cancers

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*Article*

# Ramucirumab in Combination with Pembrolizumab in Treatment-Naïve Advanced Gastric or GEJ Adenocarcinoma: Safety and Antitumor Activity from the Phase 1a/b JVDF Trial

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**Supplementary**

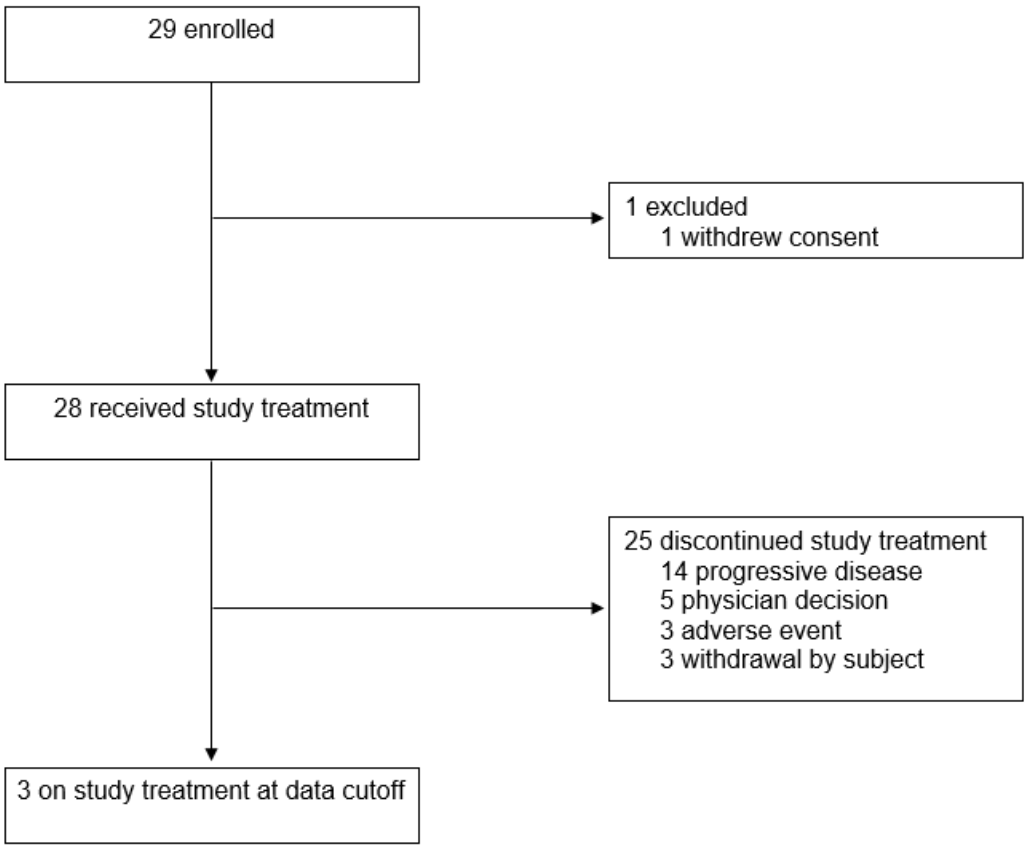
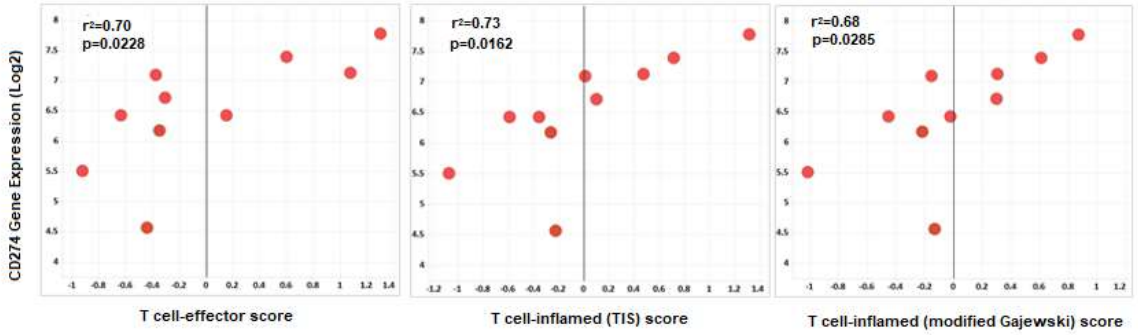
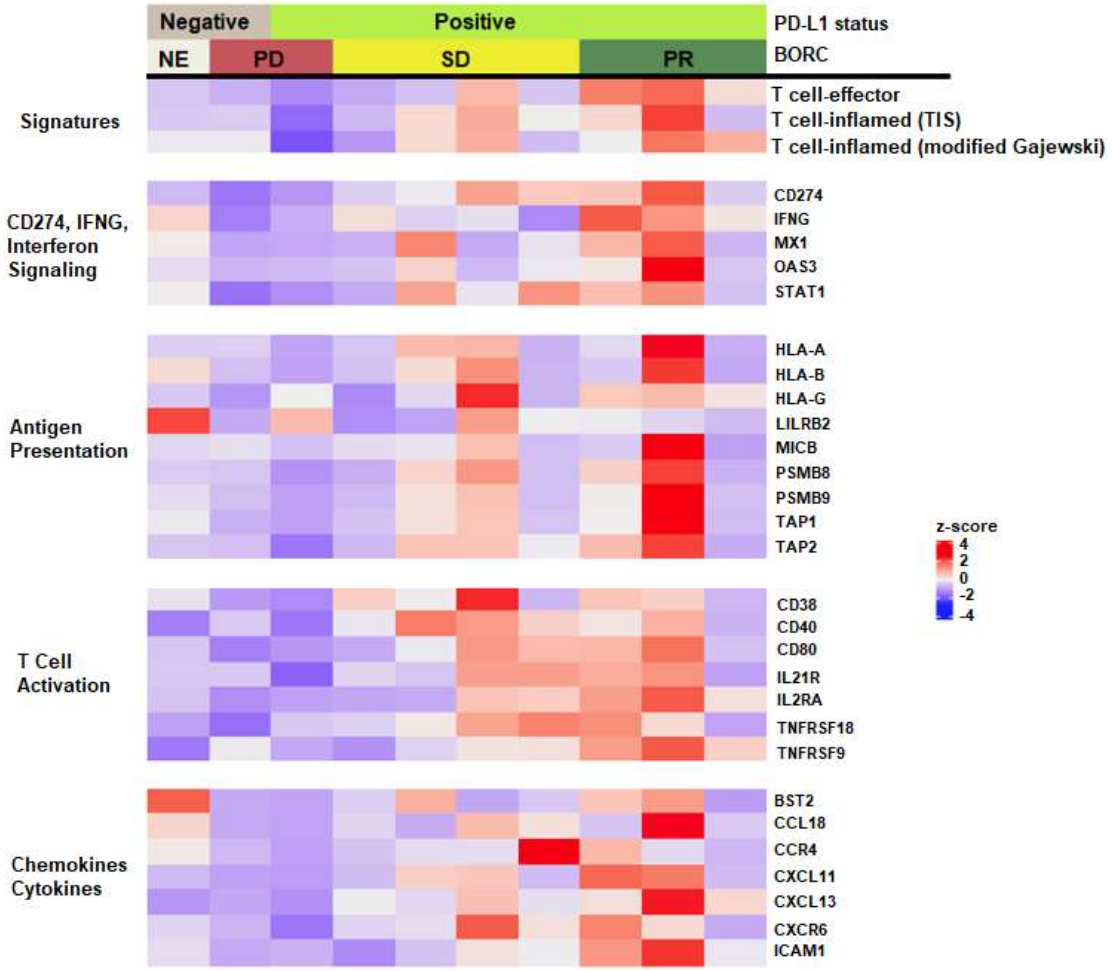


