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# Improved efficacy of taxanes and ramucirumab combination chemotherapy after exposure to anti-PD-1 therapy in advanced gastric cancer

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## ABSTRACT

**Background** The efficacy and safety of chemotherapy (CTx) after anti-PD-1 therapy in patients with advanced gastric cancer (AGC) remains unclear.

**Methods** Medical records of consecutive patients with AGC treated with both CTx (taxanes plus ramucirumab, taxanes monotherapy or irinotecan) and anti-PD-1 therapy from June 2015 to April 2019 were retrospectively analysed. Patients were divided into two groups based on prior exposure to anti-PD-1 therapy: anti-PD-1-exposed and anti-PD-1-naïve groups. CTx-related outcomes were compared between two groups in the overall population and each CTx population.

**Results** In total, 233 patients (67 anti-PD-1-exposed, 166 anti-PD-1-naïve) were included. In the overall population, the objective response rate (ORR) to CTX was 44.6% in the anti-PD-1-exposed group and 19.6% in the anti-PD-1-naïve group (p=0.001); the median progression-free survivals (PFS) were 3.7 months and 3.3 months (HR=0.82, p=0.20), respectively. Among patients receiving taxanes plus ramucirumab (n=149), ORR (60.6% vs 20.0%, p<0.001) and median PFS (4.8 vs 3.4 months, p=0.004, HR=0.56) were significantly better in the anti-PD-1-exposed group (n=39) compared with the anti-PD-1-naïve group (n=110). These differences were not observed in patients receiving taxane monotherapy (n=34) or irinotecan (n=50). CTx after anti-PD-1 therapy showed no severe or unexpected adverse events.

**Conclusions** Prior anti-PD-1 therapy might increase tumour response to taxanes plus ramucirumab without unexpected adverse events, which warrants further investigations in a large cohort.

### Key questions

**What is already known about this subject?**

- Anti-PD-1 therapy might improve responses to subsequent chemotherapy without unexpected safety signals in patients with several cancers.
- The efficacy and safety of chemotherapy after anti-PD-1 therapy in patients with advanced gastric cancer remains unclear.

**What does this study add?**

- We assessed the tumour response to chemotherapy including taxanes plus ramucirumab, taxanes monotherapy, or irinotecan and toxicities in patients with advanced gastric cancer, with or without prior exposure to anti-PD-1 therapy.

**How might this impact on clinical practice?**

- Prior exposure to anti-PD-1 therapy might improve tumour responses to taxanes plus ramucirumab. Further, chemotherapy administered after anti-PD-1 therapy was manageable without unexpected toxicities, but immune-related adverse events during chemotherapy after anti-PD-1 therapy should be monitored carefully.

## INTRODUCTION

Gastric cancer is the fifth most common type of cancer and the third leading cause of cancer-related death globally.[1] Although some chemotherapy (CTx) regimens, including a platinum and fluoropyrimidine combination, trastuzumab (for human epidermal growth factor receptor 2 (HER2)-positive cases), taxanes with or without ramucirumab (RAM), irinotecan and trifluridine/tipiracil improve the survival outcomes of patients with advanced gastric cancer (AGC),[2–7] its prognosis remains poor with a median survival of approximately 1 year. Therefore, further therapeutic development is needed for AGC.

Immune checkpoint inhibitors demonstrate antitumour immune responses by activating effector T cells in various cancers.[8–12] In third-line or later-line treatments, two anti-programmed cell death 1 (PD-1) monoclonal antibodies (mAbs) have been approved for AGC based on the results of phase II and phase III trials:[13 14] pembrolizumab by the US Food and Drug Administration for programmed death-ligand 1 (PD-L1)-positive

tumours and nivolumab in Asian countries, irrespective of PD-L1 status. However, response rates with these anti-PD-1 mAbs are limited to 10%–15% in patients with AGC,[13] necessitating more effective therapies to achieve tumour shrinkage.

Prior PD-1 blockade enhances the antitumour effect of CTx in a melanoma mouse model.[15] Indeed, anti-PD-1 therapy might improve responses to subsequent CTx without unexpected safety signals in patients with non-small cell lung cancer (NSCLC).[16–19] Further, the phase III KEYNOTE-024 trial showed that patients with NSCLC treated with first-line pembrolizumab followed by cytotoxic CTx showed longer time to progression after initiation of second-line therapy than patients with first-line cytotoxic CTx followed by anti-PD-1 mAb.[20] However, the effect of prior anti-PD-1 therapy on the efficacy and safety of CTx in patients with AGC remains unclear. Here, we assessed the tumour response to CTx and toxicities in patients with AGC, with or without prior exposure to anti-PD-1 therapy.

