Phase Ib/II, Open-label, Randomised Evaluation of Second-line Atezolizumab + Linagliptin vs Ramucirumab + Paclitaxel in MORPHEUS-Gastric Cancer

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## MORPHEUS PLATFORM AND COMBINATION THERAPY

- The MORPHEUS platform consists of multiple, global, open-label, randomised, umbrella Phase Ib/II trials designed to accelerate the development of combinations in several indications by identifying early signals and establishing proof-of-concept clinical data[1,2]
- Trials under the MORPHEUS platform are assessing the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumour infiltration and/or recognition of tumour cells for elimination
  - Using a randomised trial design, multiple combination arms are being compared with a single control arm, thereby reducing the number of patients receiving control treatment
- Atezolizumab is an engineered monoclonal antibody that inhibits the binding of programmed death-ligand 1 (PD-L1) to its receptors programmed death-1 (PD-1) and B7.1, thus restoring tumour-specific immunity[3-5]
- Dipeptidyl peptidase-4 (DPP-4) inhibition has been shown to promote immune cell recruitment in the tumour parenchyma, leading to increased tumour control in several cancers, including gastric[6-7]
- Linagliptin, an approved antidiabetic treatment, is a DPP-4 inhibitor that regulates the activity of pro-inflammatory chemokines such as CXCL9, CXCL10, and CXCL11,[8] which can mediate the recruitment of tumour-suppressive CXCR3-positive T cells and natural killer cells into solid tumours[9-11]
- Given the role of DPP-4 in the regulation of several pro-inflammatory chemokines and intratumoural T-cell recruitment, we hypothesised that adding linagliptin to atezolizumab could stimulate anti-tumour immune responses in solid tumours, including gastric cancer

MORPHEUS-GC (NCT03281369)

Study Design

- Here, we report the results from patients receiving atezolizumab + linagliptin in patients with gastroesophageal junction cancer and gastric cancer (GEJ/GC; Figure 1)

Figure 1. Study Design of MORPHEUS-GC

R, randomisation.
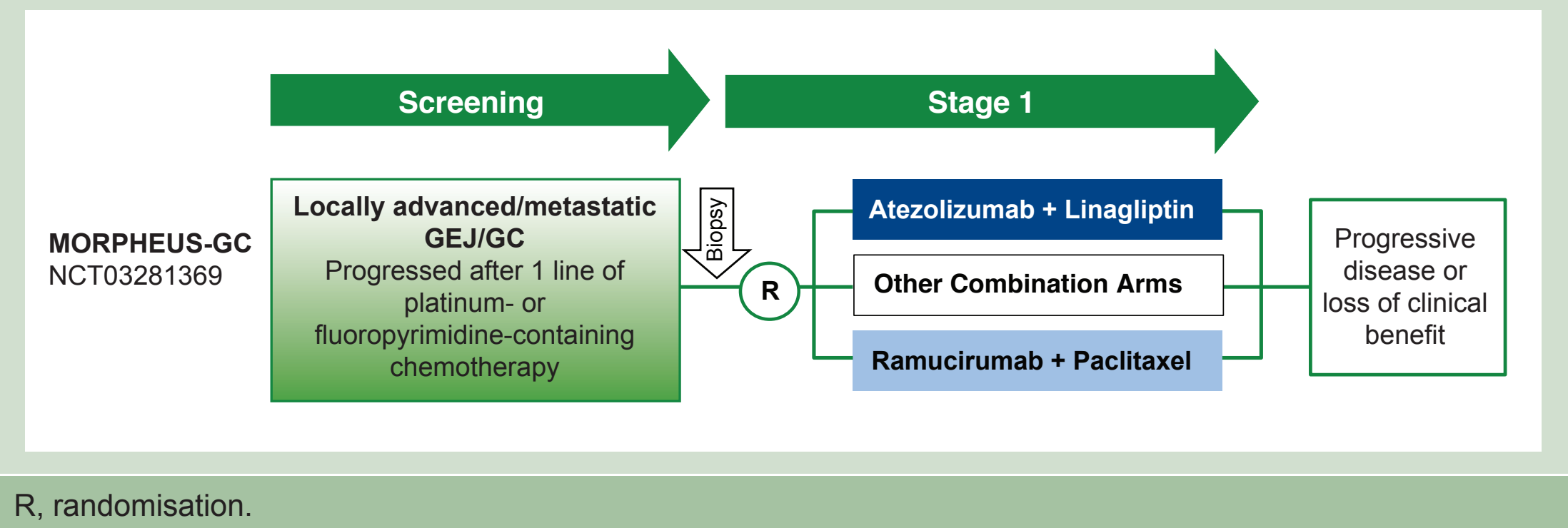
- **Primary endpoint:**
  - Investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1)
- **Key secondary endpoints:**
  - Investigator-assessed progression-free survival (PFS), disease control rate (DCR) and duration of response (DOR) per RECIST 1.1
  - Overall survival (OS)
  - Percentage of participants with adverse events (AEs)
  - Pharmacokinetics (PK) and percentage of patients with anti-drug antibodies (ADAs) to atezolizumab
- Exploratory biomarker analyses were also conducted

