemotherapy-naive AGC patients received toripalimab (360 mg d1, Q3W) with oxaliplatin 130 mg/m^2 qd, d1, capecitabine 1000 mg/m^2 b.i.d., d1–d14, Q3W as first-line treatment. Primary end point was ORR. Biomarkers such as PD-L1 and TMB were evaluated for correlation with clinical efficacy.

Results: In cohort 1, the ORR was 12.1% and the disease control rate (DCR) was 39.7%. Median PFS was 1.9 months and median OS was 4.8 months. The TMB-H group showed significant superior OS than the TMB-L group [14.6 versus 4.0 months, HR = 0.48 (96% CI 0.24–0.96), $P = 0.038$], while PD-L1 overexpression did not correlate with significant survival benefit. A 77.6% of patients experienced at least one treatment-related adverse event (TRAE), and 22.4% of patients experienced a grade 3 or higher TRAE. In cohort 2, the ORR was 66.7% and the DCR was 88.9%. A 94.4% of patients experienced at least one TRAE and 38.9% of patients experienced grade 3 or higher TRAEs.

Conclusions: Toripalimab has demonstrated a manageable safety profile and promising antitumor activity in AGC patients, especially in combination with XELOX. High TMB may be a predictive marker for OS of AGC patients receiving toripalimab as a single agent.

Trial registration: ClinicalTrials.gov NCT02915432.

Key words: gastric cancer, immunotherapy, programmed death ligand-1, tumor mutational burden

Introduction

As the fifth most common cancer worldwide and the third in China [1], advanced gastric cancer (AGC) has a poor prognosis and limited therapeutic options. In addition to chemotherapy, targeted therapy including trastuzumab, ramucirumab, and apatinib, has improved the survival of GC patients in recent years [2].

With the regulatory approval of programmed death-1 (PD-1) blockade-based immunotherapy in various solid tumors [3], the safety and efficacy of anti-PD-1 treatment has also been tested in AGC. From KEYNOTE-012 and KEYNOTE-059 trials, pembrolizumab showed a 22% objective response rate (ORR) in PD-L1 positive AGC patients ($n = 36$) [4], and a 11.6% ORR in PD-L1 non-selected patients ($n = 259$) with at least two lines of previous chemotherapy [5]. Nivolumab also achieved a similar efficacy (11.2% ORR) in chemo-refractory PD-L1 non-selected AGC patients [6]. The result from the KEYNOTE-059 study led to the FDA's accelerated approval of pembrolizumab for AGC patients whose tumors express PD-L1 and have progressed after at least two prior systemic therapies. However, in the randomized phase III trial KEYNOTE-061 with AGC patients whose disease progressed after first-line treatment with platinum and fluoropyrimidine doublet therapy, pembrolizumab failed to provide a survival benefit over paclitaxel [7]. Therefore, further improvement of clinical efficacy and additional prognostic and predictive markers for the treatment of advanced GC with immunotherapy is warranted.

Tumor mutational burden (TMB) has been correlated with enhanced clinical response to immunotherapy recently, including patients with melanoma and non-small-cell lung cancer (NSCLC) [8, 9]. The improved clinical efficacy associated with high TMB (TMB-H) patients included ORR and progression-free survival (PFS). The benefit in overall survival (OS), the gold standard for cancer therapeutics, has yet to be shown. The clinical relevance of TMB in AGC patients remains unclear.

Combination therapy of PD-1 blockade with chemotherapy or targeted therapy has become the focus of recent clinical development against various solid tumors and has shown promising results. Notably, pembrolizumab was approved for use in combination with chemotherapy as a first-line treatment of NSCLC patients [10]. In contrast, limited data were available for a combination study against AGC, with an ORR ranging from 57.1% to 76.5% [11].

Here, we report the results from a multi-center phase Ib/II study evaluating the safety and efficacy of toripalimab, also known as JS001 [12], a humanized IgG4 monoclonal antibody against PD-1 as a monotherapy or in combination with XELOX for the treatment of AGC.

Patients and methods

Study design and patients

This study is part of an ongoing, open-label, multicenter phase Ib/II trial (NCT02915432) evaluating the safety and clinical activity of toripalimab, a PD-1 antibody in eight independent cohorts of four solid tumor indications. Here we report the results of two AGC cohorts. In cohort 1, patients had progressed after at least one line of systemic chemotherapy. In cohort 2, eligible patients had to be naive to systemic chemotherapy, or had tumor recurrence/metastasis at least 6 months after curative therapy.