## METHODS

### Patients

The effect of prior anti-PD-1 therapy on the efficacy and safety of CTx in patients with AGC was evaluated retrospectively. We reviewed the medical records of consecutive patients with AGC who were treated with both CTx including taxanes plus RAM, taxanes monotherapy, or irinotecan, and anti-PD-1 therapy in the metastatic setting from June 2015 to April 2019 at the National Cancer Hospital East. Patients received 80 mg/m$^2$ paclitaxel (PTX) or 100 mg/m$^2$ nanoparticle albumin-bound PTX (days 1, 8 and 15) with or without 8 mg/kg RAM (days 1 and 15) or 150 mg/m$^2$ irinotecan, every 2 weeks before and after anti-PD-1 therapy. The doses of taxanes or irinotecan could be reduced at the investigators' judgement. Patients who met the following criteria were included: (1) Presence of histologically proven gastric adenocarcinoma. (2) Underwent at least one administration with both CTx including taxanes plus RAM, taxanes monotherapy, or irinotecan, and anti-PD-1 therapy. (3) An Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2. (4) Adequate bone marrow, hepatic and renal function. Patients were divided into two groups based on prior exposure to anti-PD-1 therapy: anti-PD-1-exposed and anti-PD-1-naïve groups. Clinical outcomes after CTx were compared between anti-PD-1-exposed and anti-PD-1-naïve groups in the overall population and in each CTx population.

### Assessment

The study primarily aimed to investigate the efficacy and safety of CTx after prior anti-PD-1 therapy. We assessed the objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS). Tumour response was retrospectively assessed in patients with measurable lesions according to the guidelines of the Response Evaluation Criteria in Solid Tumours V.1.1. ORR was defined as the proportion of patients with the best overall response of complete response (CR) or partial response (PR). DCR was defined as the proportion of patients with the best overall CR, PR or stable disease (SD). PFS was defined as the time from the start of the study treatment to disease progression or death from any cause. Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events V.5.0.

Molecular characteristics such as the status of HER2, PD-L1, mismatch repair (MMR) and Epstein-Barr virus (EBV) were analysed using formalin-fixed, paraffin-embedded tissue specimens from archival tissue samples where available.[21]

### Statistical analysis

The $\chi^2$ test or Fisher's exact test was used to compare baseline characteristics and response rates between anti-PD-1-exposed and anti-PD-1-naïve groups. PFS rate was estimated by the Kaplan-Meier method, compared between these two groups using the Cox proportional hazards model, and presented as HRs with 95% CIs. Confounders in the multivariate analyses of PFS in the overall population or patients with taxanes plus RAM included prior anti-PD-1 therapies (yes vs no), age (≥65 years vs <65 years), sex (male vs female), ECOG PS (1–2 vs 0), number of previous treatment regimens (≥2 vs 1), a measurable lesion (no vs yes), number of metastatic sites (≥3 vs ≤2), liver metastasis (yes vs no), peritoneal metastasis (yes vs no) and prior gastrectomy (no vs yes). Statistical analyses were performed using the SPSS Statistics software V.25 (IBM, Chicago, Illinois, USA). All tests were two-sided; a value of $p<0.05$ was considered to indicate statistical significance.

## RESULTS

### Patient characteristics

In total, 233 patients (67 in the anti-PD-1-exposed group and 166 in the anti-PD-1-naïve group) were included in this study (table 1). Of these, 149 patients received taxanes plus RAM (39 in the anti-PD-1-exposed group and 110 in the anti-PD-1-naïve group) (online supplementary table S1), 34 received taxanes monotherapy (14 in the anti-PD-1-exposed group and 20 in the anti-PD-1-naïve group) (online supplementary table S2) and 50 received irinotecan (14 in the anti-PD-1-exposed group and 36 in the anti-PD-1-naïve group) (online supplementary table S3). In the anti-PD-1 exposed group (n=67), 31, 30 and 6 patients received anti-PD-1 therapy as the first, second, and third or later line, respectively. On the other hand, in the anti-PD-1 naïve group (n=166), all patients received anti-PD-1 therapy as third or later line. Anti-PD-1-exposed groups were associated with significantly higher frequencies of two or more previous treatment regimens than the anti-PD-1-naïve groups in the overall population (table 1) and each CTx population (online supplementary table