Inclusion Criteria and Treatment

- Key inclusion criteria were a histologically or cytologically confirmed diagnosis of locally advanced, unresectable or metastatic gastric adenocarcinoma or carcinoma gastroesophageal junction that had progressed during or following a first-line platinum- or fluoropyrimidine-containing chemotherapy regimen; age ≥ 18 years; ECOG PS score 0-1 and measurable disease per RECIST 1.1
- Eligible patients had to provide an entry biopsy before being randomised to receive either atezolizumab 1200 mg intravenously (IV) every 3 weeks + linagliptin 5 mg orally daily, or ramucirumab + paclitaxel until they experienced unacceptable toxicity and/or loss of clinical benefit as determined by the investigator in the experimental arm or PD per RECIST 1.1 (Figure 1)

Key Exclusion Criteria

- Key exclusion criteria included symptomatic, untreated or actively progressing central nervous system metastases; active or history of autoimmune disease or immune deficiency; and a history of idiopathic pulmonary fibrosis, organising pneumonia, drug-induced pneumonitis or idiopathic pneumonitis, or evidence of active pneumonitis

Patient Demographics and Disposition

- Fourteen patients were randomised and treated with atezolizumab + linagliptin in the experimental arm, and 12 patients were treated with ramucirumab + paclitaxel in the control arm
- Patient baseline characteristics and demographics are presented in Table 1

Table 1. Baseline Demographics and Disease Characteristics in MORPHEUS-GC

n (%)	Atezolizumab + Linagliptin (n = 14)	Ramucirumab + Paclitaxel (n = 12)
Age ≥ 65 years	2 (14.3)	6 (50.0)
Male	12 (85.7)	9 (75.0)
ECOG PS 1	11 (78.6)	8 (66.7)
Albumin level ≥ 35 g/dL	11 (78.6)	11 (91.7)
CRP level > 12 mg/dL	5 (41.7)	4 (36.4)
LDH level		
< 1.5 × ULN	13 (100.0)	7 (58.3)
1.5 × ULN and < 2.5 × ULN	0	5 (41.7)

Clinical cutoff, 10 June 2021.
CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; ULN, upper limit of normal.

- Demographics and disease characteristics were generally similar between arms, with a slight difference in age

Efficacy

- Efficacy data are summarised in Table 2

Table 2. Efficacy in MORPHEUS-GC

	Atezolizumab + Linagliptin (n = 14)	Ramucirumab + Paclitaxel (n = 12)
Confirmed investigator-assessed ORR per RECIST 1.1, n (%) [95% CI]	3 (21.4) [4.7, 50.1]	2 (16.7) [2.1, 48.4]
CR	1 (7.1) [0.2, 33.9]	0 [0.0, 26.5]
PR	2 (14.3) [1.8, 42.8]	2 (16.7) [2.1, 48.4]
SD, n (%) [95% CI]	2 (14.3) [1.8, 42.8]	8 (66.7) [34.9, 90.1]
PD, n (%) [95% CI]	8 (57.1) [28.9, 82.3]	2 (16.7) [2.1, 48.4]
DCR, n (%), mo [95% CI]ª	3 (21.4) [4.7, 50.8]	8 (66.7) [34.9, 90.1]
Median DOR (range), mo	20.0 (3.5-31.3)	3.3 (2.9-3.7)
Progression event or death, n (%)	13 (92.9)	12 (100.0)
Median PFS per investigator–assessed RECIST 1.1, mo [95% CI]	2.0 [1.6, 4.9]	6.1 [3.7, 8.8]
Median OS, mo [95% CI]	8.6 [4.3, 28.1]	8.3 [6.4, 10.9]
Deaths, n (%)	10 (71.4)	12 (100.0)

Clinical cutoff, 10 June 2021.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
ª Criteria for disease control: SD for ≥ 12 weeks or CR or PR as determined by the investigator per RECIST 1.1.

