The Oncologist, 2023, **28**, 553–e472
https://doi.org/10.1093/oncolo/oyad022
Advance access publication 21 March 2023
Clinical Trial Results

Atezolizumab Plus PEGPH20 Versus Chemotherapy in Advanced Pancreatic Ductal Adenocarcinoma and Gastric Cancer: MORPHEUS Phase Ib/II Umbrella Randomized Study Platform

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Abstract

Background: The MORPHEUS platform comprises multiple open-label, randomized, phase Ib/II trials designed to identify early efficacy and safety signals of treatment combinations across cancers. Atezolizumab (anti-programmed cell death 1 ligand 1 [PD-L1]) was evaluated in combination with PEGylated recombinant human hyaluronidase (PEGPH20).

Methods: In 2 randomized MORPHEUS trials, eligible patients with advanced, previously treated pancreatic ductal adenocarcinoma (PDAC) or gastric cancer (GC) received atezolizumab plus PEGPH20, or control treatment (mFOLFOX6 or gemcitabine plus *nab*-paclitaxel [MORPHEUS-PDAC]; ramucirumab plus paclitaxel [MORPHEUS-GC]). Primary endpoints were objective response rates (ORR) per RECIST 1.1 and safety.

Results: In MORPHEUS-PDAC, ORRs with atezolizumab plus PEGPH20 ($n = 66$) were 6.1% (95% CI, 1.68%-14.80%) vs. 2.4% (95% CI, 0.06%-12.57%) with chemotherapy ($n = 42$). In the respective arms, 65.2% and 61.9% had grade 3/4 adverse events (AEs); 4.5% and 2.4% had grade 5 AEs. In MORPHEUS-GC, confirmed ORRs with atezolizumab plus PEGPH20 ($n = 13$) were 0% (95% CI, 0%-24.7%) vs. 16.7% (95% CI, 2.1%-48.4%) with control ($n = 12$). Grade 3/4 AEs occurred in 30.8% and 75.0% of patients, respectively; no grade 5 AEs occurred.

Conclusion: Atezolizumab plus PEGPH20 showed limited clinical activity in patients with PDAC and none in patients with GC. The safety of atezolizumab plus PEGPH20 was consistent with each agent's known safety profile. (ClinicalTrials.gov Identifier: NCT03193190 and NCT03281369).

Key words: pancreatic cancer; gastric cancer; basket study; proof of concept; PD-L1; combination therapy; hyaluronan; immunotherapy.

Received: 30 November 2022; Accepted: 18 January 2023.

Lessons Learned

- Combining atezolizumab with PEGPH20 did not improve clinical outcomes vs. standard-of-care chemotherapy combination regimens in patients with previously treated advanced PDAC or GC.
- The safety of atezolizumab plus PEGPH20 was consistent with each agent's known safety profile, and no new safety signals were detected.

Discussion

The outcomes for patients with advanced PDAC or GC remain limited with current standard-of-care combination chemotherapy regimens, and more effective treatments are urgently needed. The MORPHEUS platform of studies is designed to detect proof-of-concept clinical data in small cohorts to accelerate the development of treatment combinations across a range of cancer indications. The PD-L1 inhibitor atezolizumab reduces immunosuppressive signals in the tumor microenvironment (TME) and increases T-cell-mediated immunity against tumors.[1] The engineered enzyme PEGPH20 breaks down the extracellular matrix (ECM) component hyaluronic acid (HA), which is abnormally dense in solid tumors, reducing anticancer drug penetration.[2] The rationale for combining PEGPH20 with atezolizumab was to reduce overexpressed HA in the tumor ECM and remodel the TME so that both atezolizumab and immune cells could penetrate the tumor more effectively and activate local tumor responses.

In MORPHEUS-PDAC and MORPHEUS-GC, patients were randomized to one of several experimental treatment arms (in this case, atezolizumab 1200 mg intravenously [IV] every 3 weeks plus PEGPH20 3 μg/kg IV on days 1, 8, and 15 of each 21-day cycle) or a standard-of-care control arm (Fig. 1). In both studies, the primary endpoint was ORR and secondary endpoints were overall survival (OS), progression-free survival (PFS), disease control rate (DCR), duration of response (DOR), and safety. In addition, exploratory biomarker analyses were conducted in MORPHEUS-PDAC to determine whether there was any relationship between clinical response or OS and baseline tumor PD-L1 expression or HA status.

Both studies showed that atezolizumab in combination with PEGPH20 was tolerable. The primary endpoint of ORR was not significantly improved with atezolizumab plus PEGPH20 vs control in either study. Given the small patient numbers, it was difficult to draw any meaningful conclusions from the biomarker analyses. These and other negative findings from HALO-301, a phase III study of PEGPH20 plus chemotherapy in patients with metastatic HA-high PDAC,[3] suggest that simply reducing HA and remodeling the stroma are not sufficient to improve clinical outcomes, and that a better understanding of the mechanisms and interactions within the TME is needed to target them more effectively. Nevertheless, although atezolizumab plus PEGPH20 did not meet the primary endpoint by demonstrating improved ORR in the MORPHEUS-PDAC or MORPHEUS-GC studies, their signal-seeking design enabled this to be determined more quickly than in typical oncology efficacy trials, in a randomized setting, and with fewer patients allocated to control treatment. On the basis of these findings, this combination is not being further investigated as a treatment option for PDAC or GC, but the MORPHEUS-PDAC and MORPHEUS-GC studies are actively ongoing to evaluate additional novel atezolizumab-based combination strategies.