Eligible patients were between 18 and 75 years old with pathological confirmed advanced adenocarcinoma of the stomach or gastro-esophageal junction. Patients had at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at baseline, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ and bone marrow function, and willingness to provide consent for biopsy samples. Exclusion criteria included history of autoimmune diseases, ongoing infections, or prior CTLA-4 or PD-1 checkpoint blockade immunotherapies. The study protocol and all amendments were approved by the institutional ethics committees of all participating centers. This study was conducted in accordance with the Declaration of Helsinki and the international standards of good clinical practice.

Treatments

In cohort 1, AGC patients received toripalimab (3 mg/kg, d1, Q2W) as a monotherapy. In cohort 2, AGC patients received the combination of toripalimab (360 mg d1) with XELOX (oxaliplatin 130 mg/m^2 QD, d1, capecitabine 1000 mg/m^2 b.i.d., d1–d14) of a 3-week treatment cycle. Treatment continued until the absence of further benefits judged by the investigator, disease progression, intolerable toxicity, investigator's decision, withdrawal of informed consent by the subject, or death. Adverse events were monitored continuously and graded according to the National Cancer Institute Common Terminology Criteria (CTCAE) version 4.0. According to 'NCI guidelines for investigators: adverse event reporting requirements', 'definitely related', 'probably related', and 'possibly related' were classified as 'treatment-related' AE (TRAE). 'Unlikely related' and 'definitely unrelated' were classified as 'treatment unrelated'. Radiographic imaging was carried out before treatment, then every 8 weeks for monotherapy and every 6 weeks for combination-therapy until disease progression by computed tomography and evaluated by investigators per RECIST v1.1.

End points

The primary end point was ORR. The secondary end points included safety, disease control rate (DCR), duration of response (DOR), PFS, and OS. Exploratory end points were also preplanned, as to evaluate the correlation of biomarkers such as PD-L1 expression and TMB with clinical efficacy.

PD-L1 expression

Tumor biopsies were obtained before treatment. PD-L1 expression was detected by immunohistochemistry (IHC) staining with an antihuman PD-L1 monoclonal antibody SP142 [13]. PD-L1 expression was evaluated on tumor cells (TC) as well as on tumor-infiltrating immune cells (IC) by certified pathologists. PD-L1 positive status was defined as the presence of membrane staining of any intensity in ≥1% of tumor cells or the presence of PD-L1 staining of any intensity in tumor-infiltrating immune cells.

Tumor mutational burden analysis

Whole exome sequencing was carried out on tumor biopsies and matched peripheral blood mononuclear cell samples from patients of the monotherapy cohort. Genomic alterations were assessed. TMB was determined by analyzing somatic mutations per mega-base (Mb). A cut-off of the top 20% of the TMB (12 mutations/Mb) in this study was selected as defining a tumor as TMB-H. Patients with TMB <12 mutations/Mb were defined as TMB-L.

Tumor tissue Epstein–Barr virus analysis

The Epstein–Barr virus (EBV) deoxyribonucleic acid (DNA) copy number in tumor tissues was evaluated by unique reads detected in tumor biopsies with probes against EBV genes.

Statistical analysis

Safety and efficacy analysis was conducted with patients who received at least one dose of study drug(s). PFS and OS were estimated with the Kaplan–Meier method. Statistical analysis was conducted with SAS version 9.4 or Prism 5 software.

Results

Patient population

From 18 participating centers, we enrolled 58 chemo-refractory AGC patients in cohort 1 from 28 December 2016 to 26 September 2017, and 18 chemotherapy-naive GC patients in cohort 2 from 19 December 2017 to 9 August 2018. Baseline characteristics are summarized in Table 1. Notably, the majority of patients in the monotherapy cohort were heavily pretreated, with 45 (77.6%) patients having at least 2 prior lines of systemic treatment.