- The 3 responders receiving atezolizumab + linagliptin, including 1 with a CR, had a long median DOR of 20 months

Safety

- Safety data are summarised in Table 3

Table 3. Safety Summary for MORPHEUS-GC

n (%)	Atezolizumab + Linagliptin (n = 14)	Ramucirumab + Paclitaxel (n = 12)
Patients with ≥ 1 AE	14 (100.0)	12 (100.0)
Treatment-related AEs	7 (50.0)	12 (100.0)
Serious AEs	4 (28.6)	6 (50.0)
Related serious AEs	0	1 (8.3)ª
Grade 3-4 AEs	7 (50.0)	9 (75.0)
Grade 5	0	0
Related AEs leading to dose modification/interruptionᵇ	1 (7.1)	9 (75.0)
Related AEs leading to withdrawal from treatmentᵇ,ᶜ	0	1 (8.3)ᵇ

Clinical cutoff, 11 July 2019.
ª Causality relationship was determined per investigator's judgment.
ᵇ AE leading to withdrawal from treatment/dose modification/interruption of any drug.
ᶜ Patient discontinued study drug due to nausea (Grade 3).

- No new safety signals were observed
  - More Grade 3-4 AEs, related all-grade AEs, and AEs leading to dose modifications/interruption were observed in the ramucirumab + paclitaxel arm than in the atezolizumab + linagliptin arm
  - There were no Grade 5 AEs in either arm

Pharmacokinetic Analyses

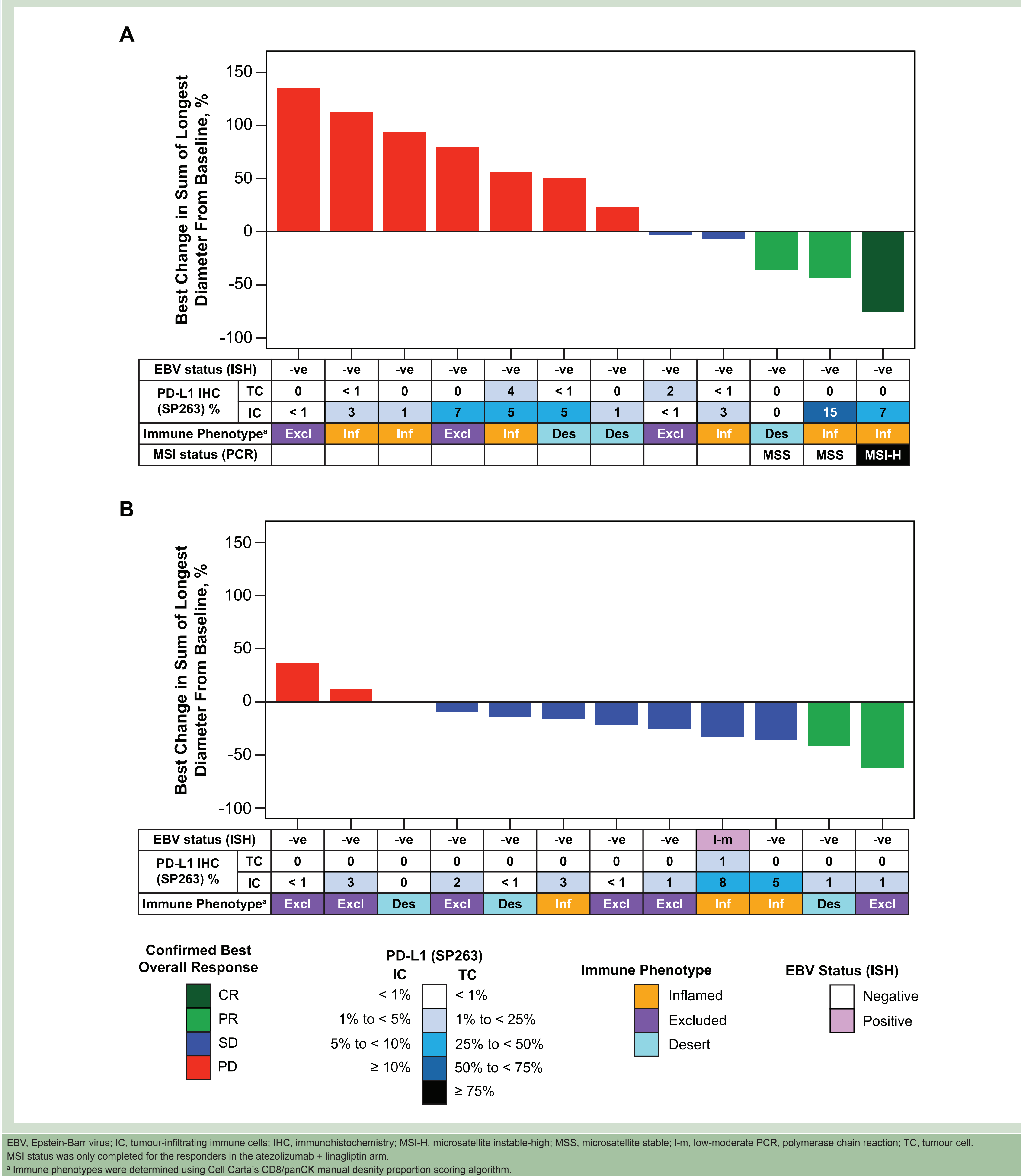- Concentration data for atezolizumab are summarised in Table 4