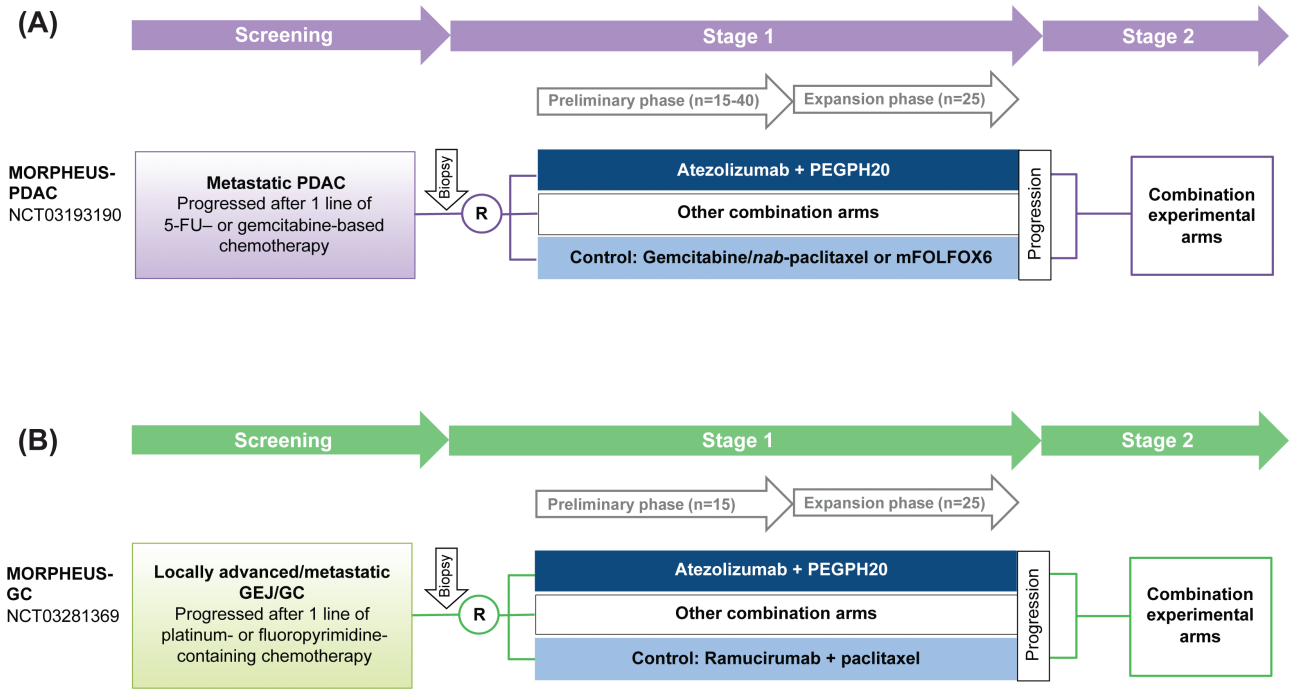

Figure 1. Study design of (A) MORPHEUS-PDAC and (B) MORPHEUS-GC. FU, fluorouracil; GC, gastric cancer; GEJ, gastroesophageal junction; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PEGPH20, PEGylated recombinant human hyaluronidase; R, randomization.

Trial Information		
Disease	MORPHEUS-PDAC Pancreatic ductal adenocarcinoma (PDAC)	MORPHEUS-GC Gastric cancer (GC) or gastroesophageal junction cancer
Stage of disease/treatment	Metastatic	Metastatic
Prior therapy	One regimen of 5-fluorouracil (5-FU)- or gemcitabine-based chemotherapy	One regimen of platinum- or fluoropyrimidine-containing chemotherapy
Type of study	Phase Ib/II, global, open label, randomized, umbrella	
Primary endpoint	Investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1	
Secondary endpoints	Progression-free survival (PFS) by investigator, disease control rate (DCR), and duration of response (DOR); overall survival (OS); and safety	
Investigator's analysis	Inactive because results did not meet primary endpoint	

Additional Details of Endpoints and Study Design (Methods)

Study Design and Patients

In MORPHEUS-PDAC and MORPHEUS-GC, patients were randomized to a control arm or 1 of several experimental arms, 1 of which involved treatment with atezolizumab plus PEGylated recombinant human hyaluronidase (PEGPH20) (Fig. 1). In stage 1, if clinical activity was observed in the preliminary phase after enrolling 15-40 patients, additional patients could be enrolled in the expansion phase. If a patient experienced progressive disease (PD), unacceptable toxicity, or loss of clinical benefit in stage 1, they could enroll in stage 2 to receive a different treatment combination, provided that they still met the eligibility criteria. The randomization ratio depended on the number of experimental arms that were open, with the stipulation that no more than 35% of patients were to be randomized to the control arms at a given time.

MORPHEUS-PDAC enrolled patients with a confirmed diagnosis of metastatic pancreatic ductal adenocarcinoma (PDAC) and PD ≤6 months after treatment with 1 line of 5-fluorouracil (5-FU)- or gemcitabine-based chemotherapy (Fig. 1A). MORPHEUS-GC enrolled patients with a confirmed diagnosis of locally advanced unresectable or metastatic gastric cancer (GC) or gastroesophageal junction cancer that had progressed during or following a first-line platinum- or fluoropyrimidine-containing chemotherapy regimen (Fig. 1B). Additional key inclusion criteria for both studies included providing an entry biopsy before randomization to treatment, age ≥18 years, an Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease by RECIST 1.1. Key exclusion criteria in both studies 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, organizing pneumonia, drug-induced pneumonitis or idiopathic pneumonitis, or evidence of active pneumonitis.

Procedures and Assessments

Treatment continued until patients experienced unacceptable toxicity and/or loss of clinical benefit as determined by the investigator or PD per RECIST 1.1.