**Table 1** Patient characteristics in the overall population

| Features | Available | Anti-PD-1-exposed group (n=67) | Anti-PD-1-naive group (n=166) | P value |
|---|---|---|---|---|
| Age, ≥65 years, n (%) | | 46 (68.7) | 113 (68.1) | 1.00 |
| Male, n (%) | | 43 (64.2) | 122 (73.5) | 0.20 |
| ECOG PS, n (%) | | | | |
| 0 | | 49 (73.1) | 119 (71.7) | 0.58 |
| 1 | | 16 (23.9) | 45 (27.1) | |
| 2 | | 2 (3.0) | 2 (1.2) | |
| Previous treatment regimens, n (%) | | | | |
| 1 | | 31 (46.3) | 123 (74.1) | <0.001 |
| ≥2 | | 36 (53.7) | 43 (25.9) | |
| Organs with metastases, n (%) | | | | |
| ≤2 | | 55 (82.1) | 138 (83.1) | 0.85 |
| ≥3 | | 12 (17.9) | 28 (16.9) | |
| Site of metastases, n (%) | | | | |
| Liver | | 25 (37.3) | 57 (34.3) | 0.76 |
| Lung | | 5 (7.5) | 25 (15.1) | 0.14 |
| Peritoneum | | 36 (53.7) | 77 (46.4) | 0.32 |
| Lymph node | | 58 (86.6) | 139 (83.7) | 0.69 |
| Other | | 5 (7.5) | 27 (16.3) | 0.093 |
| HER2, n (%) | 228 | | | |
| Negative | | 62 (93.9) | 136 (84.0) | 0.051 |
| Positive | | 4 (6.1) | 26 (16.0) | |
| MMR, n (%) | 212 | | | |
| Proficient | | 56 (96.6) | 143 (92.9) | 0.52 |
| Deficient | | 2 (3.4) | 11 (7.1) | |
| EBV, n (%) | 215 | | | |
| Negative | | 55 (91.7) | 154 (99.4) | 0.007 |
| Positive | | 5 (8.3) | 1 (0.6) | |
| PD-L1 CPS, n (%) | 211 | | | |
| <1 | | 11 (18.6) | 22 (14.5) | 0.53 |
| ≥1 | | 48 (81.4) | 130 (85.5) | |
| PD-L1 CPS, n (%) | 211 | | | |
| <10 | | 49 (84.5) | 135 (88.2) | 0.49 |
| ≥10 | | 9 (15.5) | 18 (11.8) | |
| Response to first line chemotherapy | 194 | | | |
| ORR (%) | | 51.8 | 50.0 | 0.88 |
| DCR (%) | | 76.8 | 79.0 | 0.85 |
| Median PFS (month) | | 6.3 (95% CI 5.5 to 7.2) | 6.7 (95% CI 5.7 to 7.7) | 0.18 |

CPS, combined positive score; DCR, disease control rate; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor related 2; MMR, mismatch repair; ORR, objective response rate ; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumour cell.

S1-S3). There was no difference in the response to first-line CTx between anti-PD-1-exposed groups and anti-PD-1-naïve groups in the overall population. Among patients with taxanes plus RAM, the anti-PD-1-exposed group was associated with a significantly lower frequency of HER2-positive status (p=0.012) and a higher frequency of EBV-positive status (p=0.014) (online supplementary table S1). Among patients with taxanes monotherapy, the anti-PD-1-exposed group was associated with a significantly lower frequency of age ≥65 years (p=0.005) and

a higher frequency of peritoneal metastasis (p=0.035) (online supplementary table S2). No other significant difference was observed.

## Efficacy

### Overall population

In the overall population (n=233), the median follow-up by Kaplan-Meier estimates was 13.8 months (95% CI 10.1 to 17.5) with the anti-PD-1-exposed group and 17.7 months (95% CI 15.3 to 20.1) with the anti-PD-1-naïve group. Further, 25 patients of the anti-PD-1-exposed group and 27 patients of the anti-PD-1-naïve group had PR, resulting in a significantly higher ORR in the anti-PD-1-exposed group than the anti-PD-1-naïve group (44.6% vs 19.6%, p=0.001). Disease control was achieved in 45 patients (80.6%) of the anti-PD-1-exposed group and in 95 patients (68.8%) of the anti-PD-1-naïve group (p=0.12) (table 2, online supplementary figure S1). The median PFS was 3.7 months (95% CI 2.5 to 4.9) and 3.3 months (95% CI 2.9 to 3.6) with anti-PD-1-exposed and anti-PD-1-naïve groups (HR 0.82; 95% CI 0.61 to 1.1, p=0.20), respectively (figure 1a). Online supplementary table S4 shows the multivariate analysis of PFS after adjusting the confounding factors (HR of the anti-PD-1-exposed group to anti-PD-1-naïve group 0.80, 95% CI 0.58 to 1.1, p=0.16).