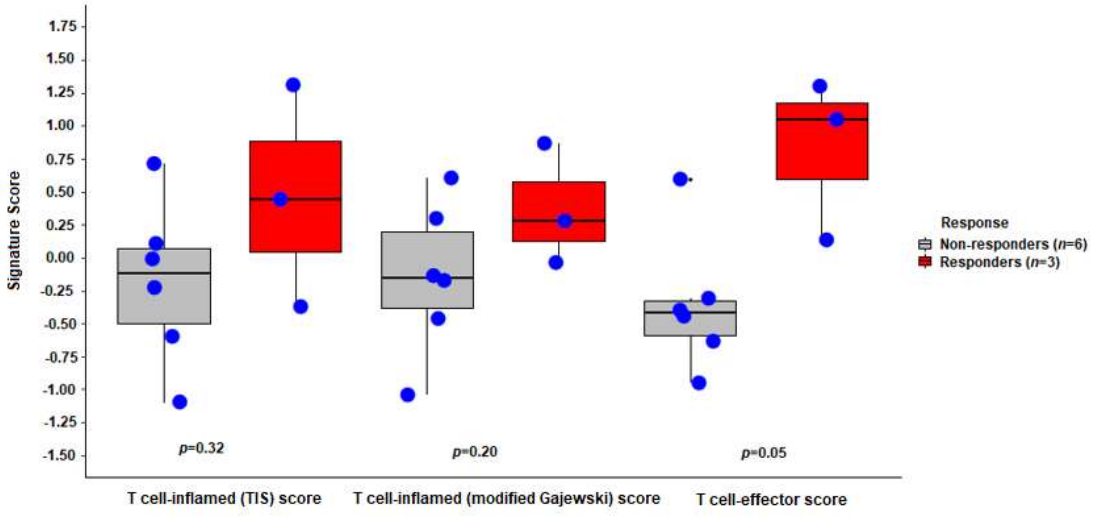

**Figure S1.** CONSORT diagram in the treatment-naïve, advanced gastric/gastroesophageal junction (G/GEJ) cancer Cohort A2.




(a)

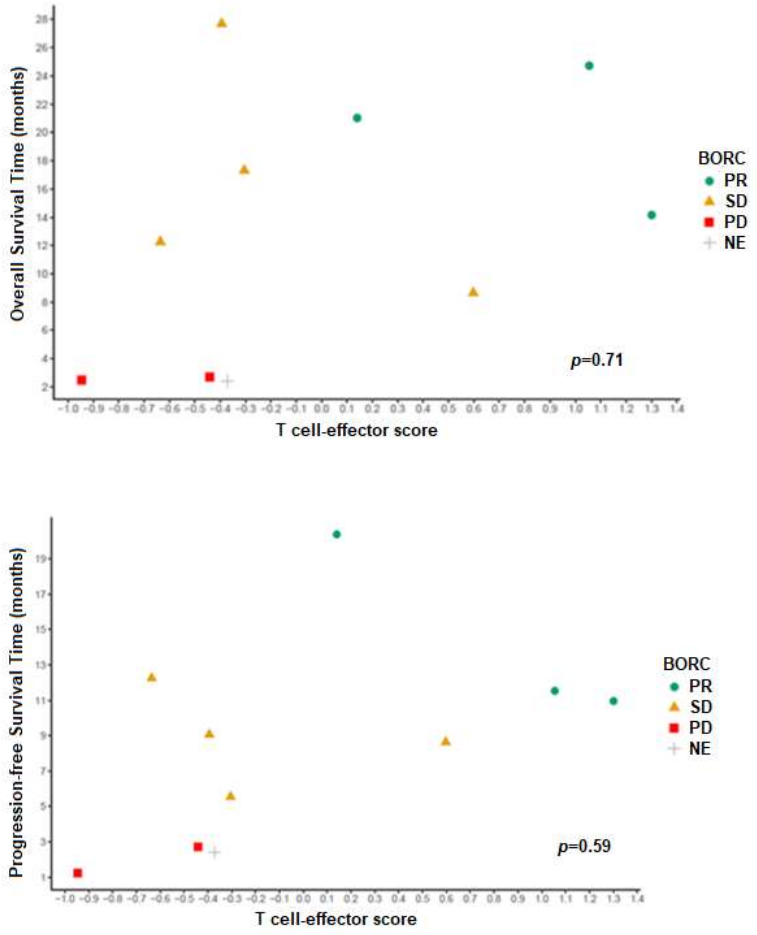

Negative
Positive
PD-L1 status
NE
PD
SD
PR
BORC
Signatures
T cell-effector
T cell-inflamed (TIS)
T cell-inflamed (modified Gajewski)
CD274, IFNG, Interferon Signaling
CD274
IFNG
MX1
OAS3
STAT1
Antigen Presentation
HLA-A
HLA-B
HLA-G
LILRB2
MICB
PSMB8
PSMB9
TAP1
TAP2
T Cell Activation
CD38
CD40
CD80
IL21R
IL2RA
TNFRSF18
TNFRSF9
Chemokines Cytokines
BST2
CCL18
CCR4
CXCL11
CXCL13
CXCR6
ICAM1
z-score
4
2
0
-2
-4

(b)