All patients had a pretreatment biopsy for biomarker analysis. Patients underwent tumor assessments at baseline, then in MORPHEUS-PDAC, every 6 weeks for the first 48 weeks, and every 12 weeks thereafter, and in MORPHEUS-GC, every 8 weeks for the first 12 months, and every 12 weeks thereafter, regardless of dose delays, until radiographic PD per RECIST 1.1. Patients who continued treatment after radiographic PD underwent tumor assessments every 6 or 8 weeks until loss of clinical benefit as determined by the investigator.

To characterize the pharmacokinetic properties and immunogenicity of atezolizumab and PEGPH20, blood samples were collected at various time points before and during study treatment administration. Positivity for antidrug antibodies (ADAs) to atezolizumab and PEGPH20 was determined according to standard methods established for previous studies.[4]

Programmed cell death 1 ligand 1 (PD-L1) status was assessed by immunohistochemistry using the VENTANA SP263 immunohistochemistry assay. Tumor samples were scored for percentage tumor cell (TC) positivity for PD-L1 expression with the number of tumor cells as the denominator, and percentage immune cell (IC) positivity using tumor area as the denominator. The measures were combined in an IC and/or TC basis for the application of cutoffs. Hyaluronic acid (HA) status was evaluated using the VENTANA HA assay, with positivity defined as a percentage of tumor area. PDAC HA-high status was defined as HA ≥50%, as defined by Halozyme based on data from the HALO-109-202 trial.[5] Microsatellite instability (MSI) status was assessed in responders enrolled in the atezolizumab plus PEGPH20 arm using the MSI PCR testing kit (Promega).

Study Endpoints

The primary endpoint of investigator-assessed objective response rate (ORR) per RECIST 1.1 was defined as the proportion of patients with a complete response (CR) or partial response (PR) on 2 consecutive occasions >4 weeks apart.

Secondary endpoints included investigator-assessed progression-free survival (PFS, defined as the time from randomization to the date of the first recorded occurrence of PD or death from any cause), disease control rate (DCR, defined as stable disease for ≥12 weeks or a CR or PR), and duration of response (DOR, defined as the time from the first occurrence of a documented objective response to PD or death from any cause, whichever occurred first), all per RECIST 1.1; overall survival (OS, defined as the time from randomization to death from any cause); the incidence of participants with adverse events (AEs) with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0; pharmacokinetics; and the percentage of patients with ADAs to atezolizumab.

Exploratory biomarker analyses were conducted in MORPHEUS-PDAC to evaluate the relationship between outcomes (clinical response, PFS, OS) and pretreatment PD-L1 and HA status. Exploratory biomarker analyses were not conducted for MORPHEUS-GC due to the lack of responders among the patients enrolled in the experimental arm.

Statistical Analyses

MORPHEUS studies are not designed to make explicit power and type 1 error considerations for a hypothesis test, but rather to obtain preliminary efficacy, safety, and pharmacokinetic data on immunotherapy-based treatment combinations. Interim analyses were planned for when the treatment arm had completed enrollment in the preliminary phase. At the time of the interim analyses, a Bayesian posterior probability was used to guide the go/no-go decision for expansion. While no formal hypothesis testing was conducted, a sample size of approximately 15-40 patients in the treatment and control arms was considered sufficient to calculate a clinically meaningful posterior probability of ORR to guide the expansion decision.

Retrospective analysis of HA levels in baseline PDAC tumor biopsies showed that patients with high HA accumulation had lower median survival rates,[6] suggesting that HA levels might be predictive of survival. Therefore, in MORPHEUS-PDAC, approximately 40 patients were planned to be enrolled into the atezolizumab plus PEGPH20 arm in the preliminary phase of stage 1 to ensure a sufficient number of patients for stratification by HA expression when evaluating treatment benefit and risk. Additional patient enrollment in the expansion phase was gated on a clinically meaningful improvement in ORR in the atezolizumab plus PEGPH20 arm relative to the control. As early clinical activity was observed in the preliminary enrollment phase, expansion enrollment was ungated for a total enrollment of approximately 65 patients in the atezolizumab plus PEGPH20 arm.

In MORPHEUS-GC, approximately 15 patients were planned to be enrolled in the atezolizumab plus PEGPH20 arm for the preliminary phase of stage 1, with an additional 25 patients to be enrolled in the expansion if clinical activity was observed in the experimental arm.

In both studies, the ORR was calculated for each arm, along with 95% CIs using the Clopper-Pearson method. Patients with missing or no response assessments were classified as non-responders. DOR was derived for efficacy-evaluable patients who had a confirmed CR or PR. Median DOR, PFS, and OS were estimated using the Kaplan-Meier method, with 95% CIs constructed using the Brookmeyer and Crowley method. For patients who did not have documented PD or death, PFS and DOR were censored at the day of the last tumor assessment. Patients who were still alive at the time of OS analysis were censored at the last date they were known to be alive.

Enrollment and Clinical Cutoff Information

MORPHEUS-PDAC: 117 patients were enrolled at 16 sites and randomized to receive atezolizumab plus PEGPH20 (n = 71) or chemotherapy control treatment (n = 46). A total of 108 patients (66 in the atezolizumab plus PEGPH20 arm and 42 in the control arm) received ≥1 dose of any component of study treatment and were evaluable for efficacy. The atezolizumab plus PEGPH20 arm was closed after full enrollment in the expansion phase was completed. Four patients from the atezolizumab plus PEGPH20 arm and 15 patients from the control arm of stage 1 entered stage 2. MORPHEUS-PDAC data presented here are from stage 1 at the clinical cutoff date (CCOD) of June 25, 2021, except for study discontinuation, survival follow-up, and OS, which included data from stage 2. See also Table 1 (Patient disposition in MORPHEUS-PDAC at clinical cutoff date).