### Taxanes plus RAM

Among patients with taxanes plus RAM (n=149), 20 patients of the anti-PD-1-exposed group and 17 patients of the anti-PD-1-naïve group had PR, resulting in a significantly higher ORR in the anti-PD-1-exposed group than the anti-PD-1-naïve group (60.6% vs 20.0%, p<0.001). DCR was also significantly higher in the anti-PD-1-exposed group than the anti-PD-1-naïve group (87.9% vs 67.1%, p=0.023) (table 2, online supplementary figure S2). Median PFS was significantly longer in the anti-PD-1-exposed group than the anti-PD-1-naïve group (4.8 months, 95% CI 4.2 to 5.4 vs 3.4 months, 95% CI 2.9 to 3.9, HR 0.56; 95% CI 0.37 to 0.84; p=0.004) (figure 1b). This difference was also statistically significant by multivariate analysis after adjustment for confounding factors (HR 0.50, 95% CI 0.32 to 0.78, p=0.003) (online supplementary table S5). In the anti-PD-1-exposed group, one patient showed PR and one showed SD to prior anti-PD-1 monotherapy among two patients with PR to taxanes plus RAM, whereas one patient showed SD and five patients showed PD to prior anti-PD-1 monotherapy among six patients with SD or PD to taxanes plus RAM, though it was not statistically significant (p=0.069) (online supplementary table S6). There was no difference in the baseline characteristics, including molecular status such as HER2, MMR, EBV and PD-L1 CPS status, between patients with PR and those with SD or PD to taxanes plus RAM in the anti-PD-1-exposed group. In the anti-PD-1-naïve group, 11 patients received rechallenge with taxanes plus RAM after exposure to anti-PD-1 therapy. Three of 11 patients achieved PR to rechallenge with taxanes plus RAM, though all 11 patients discontinued the first CTx with taxanes plus RAM due to disease progression. Among three patients with PR to rechallenge with taxanes plus RAM, one patient showed PR and two patients showed SD to the first CTx with taxanes plus RAM.

**Table 2** Tumour responses

| | Anti-PD-1-exposed group | Anti-PD-1-naive group | P value |
|---|---|---|---|
| Overall population | **n=56** | **n=138** | |
| CR | 0 | 0 | |
| PR | 25 (45.5%) | 27 (19.6%) | |
| SD | 20 (35.7%) | 68 (49.3%) | |
| PD | 10 (17.9%) | 43 (31.2%) | |
| NE | 1 (1.8%) | 0 (0.0%) | |
| ORR (%) | 44.6 | 19.6 | 0.001 |
| DCR (%) | 80.6 | 68.8 | 0.12 |
| Taxanes+RAM | **n=33** | **n=85** | |
| CR | 0 | 0 | |
| PR | 20 (60.6%) | 17 (20.0%) | |
| SD | 9 (27.3%) | 40 (47.1%) | |
| PD | 4 (12.1%) | 28 (32.9%) | |
| ORR (%) | 60.6 | 20.0 | <0.001 |
| DCR (%) | 87.9 | 67.1 | 0.023 |
| Taxanes | **n=9** | **n=17** | |
| CR | 0 | 0 | |
| PR | 2 (22.2%) | 4 (23.5%) | |
| SD | 4 (44.4%) | 9 (52.9%) | |
| PD | 2 (22.2%) | 4 (23.5%) | |
| NE | 1 (11.1%) | 0 (0.0%) | |
| ORR (%) | 22.2 | 23.5 | 1.00 |
| DCR (%) | 66.7 | 76.5 | 0.66 |
| Irinotecan | **n=14** | **n=36** | |
| CR | 0 | 0 | |
| PR | 3 (21.4%) | 6 (16.7%) | |
| SD | 6 (42.9%) | 13 (36.1%) | |
| PD | 5 (35.7%) | 17 (47.2%) | |
| ORR (%) | 21.4 | 16.7 | 0.70 |
| DCR (%) | 64.2 | 52.8 | 0.54 |

CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; RAM, ramucirumab; SD, stable disease.

### Taxanes

Among patients with taxanes monotherapy (n=34), two patients of the anti-PD-1-exposed group and four patients of the anti-PD-1-naïve group had PR, resulting in 22.2% and 23.5% ORR, respectively (p=1.00). Disease control was achieved in 6 patients (66.7%) of the anti-PD-1-exposed group and in 13 patients (76.5%) of the anti-PD-1-naïve group (p=0.,66) (table 2). Median PFS was 2.2