Table 4. Concentrations of Atezolizumab Over Time

Visit	Patients, n	Mean, µg/mL	Coefficient of Variation, %
Cycle 1 Day 1 30-min post-dose	13	377	34.3
Cycle 2 Day 1 Pre-dose	13	74.4	41.3
Cycle 3 Day 1 Pre-dose	7	124	33.5
Cycle 4 Day 1 Pre-dose	5	155	50.7
Cycle 8 Day 1 Pre-dose	3	221	45.6

- After the first dose of atezolizumab, the mean Cycle 2 Day 1 (pre-dose) atezolizumab concentration was 74.4 µg/mL, which was higher than the target concentration of 6 µg/mL
- Peak and trough exposures of atezolizumab were in line with expectations and are consistent with clinical experience to date
- 13 atezolizumab-treated patients were evaluated for baseline prevalence of ADAs to atezolizumab; none of the 13 patients (0%) became positive for treatment-emergent ADAs

Biomarker Analysis

- Biomarker data according to best overall response to atezolizumab + linagliptin are summarised in Figure 2

Figure 2. Relationship Between PD-L1 Status, Tumour Immune Phenotype and Best Overall Response with (A) Atezolizumab + Linagliptin and (B) Ramucirumab + Paclitaxel

EBV, Epstein-Barr virus; IC, tumour-infiltrating immune cells; IHC, immunohistochemistry; MSI-H, microsatellite instable-high; MSS, microsatellite stable; l-m, low-moderate PCR, polymerase chain reaction; TC, tumour cell.
MSI status was only completed for the responders in the atezolizumab + linagliptin arm.
ª Immune phenotypes were determined using Cell Carta's CD8/panCK manual density proportion scoring algorithm.

- 1 patient in the atezolizumab + linagliptin arm who achieved a CR had microsatellite instability–high status, an inflamed tumour phenotype, and had moderate PD-L1 IC staining
- 2 patients in the atezolizumab + linagliptin arm had a PR; 1 had an inflamed tumour phenotype and PD-L1 IC high (15%) expression and the other had a desert tumour phenotype and low PD-L1 expression

- Longitudinal DPP-4 activity vs response in patients receiving atezolizumab + linagliptin is shown in Figure 3