MORPHEUS-GC: 31 patients were enrolled at 12 sites and randomized to receive atezolizumab plus PEGPH20 (n = 15, with 13 treated) or control treatment (n = 16, with 12 treated). Due to the lack of clinical response observed at the per-protocol interim analysis, the atezolizumab plus PEGPH20 arm did not enroll patients in the expansion phase. MORPHEUS-GC data presented here are from stage 1 at the CCOD of November 26, 2020.

Drug Information—MORPHEUS-PDAC	**Arm 1: Atezolizumab and PEGPH20 combination**	
Generic/working name	Atezolizumab	PEGylated recombinant human hyaluronidase (PEGPH20)
Drug type	Monoclonal antibody	Engineered enzyme
Drug class	Immune therapy (PD-L1 inhibitor)	Hyaluronidase
Dose	1200 mg	3 μg/kg
Route	IV	IV
Schedule of administration	Every 3 weeks	Days 1, 8, and 15 of each 21-day cycle

Drug Information—MORPHEUS-PDAC	**Arm 2: Chemotherapy control (*nab*-paclitaxel plus gemcitabine or mFOLFOX6)**	
Generic name	*nab*-Paclitaxel	Gemcitabine
Drug type	Chemotherapy	Chemotherapy
Drug class	Antimicrotubule agent	Nucleoside metabolic inhibitor
Dose	125 mg/m^2	1000 mg/m^2
Route	IV	IV
Schedule of administration	Days 1, 8, and 15 of each 28-day cycle	Days 1, 8, and 15 of each 28-day cycle

Drug Information—MORPHEUS-PDAC	**Arm 2: Chemotherapy control (*nab*-paclitaxel plus gemcitabine or mFOLFOX6)**			
Generic name	Oxaliplatin	Leucovorin	5-Fluorouracil (5-FU)	
Drug type	Chemotherapy	Chemotherapy	Chemotherapy	
Drug class	Platinum-based antineoplastic	Folic acid analog	Antimetabolite	
Dose	85 mg/m^2	400 mg/m^2	400 mg/m^2	2400 mg/m^2
Route	IV	IV	IV	IV
Schedule of administration	Days 1 and 15 of each 28-day cycle	Days 1 and 15 of each 28-day cycle	Days 1 and 15 of each 28-day cycle	Days 1, 2, 15, and 16 of each 28-day cycle

Drug Information—MORPHEUS-GC	**Arm 1: Atezolizumab and PEGPH20 combination**	
Generic/working name	Atezolizumab	PEGylated recombinant human hyaluronidase (PEGPH20)
Drug type	Monoclonal antibody	Engineered enzyme
Drug class	Immune therapy (PD-L1 inhibitor)	Hyaluronidase
Dose	1200 mg	3 μg/kg
Route	IV	IV
Schedule of administration	Every 3 weeks	Days 1, 8, and 15 of each 21-day cycle

Drug Information—MORPHEUS-GC	**Arm 2: Control (ramucirumab plus paclitaxel)**	
Generic name	Ramucirumab	Paclitaxel
Drug type	Monoclonal antibody	Chemotherapy
Drug class	Antineoplastic agent and vascular endothelial growth factor receptor 2 (VEGFR2) inhibitor	Antimicrotubule agent
Dose	8 mg/kg	80 mg/m^2
Route	IV	IV
Schedule of administration	Days 1 and 15 of each 28-day cycle	Days 1, 8, and 15 of each 28-day cycle

Patient Characteristics—MORPHEUS-PDAC	**Arm 1**	**Arm 2**
Number of patients, male	43	23
Number of patients, female	28	23
Stage	Stage 4	Stage 4
Age, median (range)	60 (36-82)	62 (39-78)
Number of prior systemic therapies, median (range)	1	1
Performance status, ECOG	0: 26	0: 19
	1: 44	1: 27
	2: 0	2: 0
	3: 1	3: 0
	4: 0	4: 0

Note: Table 2 shows detailed baseline patient demographic and clinical characteristics in both studies.

Patient Characteristics—MORPHEUS-GC	**Arm 1**	**Arm 2**
Number of patients, male	12	12
Number of patients, female	3	4
Stage	Metastatic	Metastatic
Age, median (range)	58 (45-72)	62 (39-80)
Number of prior systemic therapies, median (range)	1	1
Performance status, ECOG	0: 4	0: 4
	1: 11	1: 11
	2: 0	2: 0
	3: 0	3: 0
	4: 0	4:0