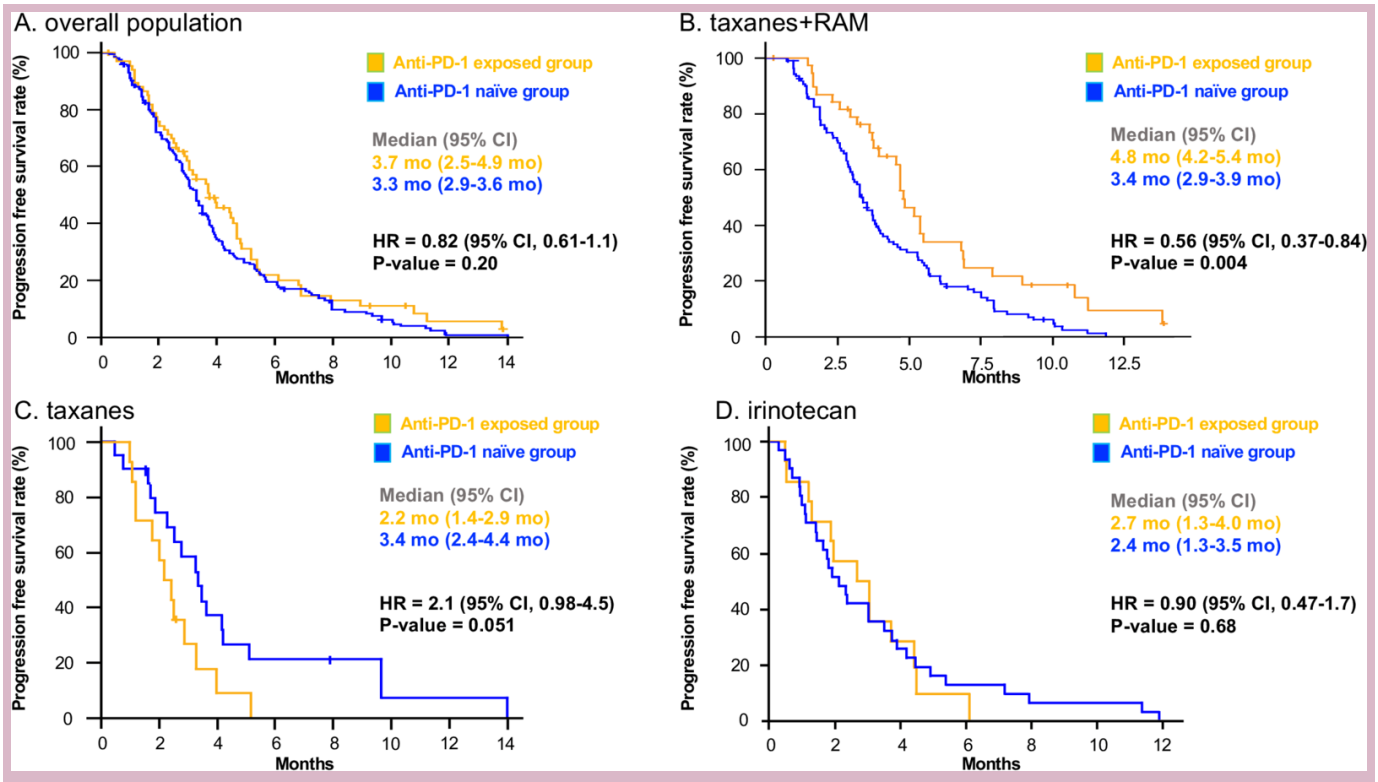


**Figure 1** Kaplan-Meier estimates of progression-free survival. (A) Overall population. (B) Taxanes+RAM. (C) Taxanes. (D) Irinotecan. RAM, ramucirumab

months (95% CI 1.4 to 2.9) with the anti-PD-1-exposed group and 3.4 months (95% CI 2.4 to 4.4) with the anti-PD-1-naïve group (HR 2.1; 95% CI 0.98 to 4.5, p=0.051) (figure 1c).

### Irinotecan

Among patients treated with irinotecan (n=50), three patients of the anti-PD-1-exposed group and six patients of the anti-PD-1-naïve group had PR, resulting in 21.4% and 16.7% ORR for each group (p=0.70). Disease control was achieved in 9 patients (64.2%) of the anti-PD-1-exposed group and in 19 patients (52.8%) of the anti-PD-1-naïve group (p=0.54) (table 2). Median PFS was 2.7 months (95% CI 1.3 to 4.0) with the anti-PD-1-exposed group and 2.4 months (95% CI 1.3 to 3.5) with the anti-PD-1-naïve group (HR 0.90; 95% CI 0.47 to 1.7, p=0.68) (figure 1d).

### Safety

No severe or unexpected treatment-related adverse events occurred in the overall population (table 3).