Table 1. Baseline patient demographics and clinical characteristics

	Toripalimab monotherapy (*n* = 58)	Toripalimab–XELOX combination (*n* = 18)
Median age, years (range)	59.5 (52.0–66.0)	58.5 (48.0–69.0)
Gender		
Male	41 (70.7)	12 (66.7)
Female	17 (29.3)	6 (33.3)
ECOG performance status		
0	20 (34.5)	6 (33.3)
1	38 (65.5)	12 (66.7)
Liver metastasis		
No	41 (70.7)	11 (61.1)
Yes	17 (29.3)	7 (38.9)
Baseline LDH (IU/L)		
Normal	38 (65.5)	18 (100.0)
Abnormal,	18 (31.0)	0
N/A	2 (3.4)	0
Previous treatment line		
None	0	18 (100.0)
1L	13 (22.4)	0
2L	15 (25.8)	0
3L+	30 (51.7)	0
PD-L1 result[a]		
Negative	47 (81.0)	15 (83.3)
Positive	8 (13.8)	3 (16.7)
N/A	3 (5.2)	0

[a]Positive defined as ≥1% of tumor cells or immune cells by SP142 IHC staining.
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; N/A, not available.

Safety

By 31 October 2018, 13 months after the last enrollment in cohort 1, the median treatment duration was 2.7 months (range 0.4–19.7 months). Treatment-related AEs (TRAEs) of any grade occurred in 45 (77.6%) patients (Table 2). Grade 3 and higher TRAEs occurred in 13 (22.4%) patients. TRAEs led to discontinuation in 4 (6.9%) patients. Treatment-related death occurred in two patients (one thrombocytopenia and one interstitial lung disease).

Fifteen patients (25.9%) experienced 20 immune-related adverse events (irAE), including 7 hypothyroidism, 6 pruritus, 4 thrombocytopenia (1 grade 5), and three interstitial lung disease (1 grade 3 and 1 grade 5).

In cohort 2, the median treatment duration was 6.7 months (range 0.7–9.5 months). Seventeen (94.4%) patients experienced TRAEs (Table 2), seven (38.9%) were grade 3 and higher. TRAEs led to discontinuation in four (22.2%) patients including one toripalimab-related and three chemotherapy-related. There was no treatment-related death.

Efficacy

In cohort 1, among all 58 patients, investigator assessed ORR was 12.1% and DCR was 39.7%, including 7 confirmed partial response (PR) and 16 stable disease (SD). Responses are shown in Figure 1A and B. The median time to response was 1.8 months. The median DOR was 9.4 months. Three patients continued to have ongoing responses at 11, 12.2 and 17.4 months. Median PFS was 1.9 months and median OS was 4.8 months (Figure 2A and B).

In cohort 2, ORR was 66.7% [1 complete response (CR) and 11 PR out of 18 patients] and DCR was 88.9%, with 50% ongoing responses. The median PFS was 5.8 months and median OS was not reached (only 2 out of 18 patients deceased) (Figure 2C and D).

Table 2. Treatment-related adverse events

	Toripalimab monotherapy ($n = 58$)		Toripalimab–XELOX combination ($n = 18$)	
	TRAE	Grade ≥3	TRAE	Grade ≥3
Any	45 (77.6)	13 (22.4)	17 (94.4)	7 (38.9)
Serious adverse events	12 (20.7)	9 (15.5)	0	0
Led to discontinuation	4 (6.9)	4 (6.9)	4 (22.2)	3 (16.7)
Most common adverse events				
Anemia	7 (12.1)	2 (3.4)	5 (27.8)	0 (0)
Hypothyroidism	7 (12.1)	0	0	0
Pruritus	6 (10.3)	0	4 (22.2)	0
AST increased	6 (10.3)	1 (1.7)	6 (33.3)	0
Fatigue	6 (10.3)	0	3 (16.7)	0
Rash	5 (8.6)	0	4 (22.2)	0
Proteinuria	5 (8.6)	0	4 (22.2)	0
ALT increased	5 (8.6)	1 (1.7)	3 (16.7)	0
Leukopenia	5 (8.6)	0	7 (38.9)	0
Thrombocytopenia	4 (6.9)	1 (1.7)	4 (22.2)	4 (22.2)
Blood bilirubin increased	3 (5.2)	0	0	0
Decreased appetite	3 (5.2)	0	5 (27.8)	0
Diarrhea	3 (5.2)	0	5 (27.8)	0
Interstitial lung disease	3 (5.2)	2 (3.4)	0	0
Nausea	3 (5.2)	0	9 (50.0)	0
Fever	3 (5.2)	0	2 (11.1)	0
Vomiting	3 (5.2)	0	7 (38.9)	0
Neutropenia	1 (1.7)	0	7 (38.9)	3 (16.7)
Hands and feet numbness	0	0	5 (27.8)	0
Amylase increase	1 (1.7)	0	4 (22.2)	0
Abdominal pain	1 (1.7)	0	3 (16.7)	0
Constipation	0	0	3 (16.7)	0
Weight loss	0	0	2 (11.1)	1 (5.6)
Dizziness	1 (1.7)	0	2 (11.1)	0
Immune-related adverse events				
Hypothyroidism	7 (12.1)	0	0	0
Pruritus	6 (10.3)	0	4 (22.2)	0
Thrombocytopenia	4 (6.9)	1 (1.7)	4 (22.2)	4 (22.2)
Interstitial lung disease	3 (5.2)	2 (3.4)	0	0