Primary Assessment Method—MORPHEUS-PDAC	
Title	**Clinical response in MORPHEUS-PDAC**
Number of patients randomized	117
Number of patients evaluable for toxicity	108
Number of patients evaluated for efficacy	108
Evaluation method	RECIST 1.1
Response assessment, arm 1	ORR: 4 (6.1%); 95% CI: 1.7-14.8 CR: 0 (0%); 95% CI: 0.0-5.4 PR: 4 (6.1%); 95% CI: 1.7-14.8 SD: 18 (27.3%); 95% CI: 17.0-39.6) PD: 35 (53%); 40.3-65.4 Not evaluated: 2 (3%) Missing: 7 (10.6%) DCR: 12 (18.2%); 95% CI: 9.8-29.6
Response assessment, arm 2	ORR: 1 (2.4%); 95% CI: 0.1-12.6 CR: 0 (0%); 95% CI: 0.0-8.4 PR: 1 (2.4%); 95% CI: 0.1-12.6 SD: 16 (38.1%); 95% CI: 23.6-54.4 PD: 16 (38.1%); 95% CI: 23.6-54.4 Not evaluated: 2 (4.8%) Missing: 7 (16.7%) DCR: 12 (28.6%); 95% CI: 15.7-44.6
Median duration assessments, arm 1	PFS: 1.5 months (95% CI: 1.4-2.6) OS: 7.1 months (95% CI: 4.1-8.4) Response duration: 8.2 months (5.3-not estimable) Duration of treatment: 23 days (atezolimuab); 36 days (PEGPH20)
Median duration assessments, arm 2	PFS: 2.3 months (1.6-4.1) OS: 6.8 months (6.3-8.3) Response duration: 3.9 months (not estimable) Duration of treatment: 29 days (5-FU bolus, leucovorin, and oxaliplatin); 31 days (5-FU IV); 71 days (gemcitabine); 49 days (nab-paclitaxel)
Abbreviations	CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; recombinant human hyaluronidase; PFS, progression-free survival.
Outcome notes	See also Fig. 2A (Waterfall plots of best percentage change from baseline in tumor size), Fig. 3A (Swimlane plots of best overall responses), Fig. 4A (Kaplan-Meier plot of progression-free survival), Fig. 5A (Kaplan-Meier plot of overall survival), and Table 3 (Summary of efficacy in MORPHEUS-PDAC and MORPHEUS-GC). No patients in either arm of MORPHEUS-PDAC achieved a CR. Among the patients who demonstrated confirmed responses, 1 of the 4 responders in arm 1 (atezolizumab plus PEGPH20) had MSI-high disease; the remaining 3 had microsatellite stable disease. Another patient had an unconfirmed PR, and 1 patient demonstrated pseudoprogression with PD at the week 6 tumor assessment, SD at the week 12 tumor assessment, and PR at the target lesions from the week 18 through week 48 tumor assessments (Fig. 3A).

Secondary Assessment Method—MORPHEUS-PDAC	
Title	**Biomarker analysis in arm 1 of MORPHEUS-PDAC (atezolizumab plus PEGPH20)**
Number of patients evaluated for efficacy (biomarker-evaluable population [BEP])	53
Evaluation method	Tumor marker
Response assessment, ORR in arm 1	PD-L1 BEP: 4 of 53 (7.3%) PD-L1 IC/TC ≥1%: 4 of 41 (9.8%) PD-L1 IC/TC ≥5%: 3 of 15 (20%) HA BEP: 3 of 53 (5.7%) HA ≥50%: 1 of 29 (3.4%)
Abbreviations	BEP, biomarker-evaluable population; HA, hyaluronic acid; IC, immune cell; ITT, intention to treat; ORR, objective response rate; PD-L1, programmed cell death 1 ligand 1; PEGPH20, PEGylated recombinant human hyaluronidase; TC, tumor cell.

Secondary Assessment Method—MORPHEUS-PDAC	
Title	**Biomarker analysis in arm 1 of MORPHEUS-PDAC (atezolizumab plus PEGPH20)**
Outcome notes	To determine whether clinical activity was related to baseline PD-L1 expression or HA status in MORPHEUS-PDAC, best overall response and OS (Fig. 6 [OS by biomarker status in MORPHEUS-PDAC]) were evaluated by PD-L1 and HA status. Clinical responses were numerically enriched in the PD-L1–expressing population, with 4 of 41 (9.8%) in the PD-L1 IC/TC ≥1% subgroup and 3 of 15 (20%) in the PD-L1 IC/TC ≥5% subgroup having a clinical response to atezolizumab plus PEGPH20, compared with 4 of 66 (6.1%) in the efficacy-evaluable population and 4 of 53 (7.3%) in the PD-L1–evaluable population (Table 4 [ORR in MORPHEUS-PDAC biomarker subgroups]). These observations did not extend to time-to-event subgroup analyses; although a numerical improvement suggested OS benefit in the PD-L1 ≥1% patients, the CIs were wide (hazard ratio [HR], 0.57; 95% CI, 0.32-1.01) (Fig. 6 [OS by biomarker status in MORPHEUS-PDAC]). However, the OS HR decreased at the PD-L1 ≥5% cutoff (HR, 0.76; 95% CI, 0.34-1.69), with the PD-L1 <5% subgroup performing better (HR, 0.46; 95% CI, 0.23-0.89). Additionally, this analysis was confounded by the observation in favor of the control arm in patients not assessed for PD-L1. Analysis of PFS by PD-L1 and HA status did not show benefit in any subgroup (data not shown).