Among patients on taxanes with RAM, grade 1 or 2 diarrhoea (17.9% vs 5.5%) and stomatitis (23.1% vs 4.5%) were more frequently observed in the anti-PD-1-exposed group than the anti-PD-1-naïve group (online supplementary table S7). The common grade 3 or higher treatment-related adverse events were leukocytopenia (33.3%), neutropenia (51.3%), anaemia (7.7%) and thrombocytopenia (2.6%) in the anti-PD-1-exposed group, which were not significantly different in the anti-PD-1-naïve group. Two patients in the anti-PD-1-exposed group experienced immune-related adverse events during taxanes plus RAM; one hypophysitis and one type 1 diabetes mellitus, which occurred at 4 months and 5 months after the last dose of anti-PD-1 therapy, and were recovered by corticosteroid and insulin, respectively.

Among patients with taxanes monotherapy or irinotecan, the safety profiles were not significantly different between the anti-PD-1-exposed and anti-PD-1-naïve groups (online supplementary table S8, S9). No immune-related adverse events occurred in the anti-PD-1-exposed group.

## DISCUSSION

We investigated the clinical outcomes of patients with AGC receiving CTx with prior exposure to anti-PD-1 therapy compared with patients without prior exposure. To our knowledge, this is the first report of the impact of prior anti-PD-1 therapy on the efficacy and safety of CTx including taxanes plus RAM, taxanes monotherapy or irinotecan.

In the overall population, ORR was significantly higher in the anti-PD-1-exposed group than the anti-PD-1-naïve group. Further, analysis of each CTx regimen demonstrated that taxanes plus RAM achieved a higher ORR and longer PFS in patients with prior anti-PD-1 therapy compared with those without, consistent with a case report showing dramatic tumour response with PTX plus RAM after progression on pembrolizumab in two patients with AGC.[22] Previous studies also reported that prior

Table 3 Treatment-related adverse events

| | Anti-PD-1-exposed group (n=67) | | Anti-PD-1-naive group (n=166) | |
|---|---|---|---|---|
| | All grade, No. (%) | Grade 3 or 4, No. (%) | All grade, No. (%) | Grade 3 or 4, No. (%) |
| Leukocytopenia | 42 (62.7) | 18 (26.9) | 125 (75.3) | 38 (22.9) |
| Neutropenia | 45 (67.2) | 24 (35.8) | 122 (73.5) | 66 (39.8) |
| Anaemia | 32 (47.8) | 3 (4.5) | 96 (57.8) | 5 (3.0) |
| Thrombocytopenia | 12 (17.9) | 2 (3.0) | 30 (18.1) | 6 (3.6) |
| Febrile neutropenia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Fatigue | 13 (19.4) | 0 (0.0) | 34 (20.5) | 0 (0.0) |
| Decreased appetite | 25 (37.3) | 0 (0.0) | 62 (37.3) | 0 (0.0) |
| Nausea | 10 (14.9) | 0 (0.0) | 24 (14.5) | 0 (0.0) |
| Vomiting | 3 (4.5) | 0 (0) | 4 (2.4) | 0 (0.0) |
| Diarrhoea | 10 (14.9) | 0 (0.0) | 18 (10.8) | 0 (0.0) |
| Stomatitis | 9 (13.4) | 0 (0.0) | 5 (3.0) | 0 (0.0) |
| Peripheral sensory neuropathy | 27 (40.3) | 0 (0.0) | 77 (46.4) | 0 (0.0) |
| Arthralgia/myalgia | 5 (7.5) | 0 (0.0) | 5 (3.0) | 0 (0.0) |
| Peripheral oedema | 9 (13.4) | 0 (0.0) | 25 (15.1) | 0 (0.0) |
| Epistaxis | 4 (6.0) | 0 (0.0) | 8 (4.8) | 0 (0.0) |
| Gastric haemorrhage | 0 (0.0) | 0 (0.0) | 3 (1.8) | 0 (0.0) |
| Hypertension | 11 (16.4) | 0 (0.0) | 29 (17.5) | 0 (0.0) |
| Proteinuria | 13 (19.4) | 0 (0.0) | 25 (15.1) | 0 (0.0) |
| Hypophysitis | 1 (1.5) | 1 (1.5) | 0 (0.0) | 0 (0.0) |
| Type 1 diabetes mellitus | 1 (1.5) | 1 (1.5) | 0 (0.0) | 0 (0.0) |