Adverse events were graded according to National Cancer Institute Common Terminology Criteria (CTCAE) version 4.0. The most common TRAEs in monotherapy (>5%) and combination therapy (>10%) cohorts according to the NCI guideline.
AST, aspartate aminotransferase; ALT, alanine aminotransferase.

PD-L1 expression

Among 55 valid PD-L1 IHC staining results from the monotherapy cohort, 14.5% were PD-L1 positive and 85.5% were PD-L1 negative. PD-L1 positive patients responded significantly better than PD-L1 negative patients (ORR 37.5% versus 8.5%, $P = 0.023$; Figure 1C). PD-L1 positive patients also had high value in median PFS (5.5 versus 1.9 months, $P = 0.092$) and median OS (12.1 versus 5.3 months, $P = 0.45$), although the survival differences were not statistically significant (Figure 3A and B).

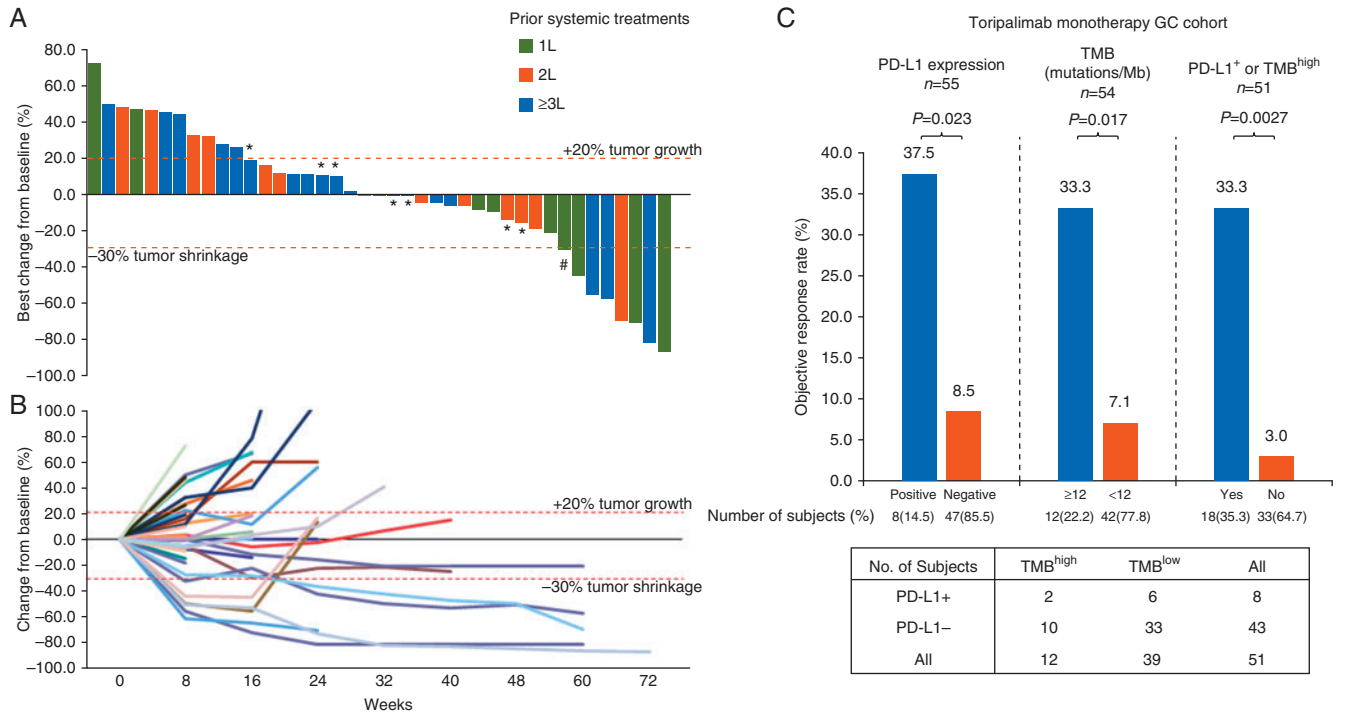
PD-L1 expression in tumor biopsies was also evaluated in all 18 patients in the combination cohort, with 16.7% positive and 83.3% negative identified. Patients with positive or negative PD-L1 responded similarly to the treatment (both at 66.7% ORR).