Primary Assessment Method—MORPHEUS-GC	
Title	**Clinical response in MORPHEUS-GC**
Number of patients randomized	31
Number of patients evaluable for toxicity	25
Number of patients evaluated for efficacy	25
Evaluation method	RECIST 1.1
Response assessment, arm 1	ORR: 0 (0%); 95% CI: 0.0-24.7 CR: 0 (0%); 95% CI: 0.0-24.7 PR: 0 (0%); 95% CI: 0.0-24.7 SD: 2 (15.4%); 95% CI: 1.9-45.5 PD: 10 (76.9%); 95% CI: 46.2-95.0 Missing: 1 (7.7%) DCR: 0 (0%); 95% CI: 0.0-24.7
Response assessment, arm 2	ORR: 2 (16.7%); 95% CI: 2.1-48.4 CR: 0 (0%); 95% CI: 0.0-26.5 PR: 2 (16.7%); 95% CI: 2.1-48.4 SD: 8 (66.7%); 95% CI: 34.9-90.1 PD: 2 (16.7%); 95% CI: 2.1-48.4 DCR: 8 (66.7%); 95% CI: 34.9-90.1
Median duration assessments, arm 1	PFS: 1.8 months (95% CI: 1.5-2.1) OS: 7 months (95% CI: 5.3-8.9) Response duration: not evaluable Duration of treatment: 43 days (atezolizumab); 48 days (PEGPH20)
Median duration assessments, arm 2	PFS: 6.1 months (95% CI: 3.7-8.8) OS: 8.3 months (95% CI: 6.4-11.0) Response duration: 3.3 months (2.9-3.8) Duration of treatment: 145 days (ramucirumab); 149 days (paclitaxel)
Abbreviations	CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; OS, overall survival; PEGPH20, PEGylated recombinant human hyaluronidase; PFS, progression-free survival.
Outcome notes	In MORPHEUS-GC, none of the patients in arm 1 (atezolizumab plus PEGPH20) had a treatment response; hence, the ORR was 0%. In arm 2 (control), 2 patients had a PR, and the ORR was 16.7%. See Fig. 2B (Waterfall plots of best percentage change from baseline in tumor size), Fig. 3B (Swimlane plots of confirmed best overall responses), Fig. 4B (Kaplan-Meier plot of progression-free survival), Fig. 5B (Kaplan-Meier plot of overall survival), and Table 3 (Summary of efficacy).

Pharmacokinetics and Pharmacodynamics: Outcome Notes

In MORPHEUS-PDAC, the atezolizumab mean maximal serum concentration (C_{max}) was 367 μg/mL 30 minutes post dose on cycle 1 day 1; mean atezolizumab concentrations at cycle 2 day 1 predose (day 21) and cycle 4 day 1 predose (day 63) were 69.8 and 138 μg/mL, respectively (Table 5 [Pharmacokinetics of atezolizumab and PEGPH20 in MORPHEUS-PDAC]). The PEGPH20 mean C_{max} was 68.8 ng/mL 5 minutes post dose on cycle 1 day 1 and 69.5 ng/mL 5 minutes post dose on cycle 2 day 1. The mean concentration of PEGPH20 after 1-3 h post dose was 61.0

ng/mL on cycle 1 day 1. Mean PEGPH20 predose concentrations were 5.66 ng/mL on cycle 2 day 1 and 7.52 ng/mL on cycle 4 day 1. The interindividual variability for atezolizumab exposure (cycle 1 C_{max} and cycle 2 predose/cycle 1 minimum concentration) was 30.9% and 31.3%. The interindividual variability for PEGPH20 exposure (cycle 1 C_{max}) was 26.1%.

In MORPHEUS-GC, the atezolizumab mean C_{max} was 384 µg/mL 30 minutes post dose on cycle 1 day 1 (Table 6 [Pharmacokinetics of atezolizumab and PEGPH20 in MORPHEUS-GC]). Mean atezolizumab concentrations at cycle 2 day 1 predose and cycle 3 day 1 predose were 66.5 and 101 µg/mL, respectively. The PEGPH20 mean C_{max} was 59.7 ng/mL 5 minutes post dose on cycle 1 day 1, with a mean PEGPH20 concentration of 46.9 ng/mL 1 to 3 h post dose on cycle 1 day 1. The mean 5-minute post-dose concentration of PEGPH20 was 60.1 ng/mL on cycle 2 day 1, and 5.63 ng/mL for cycle 3 day 1 predose. The interindividual variability for atezolizumab exposure (cycle 1 C_{max} and cycle 2 predose/cycle 1 minimum concentration) was 33.9% and 24.0%. The interindividual variability for PEGPH20 exposure (cycle 1 C_{max}) was 49.9%.

Treatment-emergent atezolizumab ADAs were seen in 17 of 57 patients (29.8%) and 3 of 10 patients (30%) in the atezolizumab arms of MORPHEUS-PDAC and MORPHEUS-GC, respectively. No treatment-emergent PEGPH20 ADAs were observed in either study.

Safety Notes

See Table 7 (Safety summary in MORPHEUS-PDAC and MORPHEUS-GC); Table 8 (Treatment-related adverse events [TRAEs] reported by ≥10% of patients in either arm in MORPHEUS-PDAC); Table 9 (AESIs reported by ≥5% of patients in either arm in MORPHEUS-PDAC); Table 10 (TRAEs reported by ≥10% of patients in either arm in MORPHEUS-GC); and Table 11 (AESIs reported by ≥10% of patients [ie, >1 patient] in either arm in MORPHEUS-GC).

In MORPHEUS-PDAC, 3 patients (4.5%) in the atezolizumab plus PEGPH20 arm had grade 5 AEs (cardiorespiratory arrest, myositis, and death [cause unknown]), as did 1 patient (2.4%) in the control arm (disseminated intravascular coagulation). The most common serious adverse events (SAEs) with atezolizumab plus PEGPH20 were pyrexia (3 patients [4.5%]) and abdominal pain, intestinal obstruction, small intestinal obstruction, fatigue, bacteremia, and embolism (2 patients [3.0%] each). The most common SAEs in the control arm were pyrexia (5 patients [11.9%]) and gastrointestinal hemorrhage and duodenal obstruction (2 patients [4.8%] each).

In MORPHEUS-GC, no deaths occurred in either arm. SAEs occurred in 1 patient (7.7%) in the atezolizumab plus PEGPH20 arm (dysphagia) and 6 patients (50%) in the control arm (device-related infection, liver abscess, recurrent pyogenic cholangitis, fatigue, hypercalcemia, and meningeal metastases).