PD-1 therapy might increase the efficacy of docetaxel plus RAM in patients with NSCLC.[16 19] Efficacy results of taxanes plus RAM with an ORR of 60.6% in the anti-PD-1-exposed group also seem more favourable than those of PTX plus RAM with an ORR of 28% as second-line treatment in patients with AGC enrolled in a phase III RAINBOW Trial;[6] however, cross-trial comparison should be carefully interpreted based on different patient characteristics and the small sample size in this study. These results suggest that anti-PD-1 therapy might enhance the efficacy of subsequent CTx with taxanes plus RAM, which was also supported by the observation that 3 of 11 patients with taxanes plus RAM in the anti-PD-1-naïve group achieved objective response to rechallenge with taxanes plus RAM after exposure to anti-PD-1 therapy. Importantly, two of three patients, who achieved PR to rechallenge with taxanes plus RAM, did not show objective response to the first CTx with taxanes plus RAM. A phase II study of pembrolizumab followed by PTX plus RAM is currently being explored in patients with AGC (NCT04069273). Interestingly, a trend of better response to prior anti-PD1-therapy was observed in patients with PR to subsequent taxanes plus RAM compared with those with SD or PD, which warrants further investigations in a large cohort. However, prior anti-PD-1 therapy did not improve responses to taxanes monotherapy or irinotecan, although enhanced antitumour immune response by these drugs is described in previous preclinical studies.[23] These findings indicate that RAM, a mAb for vascular endothelial growth factor receptor-2 (VEGFR-2), might mainly contribute to the synergic effects between taxanes plus RAM and anti-PD-1 therapy. Blocking of the VEGF pathway decreased immune suppressive cells including forkhead box P3 + CD25 + regulatory T cells (Tregs) and tumour-associated macrophages, and enhanced antitumour activity by PD-1 inhibitors in vivo.[24–26] Targeting VEGFR-2 by RAM reduced Tregs in local AGC tumours of patients.[27] Indeed, a phase II study of nivolumab plus RAM showed promising antitumour activity in patients with AGC.[28] Interestingly, the PD-1 blocking effect of the anti-PD-1 antibody persisted in patients for more than 20 weeks after the last infusion,[29] which supports better responses to taxanes plus RAM in the anti-PD-1-exposed group compared with the anti-PD-1-naïve group even up to 99 days after the last dose of anti-PD-1 therapy in this study.

Among patients receiving taxanes plus RAM, a remarkable higher ORR (60.6% vs 20.0%) was observed in the anti-PD-1-exposed group compared with the anti-PD-1-naïve group, but the difference in the median PFS (4.8 vs 3.4 months) between two groups was not so large. This observation was consistent with a previous report for NSCLC.[17] These results suggest that prior anti-PD-1 therapy could increase initial response to subsequent

CTx but it might not be persistent, which warrants further investigations in future studies.

Most treatment-related adverse events during CTx after exposure to anti-PD-1 therapy in this study were manageable. No severe or unexpected adverse events occurred during either CTx. However, two patients with taxanes plus RAM in the anti-PD-1-exposed group experienced immune-related adverse events (one hypophysitis and one type 1 diabetes mellitus), which were recovered by corticosteroid and insulin. Grade 1 or 2 diarrhoea or stomatitis were also more frequent in the anti-PD-1-exposed group than the anti-PD-1-naïve group among patients with taxanes plus RAM, consistent with the safety profiles of docetaxel plus RAM before and after PD-1 therapy in NSCLC, or in a phase II study of nivolumab combined with PTX plus RAM.[19 30] Further analysis with a large sample size as well as pretreatment and post-treatment biopsies is thus essential to clarify the immunological effect of taxanes plus RAM after PD-1 therapy on such toxicities.

The major limitation of the present study was its limited sample size at a single institution, especially for patients with taxanes monotherapy or irinotecan, thus warranting further evaluation in a larger cohort. Moreover, it was not a randomised trial but a retrospective study. Thus, the current study only generates a hypothesis. Another limitation is that overall survival (OS) was not evaluated in this study. Owing to the difference in the treatment line of CTx after anti-PD-1 therapy between anti-PD-1-exposed groups and anti-PD-1-naïve groups, we considered that OS was not an appropriate end point for efficacy. Anti-PD-1-exposed groups were associated with higher frequencies of two or more previous treatment regimens than anti-PD-1-naïve groups. This might suggest that anti-PD-1-exposed groups were enriched in patients with better clinical outcomes than anti-PD-1-naïve groups, leading to group biases in this study. Finally, treatment regimens were misbalanced in the overall population. Thus, we also compared post-CTx-related outcomes between anti-PD-1-exposed and anti-PD-1-naïve groups in each CTx population.

## CONCLUSION

In conclusion, prior exposure to anti-PD-1 therapy might improve tumour responses to taxanes plus RAM. Further, CTx administered after anti-PD-1 therapy was manageable without unexpected toxicities, but immune-related adverse events during CTx after anti-PD-1 therapy should be monitored carefully.