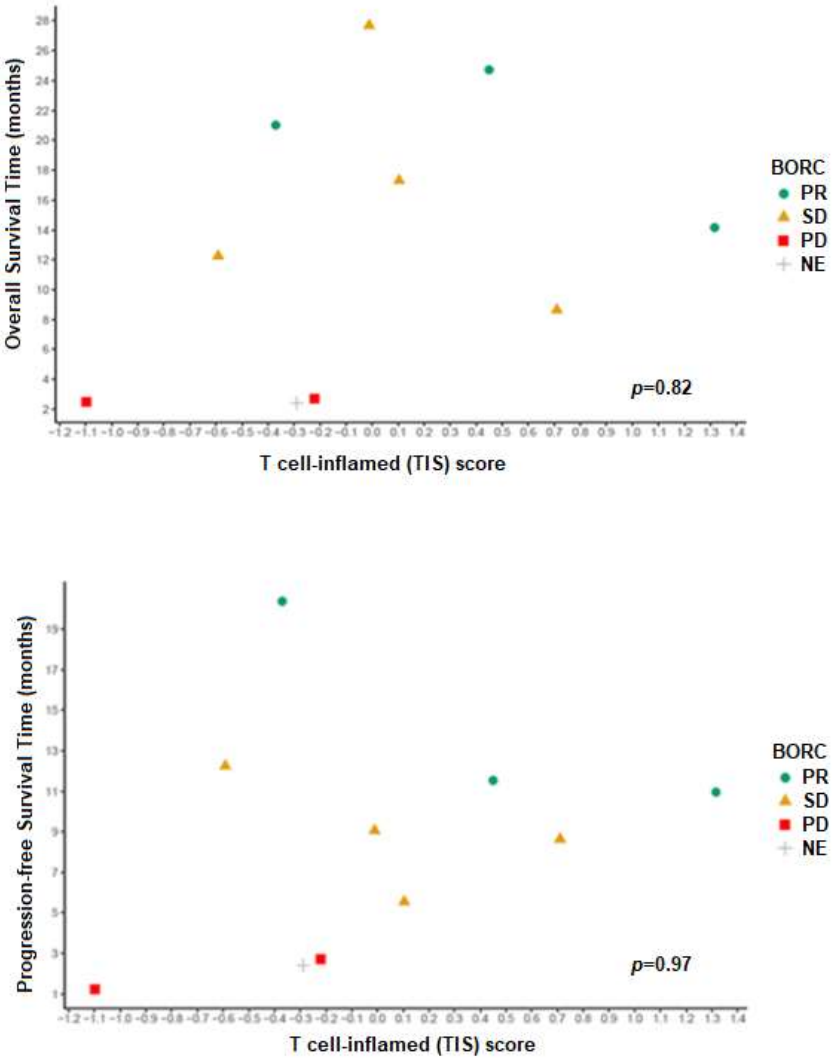

Signature Score
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
-1.25
-1.50
p=0.32
p=0.20
p=0.05
T cell-inflamed (TIS) score
T cell-inflamed (modified Gajewski) score
T cell-effector score
Response
Non-responders (n=6)
Responders (n=3)

(c)