Figure 3. DDP-4 Activity vs Response in Patients Receiving Atezolizumab + Linagliptin
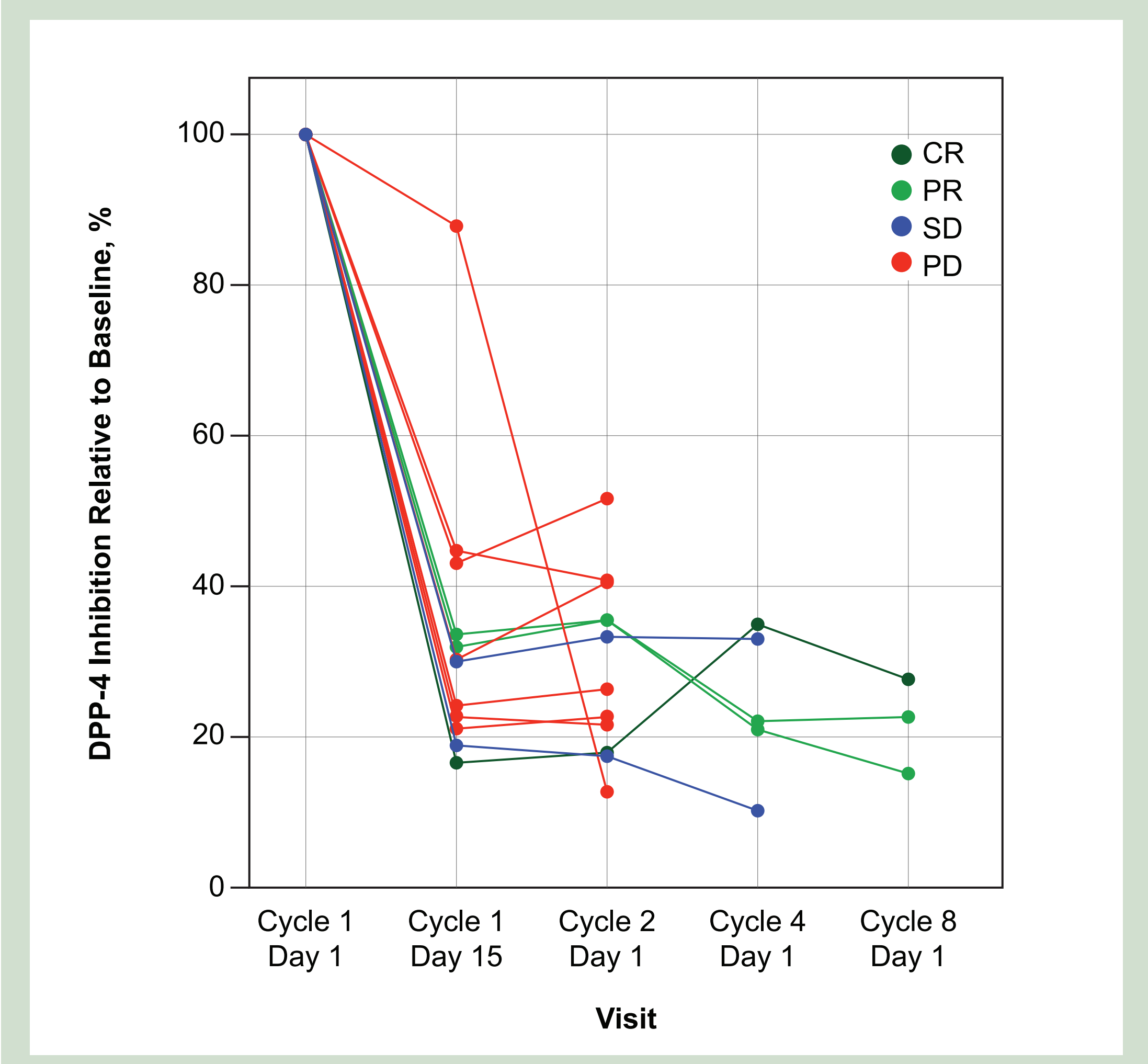
- All patients treated with atezolizumab + linagliptin had between a 50% and 90% reduction in DPP-4 activity at Cycle 1 Day 15 compared with baseline; reduced enzymatic activity was generally maintained throughout the remaining time points

CONCLUSIONS

- Treatment with atezolizumab + linagliptin led to limited responses in patients with GC; 3 responders, including 1 with a CR as best response, had a long median DOR of 20 months, while 8 patients had PD as best response
- The AEs observed were consistent with the known safety profiles of the individual study treatments. No new safety signals were identified with atezolizumab + linagliptin
- The PK findings for atezolizumab were in line with expectations and comparable to those observed in global studies
- Although the biomarker data provided additional context on the individual patient tumours, the biomarker analyses overall did not identify trends related to clinical activity

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DISCLOSURES

ACKNOWLEDGEMENTS

Confirmed Best Overall Response: CR, PR, SD, PD

PD-L1 (SP263): IC: < 1%, 1% to < 5%, 5% to < 10%, ≥ 10%; TC: < 1%, 1% to < 25%, 25% to < 50%, 50% to < 75%, ≥ 75%

Immune Phenotype: Inflamed, Excluded, Desert

EBV Status (ISH): Negative, Positive