EBV copy number in tumor biopsies

Among 55 patients tested for EBV DNA copy number in tumor biopsies, only 4 had above 100 copies which was considered EBV positive (supplementary Table S1, available at *Annals of Oncology* online). Among the four EBV+ patients, one PR, two SD, and one progressive disease (PD) responses were observed. Moreover, the patient who achieved a PR was also PD-L1 positive, while the other 3 patients were PD-L1 negative.

Tumor mutational burden

Valid results were obtained from 54 patients (supplementary Table S1, available at *Annals of Oncology* online). TMB were generally low with only 4 patients harboring more than 20 mutations



No. of Subjects	TMB^{high}	TMB^{low}	All
PD-L1+	2	6	8
PD-L1–	10	33	43
All	12	39	51

Figure 1. Tumor response in toripalimab monotherapy cohort assessed by investigator per RECIST v1.1. (A) Maximal change of tumor size from baseline in target lesion(s) ($n = 41$, patients with baseline and at least one post-treatment radiographic evaluation). #The response was unable to confirm and was classified as stable disease (SD). *The patient was characterized as progressive disease (PD) due to the development of new lesion(s) or progression of non-target lesion(s). (B) Change of individual tumor burden over time from baseline. (C) Clinical response in relation to tumor PD-L1 expression and tumor mutational burden (TMB).

per million base pairs (Mb), including 1 MSI-high patient. Higher TMB levels appeared to be correlated with enhanced clinical response. Patients with TMB-H ($n = 12$) had responded significantly better than patients with TMB-L ($n = 42$) (ORR 33.3% versus 7.1%, $P = 0.017$) (Figure 1C). The TMB-H group showed a numerically longer but not statistically significant PFS than TMB-L group, 2.5 versus 1.9 months, HR = 0.51 (95% CI 0.26–1.02), $P = 0.055$ (Figure 3C). More importantly, the TMB-H group showed significant survival advantage in OS than the TMB-L group, 14.6 versus 4.0 months, HR = 0.48 (95% CI 0.24–0.96), $P = 0.038$ (Figure 3D).

TMB-H or PD-L1 positivity was observed in 35.3% of all patients. Only 3.9% of patients were both TMB-H and PD-L1 positive. Eighteen patients who were TMB-H or PD-L1 positive showed significantly higher ORR (33.3% versus 3.0%), longer PFS (2.7 versus 1.9 months), and OS (12.1 versus 4 months) than those who had TMB-L and PD-L1 negative tumors (Figure 3E and F).

Other biomarkers and subgroups analysis

Additional biomarkers or characteristics including age, gender, ECOG score, prior lines of treatments, liver metastasis, tumor baseline volume, and serum LDH levels were analyzed for correlation with clinical efficacy (supplementary Table S2, available at *Annals of Oncology* online). None of the differences were statistically significant.

Discussion

China contributes to almost half of the global new GC cases annually and half of the Chinese patients are diagnosed at an advanced stage. Previous studies have documented the differences in disease incidence and clinical outcome with standard treatment between USA/Europe, Japan/Korea, and China. The underlying mechanisms have been attributed to regional differences in screening and early detection, divergent tumor characteristics and immune signatures, and preferred treatment strategies [14, 15]. Here, we report for the first time the safety and efficacy of anti-PD-1 therapy in Chinese AGC patients as a salvage monotherapy or in combination with XELOX at the first-line setting.

This study showed that toripalimab has a manageable safety profile and a promising antitumor activity in AGC. The incidences of AEs and grade 3–4 AEs were generally comparable with those reported in other PD-1 or PD-L1 antibodies. As a single agent, toripalimab achieved similar ORR with nivolumab and pembrolizumab in PD-L1 status non-selective and heavily pretreated patients [5, 6].

In this study, PD-L1 expression status in tumor biopsies was assessed by IHC staining using a PD-L1 antibody SP142. Previous studies reported relatively weaker staining pattern of SP142 antibody when compared with other PD-L1 antibodies including 22C3 [15]. Additionally, the small number of patients with positive PD-L1 in this study may limit the assessment of PD-L1 as a biomarker [10].