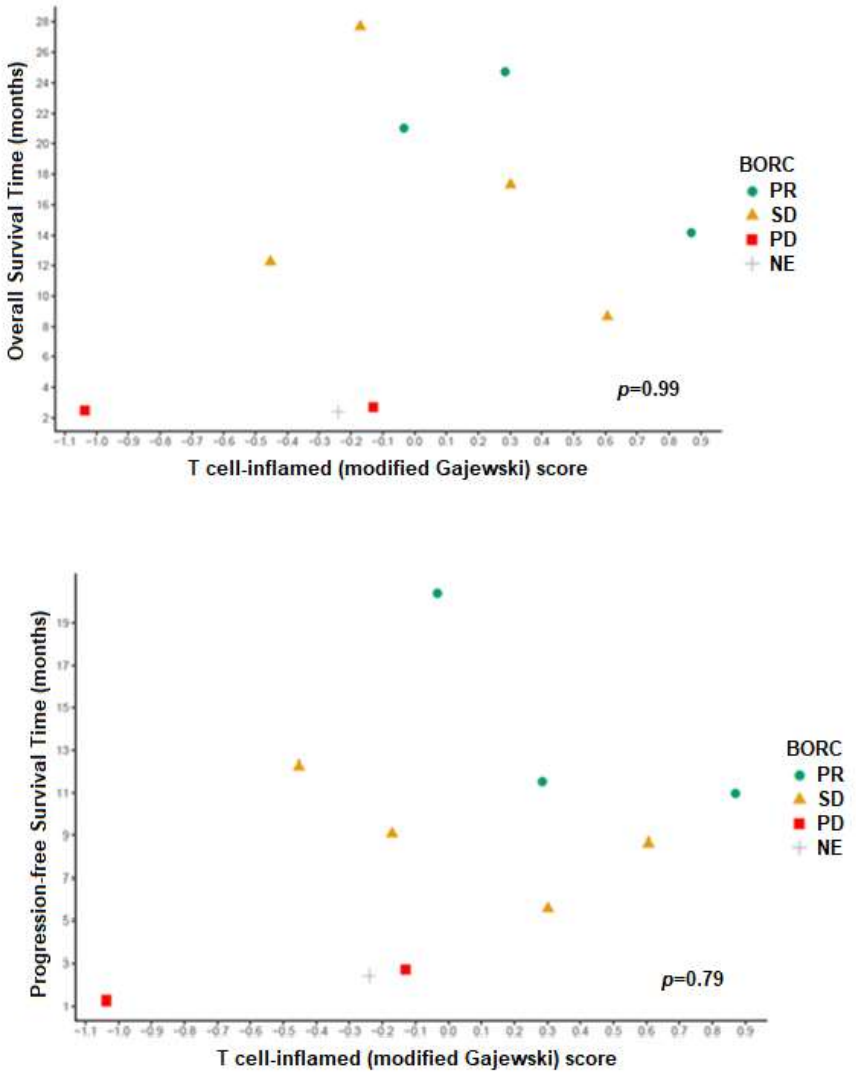
**Figure S2.** Biomarker immune profiling analysis in 10 1L G/GEJ patients (**a**) Pearson correlations of CD274 (PD-L1 gene) expression with gene signatures scores, (**b**) expression profiling of the 3 gene signatures and other genes of interest by PD-L1 protein expression and BORC, and (**c**) boxplot showing the relationship between the 3 gene signature scores and objective response by RECIST. The horizontal line represents the median. Responder, complete or partial response; nonresponder, stable disease or progressive disease. Not evaluable patients (*n*=1) excluded from this analysis. Abbreviations: BORC, best overall response (confirmed); *n*, number in sample; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.




(a)


Overall Survival Time (months)
T cell-inflamed (TIS) score
p=0.82
BORC
PR
SD
PD
NE
Progression-free Survival Time (months)
T cell-inflamed (TIS) score
p=0.97
BORC
PR
SD
PD
NE

(b)




(c)

**Figure S3.** Association between the 3 gene signatures (**a**) T cell-effector score, (**b**) T cell-inflamed (TIS) score, and (**c**) T cell-inflamed (modified Gajewski) score, with progression-free survival and overall survival after ramucirumab and pembrolizumab treatment for 10 patients.
Abbreviations: NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

**Table S1.** Dose administration.

| | **Ramucirumab + pembrolizumab** *N* **= 28** | |
|---|---|---|
| | **Ramucirumab** | **Pembrolizumab** |
| Duration of therapy, median months (IQR) | 4.5 (2.1 – 9.7) | 4.5 (2.1 – 10.1) |
| Number of cycles received, median (IQR) | 7 (3 – 13) | 7 (3 – 14) |
| Relative dose intensity, median % (range) | 94 (65 – 103) | 98 (66 – 101) |
| Dose reductions, *n* (%) | 2 (7) | Not applicable |
| Dose delays, *n* (%) | 19 (68) | 11 (39) |
| Treatment interrupted, *n* (%) | 1 (4) | 0 |

Abbreviations: IQR, interquartile range; *n*, number in sample; *N*, number of patients in overall population.

**Table S2.** Treatment-emergent adverse events[1].

| ***n* (%)** | **Ramucirumab + pembrolizumab *N* = 28** |
|---|---|
| TEAEs | |
| ≥1 TEAE | 28 (100) |
| Fatigue | 19 (68) |
| Nausea | 12 (43) |
| Diarrhea | 11 (39) |
| Hypertension | 11 (39) |
| Decreased appetite | 8 (29) |
| Dyspnoea | 8 (29) |
| Headache | 8 (29) |
| Peripheral edema | 8 (29) |
| Vomiting | 8 (29) |
| Abdominal pain | 6 (21) |
| Epistaxis | 6 (21) |
| Proteinuria | 6 (21) |
| Abdominal pain upper | 5 (18) |
| ALT increased | 5 (18) |
| AST increased | 5 (18) |
| Constipation | 5 (18) |
| Dysphagia | 5 (18) |
| Stomatitis | 5 (18) |
| Urinary tract infection | 5 (18) |

[1] Any grade TEAEs in ≥ 15% of patients are presented.Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; *n*, number in sample; *N*, number of patients in overall population; TEAE, treatment-emergent adverse event.