Assessment, Analysis, and Discussion	
Completion	Atezolizumab plus PEGPH20 experimental arms closed, but studies are ongoing to evaluate other atezolizumab combinations.
Investigator's assessment	Inactive because results did not meet primary endpoint. Level of activity did not meet planned endpoint

Despite the critical need for more effective treatment options for metastatic PDAC, little improvement in OS has been achieved since chemotherapy was first approved for this indication more than 20 years ago.[7,8] With the exception of approved therapies for patients with rare mutations, and the programmed cell death 1 protein inhibitor pembrolizumab for patients with MSI-high or mismatched repair-deficient (dMMR) unresectable or metastatic tumors, combination chemotherapy regimens remain the standard of care for patients with metastatic PDAC.[9] Likewise, the current treatment landscape for advanced GC may be defined by biomarkers such as MSI or MMR, and PD-L1 or human epidermal growth factor receptor-2,[10] but otherwise combination chemotherapy regimens remain the treatment of choice, with a focus on palliative treatment and extending survival for patients with locally advanced or metastatic GC. Hence, new and effective treatment options are urgently needed for PDAC and GC.

The MORPHEUS umbrella study platform was designed to evaluate novel immunotherapy combinations for different cancers using a design whereby multiple experimental treatment arms could be compared with a single control arm, thereby reducing the number of patients receiving control treatment. The efficacy and safety of atezolizumab combined with PEGPH20 were evaluated as second-line treatment in 2 randomized studies: MORPHEUS-PDAC and MORPHEUS-GC. The data presented here are some of the earliest to emerge from the MORPHEUS platform. Although atezolizumab plus PEGPH20 did not meet the primary endpoint by demonstrating improved ORR vs. the chemotherapy combination regimen in either study, their signal-seeking design enabled this to be determined more quickly than in conventional oncology efficacy trials, and with fewer patients allocated to receive standard-of-care treatment. Additionally, the MORPHEUS platform allowed for this treatment combination to be evaluated in a randomized setting.

The secondary efficacy endpoints were also not met in either study. Hence, the atezolizumab plus PEGPH20 arms were closed after full enrollment in the expansion phase of stage 1 in MORPHEUS-PDAC and at the end of the preliminary phase of stage 1 in MORPHEUS-GC.

Nevertheless, the ORR of 6.1% observed with atezolizumab plus PEGPH20 in MORPHEUS-PDAC was numerically greater than that in the control arm (2.4%). Although observed in a small number of patients, the PRs to atezolizumab plus PEGPH20 in MORPHEUS-PDAC were notably durable for a chemotherapy-free treatment regimen, with a median DOR of 8.2 months (range, 5.3-32.8 months), compared with 3.9 months in 1 patient who had a PR in the chemotherapy control arm. However, the median PFS was not improved vs. control with atezolizumab plus PEGPH20 in patients with PDAC, and the median OS was similar to that observed with chemotherapy, with the data for both endpoints being mature. The biomarker studies in MORPHEUS-PDAC showed a numerical trend toward increased OS and improved HR for OS with atezolizumab plus PEGPH20 vs. control in HA-positive patients. The number of responders was enriched

in PD-L1–positive subgroups, but no consistent relationship between PD-L1 status and survival was seen. Notably, given the small patient numbers and overlapping CIs between treatment arms, it is difficult to draw any meaningful conclusions from the biomarker studies in MORPHEUS-PDAC.

In MORPHEUS-GC, the atezolizumab combination showed no clinical activity and the median PFS in the atezolizumab plus PEGPH20 arm was shorter than in the control arm; the median OS was similar in both arms. Due to the absence of CR or PR in MORPHEUS-GC, no association between clinical activity and HA or PD-L1 status could be determined in patients with GC.

Our findings that atezolizumab plus PEGPH20 increased ORR numerically vs. chemotherapy in MORPHEUS-PDAC, but did not improve OS or PFS, were similar to findings from HALO-301, a phase III study of PEGPH20 plus chemotherapy vs. chemotherapy in almost 500 patients with untreated, metastatic, HA-high PDAC.[3] Differences between HALO-301 and MORPHEUS-PDAC include disease setting (first vs. second line, respectively), HA-high biomarker-selected patients in HALO-301 vs. an all-comer population in MORPHEUS-PDAC, and dosing regimens (PEGPH20 administered twice per week vs. once per week, and in combination with chemotherapy vs immunotherapy in HALO-301 and MORPHEUS-PDAC, respectively). These findings indicate that simply reducing HA to aid remodeling the stroma are not sufficient to improve outcomes, and that a better understanding of the mechanisms and interactions within the TME is needed to target them more effectively.

Overall, both MORPHEUS studies showed that atezolizumab in combination with PEGPH20 was tolerable, and the safety profile of the combination treatment regimen was consistent with the known risks of each individual study treatment component. No new safety concerns were identified. Pharmacokinetics and ADA were characterized as appropriate based on study protocol specifications, and the pharmacokinetic and pharmacodynamic findings were comparable between indications and in line with the clinical experience to date.

A study limitation was that the small sample sizes and limited number of responders in these signal-seeking studies hampered the detection of relationships between biomarker status and response. However, the strengths of the MORPHEUS platform were that the primary endpoint could be evaluated in a randomized fashion in a relatively small number of patients, and the outcomes could be determined in a more timely fashion than in large phase II or III clinical studies.

In conclusion, the treatment combination of atezolizumab and PEGPH20 did not demonstrate clinical activity when given as second-line treatment to patients with advanced PDAC or GC that had progressed during or following chemotherapy. Although, on the basis of these findings, this treatment combination is not being further investigated as treatment for PDAC or GC, MORPHEUS studies in both PDAC and GC are actively ongoing to evaluate other novel atezolizumab-based combination strategies.