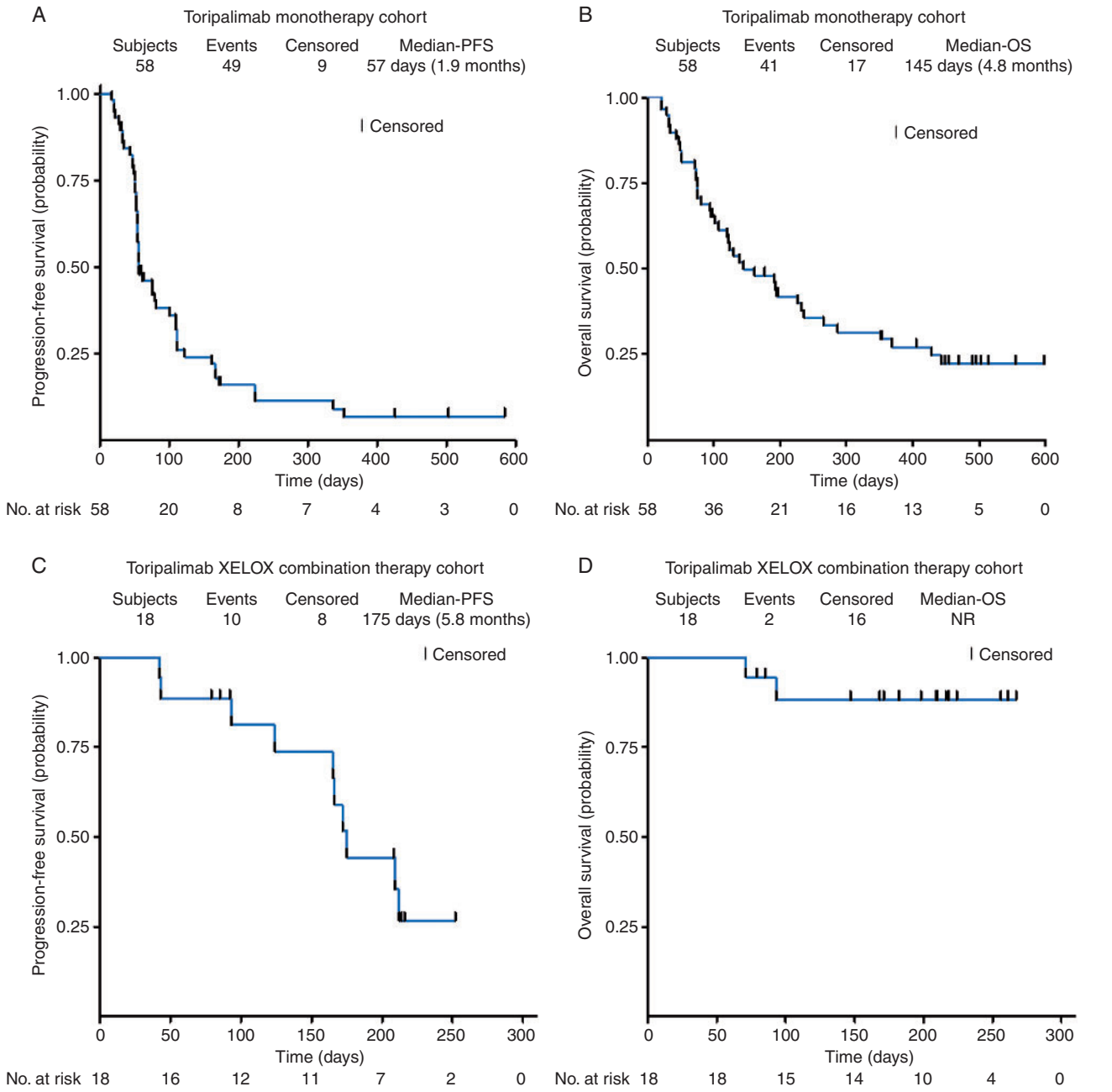


Figure 2. Kaplan–Meier plots of median (A) progression-free survival (PFS) and (B) overall survival (OS) of chemo-refractory patients treated with toripalimab monotherapy. Median (C) PFS and (D) OS of patients treated with toripalimab–XELOX combination therapy as first-line treatment. NR, not reached. Percentages of survival patients are shown at indicated time points.