**Table S3.** Treatment-related serious adverse events[1].

| ***n* (%)** | **Ramucirumab + pembrolizumab *N* = 28** |
|---|---|
| SAEs | |
| ≥1 SAE | 11 (39) |
| Colitis | 2 (7) |
| Diarrhea | 2 (7) |
| Gastrointestinal hemorrhage | 2 (7) |

[1] SAEs in ≥5% of patients by preferred term are presented. Abbreviations: *n*, number in sample; *N*, number of patients in overall population; SAE, serious adverse event.

**Table S4.** Post-discontinuation treatment[1].

| ***n* (%)** | **Ramucirumab + pembrolizumab *N* = 28** |
|---|---|
| Patients who received ≥1 PDT | 13 (47) |
| Patients who underwent ≥1 surgery | 3 (11) |
| Stomach and lymph node resection | 1 (4) |
| Other procedures | 2 (7) |
| Any systemic anticancer therapy | |
| 5-fluorouracil | 8 (29) |
| Oxaliplatin | 8 (29) |
| Cisplatin | 3 (11) |
| Leucovorin | 3 (11) |
| Capecitabine | 2 (7) |
| Irinotecan | 2 (7) |
| Carboplatin | 1 (4) |
| Epirubicin | 1 (4) |
| Paclitaxel | 1 (4) |

[1] Patients may have had more than one therapy.Abbreviations: *n*, number in sample; *N*, number of patients in overall population; PDT, post-discontinuation treatment.

**Table S5.** Summary of ramucirumab trough concentrations (pre-dose) for patients treated with 8 mg/kg of ramucirumab intravenously on days 1 and 8 Q3W in combination with pembrolizumab.

| | **Trough serum concentrations (µg/mL)** | | | | |
|---|---|---|---|---|---|
| **Dose** | **3** | **5** | **7** | **9** | **13** |
| Week | 3 | 6 | 9 | 12 | 18 |
| $n_{PK}$ | 22 | 18 | 13 | 10 | 7 |
| Min | 24 | 31 | 51 | 45 | 46 |
| Max | 71 | 114 | 118 | 137 | 151 |
| Geo mean[1] | 45 | 61 | 79 | 80 | 88 |
| Geo CV%[1] | 32 | 38 | 31 | 38 | 48 |

[1] Not calculated when $n_{PK}$ <3. Abbreviations: CV%, percentage coefficient of variation; Geo, geometric; Max, maximum; Min, minimum; $n_{PK}$, number of pharmacokinetic observations included in calculation; Q3W, every 3 weeks.

**Table S6.** Summary of ramucirumab peak (1 hour post-infusion) concentrations for patients treated with 8 mg/kg of ramucirumab intravenously on days 1 and 8 Q3W in combination with pembrolizumab.

| | **Peak serum concentrations (µg/mL)** |
|---|---|
| Dose | 1 |
| Week | 0 |
| $n_{PK}$ | 24 |
| Min | 102 |
| Max | 285 |
| Geo mean[1] | 150 |
| Geo CV%[1] | 24 |

[1] Not calculated when $n_{PK}$ <3.Abbreviations: CV%, percentage coefficient of variation; Geo, geometric; Max, maximum; Min, minimum; $n_{PK}$, number of pharmacokinetic observations included in calculation; Q3W, every 3 weeks.

**Table S7.** Efficacy endpoints definitions.

| **Objective response rate** | **The proportion of treated patients who achieved a best overall response of CR or PR.** |
|---|---|
| Time to response | The time from the date of first study treatment until the first evidence of a confirmed CR or PR. |
| Duration of response | Measured from the date of first evidence of a confirmed CR or PR to the date of objective progression or the date of death due to any cause, whichever was earlier, only for patients with a confirmed CR or PR. If a responder was not known to have died or have objective progression at the data inclusion cutoff date, the duration of response was censored at the date of the last complete objective progression-free disease assessment. |
| Disease control rate | The proportion of treated patients who had a best overall response of CR, PR, or SD. |
| Progression-free survival | The time from the date of first study treatment until the date of the first observed radiographically documented PD or death due to any cause, whichever was earlier. |
| Overall survival | Determined from the date of first study treatment until death due to any cause. |

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.