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## REFERENCES

1 Ferlay J, Soerjomataram I, Dikshit R, *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–86.
2 Koizumi W, Narahara H, Hara T, *et al*. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (spirits trial): a phase III trial. *Lancet Oncol* 2008;9:215–21.
3 Cunningham D, Starling N, Rao S, *et al*. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36–46.
4 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.
5 Janowitz T, Thuss-Patience P, Marshall A, *et al*. Chemotherapy vs supportive care alone for relapsed gastric, gastroesophageal junction, and oesophageal adenocarcinoma: a meta-analysis of patient-level data. *Br J Cancer* 2016;114:381–7.
6 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.
7 Shitara K, Doi T, Dvorkin M, *et al*. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (tags): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2018;19:1437–48.
8 Robert C, Long GV, Brady B, *et al*. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320–30.
9 Borghaei H, Paz-Ares L, Horn L, *et al*. Nivolumab versus docetaxel in advanced Nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627–39.
10 Motzer RJ, Escudier B, McDermott DF, *et al*. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1803–13.
11 Younes A, Santoro A, Shipp M, *et al*. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol* 2016;17:1283–94.
12 Ferris RL, Blumenschein G, Fayette J, *et al*. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016;375:1856–67.
13 Kang Y-K, 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.
14 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.
15 Yan Y, Cao S, Liu X, *et al*. Cx3Cr1 identifies PD-1 therapy-responsive CD8+ T cells that withstand chemotherapy during cancer chemoimmunotherapy. *JCI Insight* 2018;3. doi:10.1172/jci.insight.97828
16 Shiono A, Kaira K, Mouri A, *et al*. Improved efficacy of ramucirumab plus docetaxel after nivolumab failure in previously treated non-small cell lung cancer patients. *Thorac Cancer* 2019;10:775–81.
17 Park SE, Lee SH, Ahn JS, *et al*. Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer. *J Thorac Oncol* 2018;13:106–11.
18 Schvartsman G, Peng SA, Bis G, *et al*. Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer. *Lung Cancer* 2017;112:90–5.
19 Harada D, Takata K, Mori S, *et al*. Previous immune checkpoint inhibitor treatment to increase the efficacy of docetaxel and ramucirumab combination chemotherapy. *Anticancer Res* 2019;39:4987–93.
20 Reck M, Rodríguez-Abreu D, Robinson AG, *et al*. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. *J Clin Oncol* 2019;37:537–46.
21 Kawazoe A, Shitara K, Kuboki Y, *et al*. Clinicopathological features of 22C3 PD-L1 expression with mismatch repair, Epstein-Barr virus status, and cancer genome alterations in metastatic gastric cancer. *Gastric Cancer* 2019;22:69–76.
22 Chakrabarti S, Dong H, Paripati HR, *et al*. First report of dramatic tumor responses with ramucirumab and paclitaxel after progression on pembrolizumab in two cases of metastatic gastroesophageal adenocarcinoma. *Oncologist* 2018;23:840–3.
23 Galluzzi L, Senovilla L, Zitvogel L, *et al*. The secret ally: immunostimulation by anticancer drugs. *Nat Rev Drug Discov* 2012;11:215–33.
24 Sachdev JC, Patnaik A, Waypa J, *et al*. Safety, pharmacodynamic, and pharmacokinetic profile of TSR-042, an anti–PD–1 monoclonal antibody, in patients (PTS) with advanced solid tumors. *Annals of Oncology* 2017;28:v420–7.
25 Chen C-W, Ou D-L, Hsu C-L, *et al*. FRI-471-Regorafenib may enhance efficacy of anti-program cell death-1 therapy in hepatocellular carcinoma through modulation of macrophage polarization. *J Hepatol* 2019;70:e605–6.
26 Kato Y, Tabata K, Kimura T, *et al*. Lenvatinib plus anti-PD-1 antibody combination treatment activates CD8+ T cells through reduction of tumor-associated macrophage and activation of the interferon pathway. *PLoS One* 2019;14:e0212513.
27 Tada Y, Togashi Y, Kotani D, *et al*. Targeting VEGFR2 with Ramucirumab strongly impacts effector/ activated regulatory T cells and $CD8^+$ T cells in the tumor microenvironment. *J Immunother Cancer* 2018;6:106.
28 Kadowaki S, Izawa N, Minashi K, *et al*. Multicenter phase I/II study of nivolumab combined with paclitaxel plus ramucirumab as the second-line treatment in patients with advanced gastric cancer. *Annals of Oncology* 2019;30:iv122.
29 Osa A, Uenami T, Koyama S, *et al*. Clinical implications of monitoring nivolumab immunokinetics in non-small cell lung cancer patients. *JCI Insight* 2018;3. doi:10.1172/jci.insight.59125
30 Hara H, Shoji H, Takahari D, *et al*. Phase I/II study of ramucirumab plus nivolumab in patients in second-line treatment for advanced gastric adenocarcinoma (NivoRam study). *Journal of Clinical Oncology* 2019;37:129.