TMB has been recently correlated with enhanced clinical response to immunotherapy [8, 9]. In this study, TMB-H patients responded significantly better than TMB-L patients. Notably, the TMB-H group also showed significant survival benefit in OS. Samstein et al. [16] have reviewed TMB's correlation with OS in cancer patients under the treatment of immune checkpoint inhibitors and found that higher somatic TMB (highest 20% in each histology) was associated with better OS across multiple cancer types. Their finding is consistent with what we observed in this AGC study.

Consistent with previous reports [17], the TMB-H and PD-L1 positive were largely two independent populations, as only 2 out of 12 TMB-H patients were also PD-L1 positive. Interestingly, the combined group of TMB-H or PD-L1 positive patients (35.3%) not only responded significantly better but also had significant survival benefits than TMB-L and PD-L1 negative patients. The combined two biomarkers of TMB-H or PD-L1 positive could be used to select a wider population that would benefit from toripalimab.

In addition to tumor PD-L1 expression and TMB, underlying viral infection was also suggested to be a positive prognostic factor for anti-PD-1 treatment. A recent study found a 100% response rate for six EBV-positive AGC patients to pembrolizumab [18]. In our study, only one among four patients with positive

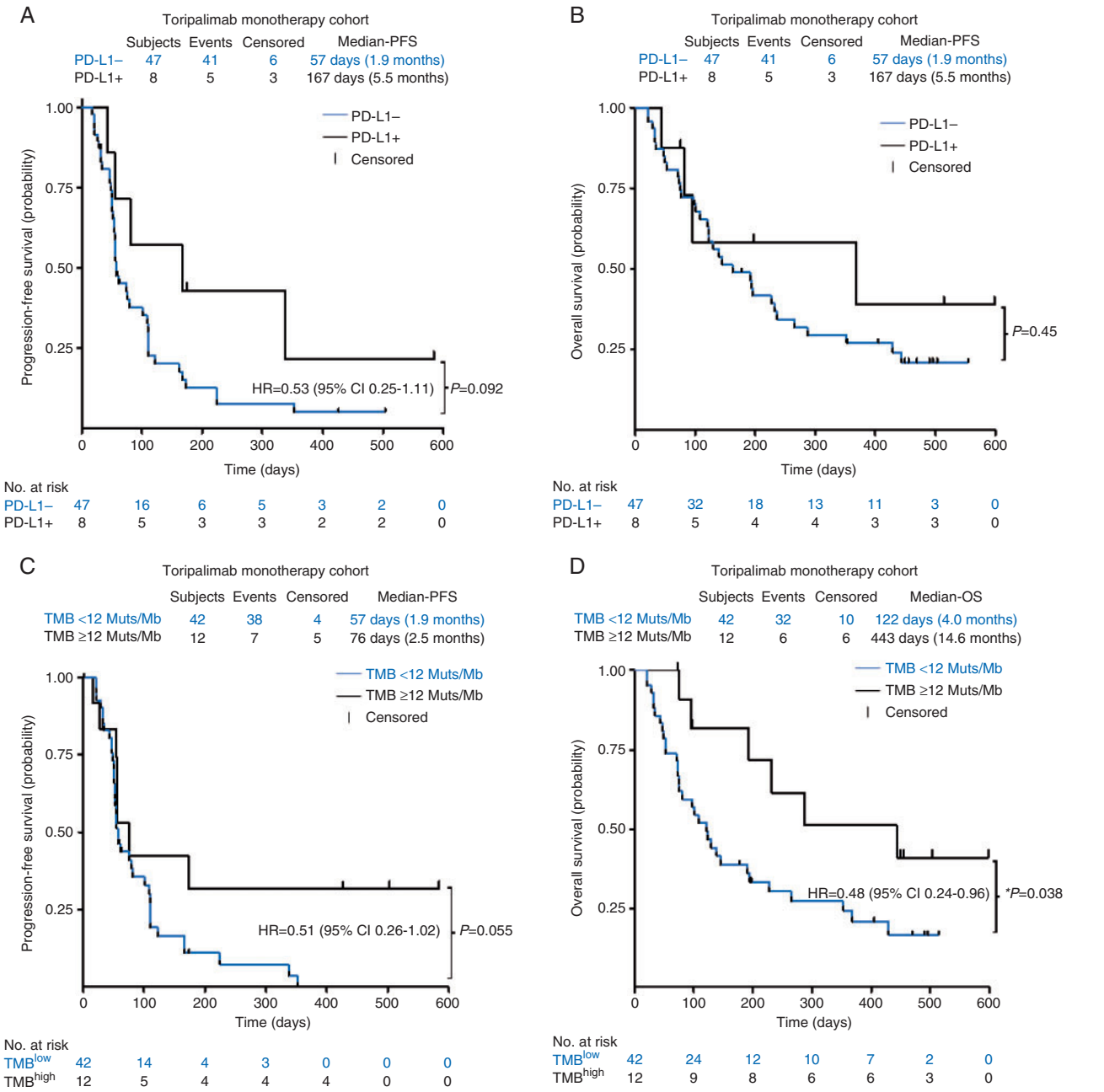


Figure 3. Kaplan–Meier plots of median (A) PFS and (B) OS of PD-L1+ versus PD-L1− patients. Median (C) PFS and (D) OS of TMB-H versus TMB-L patients. Median (E) PFS and (F) OS of PD-L1+ or TMB-H versus PD-L1- and TMB-L patients.

EBV achieved a PR. The inconsistency in efficacy could be explained by the small sample sizes of both studies. Further clinical research in a larger cohort of EBV infected GC patients is thus needed.

As a single agent, PD-1 pathway blockade could only elicit antitumor effects in a small subpopulation of solid tumor patients. Our study showed the combination potential of toripalimab with chemotherapy as a first-line treatment of AGC, which was in consistent with the results of ATTRACTION-4 trial. A randomized phase III trial of toripalimab with XELOX versus XELOX will be initiated to further evaluate the combination as a first-line treatment in AGC.

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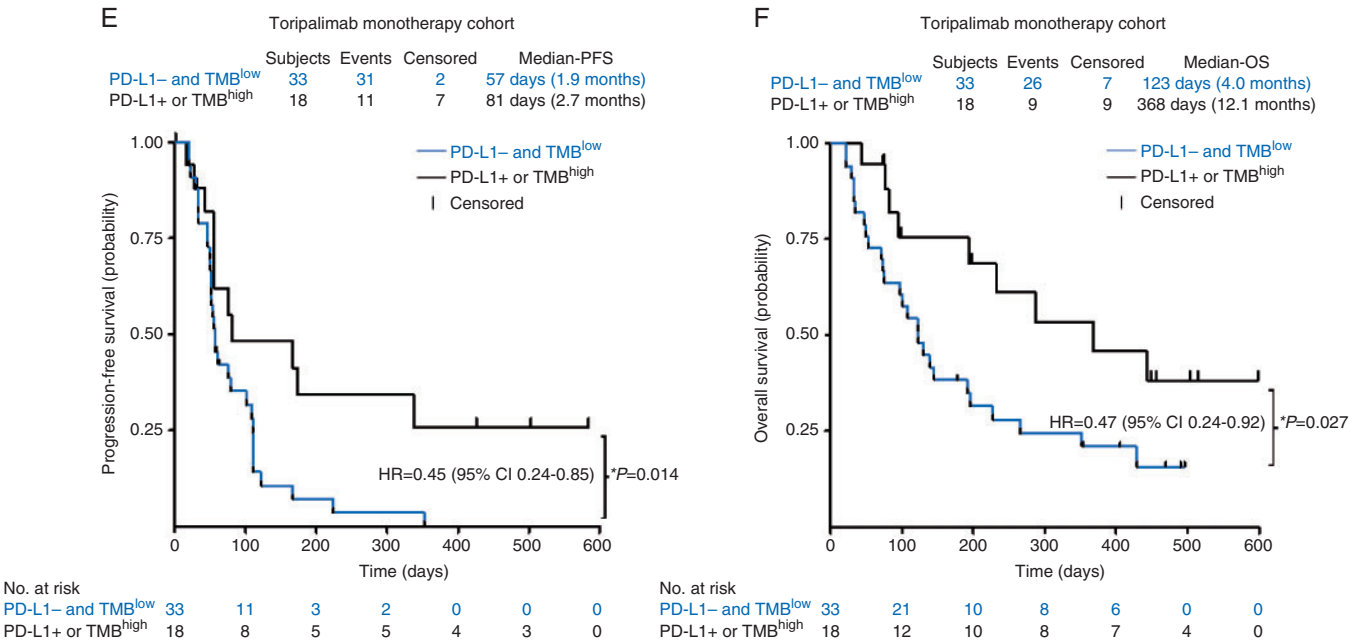

Figure 3. Continued.

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Disclosure

HW, HF, and SY declare employment with Shanghai Junshi Biosciences Co., Ltd. All remaining authors have declared no conflicts of interest.

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