Acknowledgments

Assistance with preparation of the manuscript was provided by Samantha Santangelo, PhD, of Health Interactions, Inc., funded by F. Hoffmann-La Roche.

Funding

This study was sponsored by F. Hoffmann-La Roche. The study sponsor was involved in the study design; data collection, analysis, and interpretation; and writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit the results for publication.

Conflict of Interest

All authors received support from F. Hoffmann-La Roche/Genentech during the conduct of this study. **Andrew H. Ko**: Roche/Genentech (consulting/advisory relationship and research funding). **Jens T. Siveke**: AstraZeneca, Bayer, Immunocore, Roche/Genentech, Servier (honoraria), Bristol Myers Squibb, Celgene, Roche/Genentech, Pharma15 (Board of Directors, consulting/advisory relationship), Bristol Myers Squibb, Celgene, Roche/Genentech (research funding), and Pharma15 (intellectual property rights/inventor/patent holder). **Charles D. Lopez**: Servier Pharmaceuticals, Taiho Pharmaceuticals, Genentech/Roche (research funding). **Jill Lacy**: Ipsen, Novartis, Deciphera, Merck, Equinox, Techspert, Guidepoint, KeyQuest, FirstWorld Group, Aptitude Health, Brass Tacks Health (consulting/advisory relationship). **Eileen M. O'Reilly**: CytomX Therapeutics and Rafael Therapeutics (DSMB), Seagen, Boehringer Ingelheim, BioNTech, Ipsen, Merck, IDEAYA, Silenseed, Novartis, AstraZeneca, Noxxon, BioSapien, Cend Therapeutics, Thetis, Autem, ZielBio, Tempus (consulting/advisory relationship), Agios, Genentech-Roche, Eisai, Zymeworks (spouse: consulting/advisory relationship), Genentech/Roche, Celgene/BMS, BioNTech, AstraZeneca, Arcus, Elicio, Parker Institute (research funding). **Teresa Macarulla**: Ability Pharmaceuticals SL, Amgen, Aptitude Health, AstraZeneca, Basilea Pharma, Baxter, BioLineRX Ltd., Celgene, Eisai, Ellipses, Genzyme, Hirslanden/GITZ, Imedex, Incyte, Ipsen Bioscience, Inc., Janssen, Lilly, Marketing Farmacéutico & Investigación Clínica, S.L., MDS, Medscape, Novocure, Paraxel, PPD Development, Polaris, QED Therapeutics, Roche Farma, Sanofi-Aventis, Servier, Scilink Comunicación Científica SC, Surface Oncology, Zymeworks (consulting/advisory relationship), Abbvie Farmaceútica, Ability Pharmaceuticals, Agios Pharmaceuticals, AMC Medical Research, Amgen, Armo Biosciences, Aslan Pharmaceuticals, AstraZeneca, Basilea Pharmaceutica International, Bayer, BeiGene, BioKeralty Research Institute, BioLineRx, Blueprint Medicines, Boston Biomedical, Bristol Myers Squibb (BMS), Cantargia, Celgene, Eisai, Erytech Pharma, European Organisation for Research and Treatment of Cancer (EORTC), F. Hoffmann-La Roche, FibroGen, Halozyme, Incyte, Ipsen Bioscience, Ipsen Pharma, Lilly, Loxo Oncology, Medimmune, Merck Sharp & Dohme, Nelum, Novartis, Novocure, OncoMed Pharmaceuticals, QED Therapeutics, VCN Biosciences, Zymeworks (research funding), Servier, prIME, AstraZeneca, Sanofi, and Incyte (H). **Gulam A. Manji**: Roche/Genentech, CEND Pharmaceutical (consulting/advisory relationship), Roche/Genentech, Regeneron, BiolonRX, Merck (research funding), Amgen, Lilly, Roche (honoraria), CEND Pharmaceuticals (intellectual property rights/inventor/patent holder). **Jeeyun Lee**: OncXerna, Mirati, Guardant (consulting/advisory relationship), AstraZeneca, Merck MSD (research funding). **Jaffer Ajani**: BMS, Merck, Astellas, Amgen, Novartis, Zymeworks (honoraria), BMS, Roche, Merck, Prolinx, DF, Zymeworks,

Astellas, Taiho, Leap, Gilead, LaNova (research funding). **Maria Alsina Maqueda:** Amgen, BMS, Lilly, MSD, Roche, Servier (honoraria), BMS, Lilly, MSD, Servier (consulting/advisory relationship). **Sun-Young Rha:** MSD, BMS/Ono, Daiichi Sankyo, Amgen, Indivumed, LG Biochemical (consulting/advisory relationship), Lilly, Merck, BMS, MSD (expert testimony), Amgen, BMS/Ono, Daiichi Sankyo, AstraZeneca, Roche, Merck, Lilly, MSD, BeiGene, Zymeworks (research funding). **Janet Lau, Simon Allen, Danny Lu, Colby S. Shemesh, Xinxin Gan, Edward Cha, and Nedal Al-Sakaff:** F. Hoffmann-La Roche Ltd./Genentech Inc. (employment and intellectual property rights/inventor/patent holder). **Do-Youn Oh:** AstraZeneca, Novartis, Genentech/Roche, Merck Serono, Bayer, Taiho, ASLAN, Halozyme, Zymeworks, BMS/Celgene, BeiGene, Basilea, Turning Point, Yuhan, Arcus Biosciences, IQVIA (consulting/advisory relationship), AstraZeneca, Novartis, Array, Eli Lilly, Servier, BeiGene, MSD, Handok (research funding).

Data Availability

For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, refer to the following: https://go.roche.com/data_sharing.

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Figures and Tables

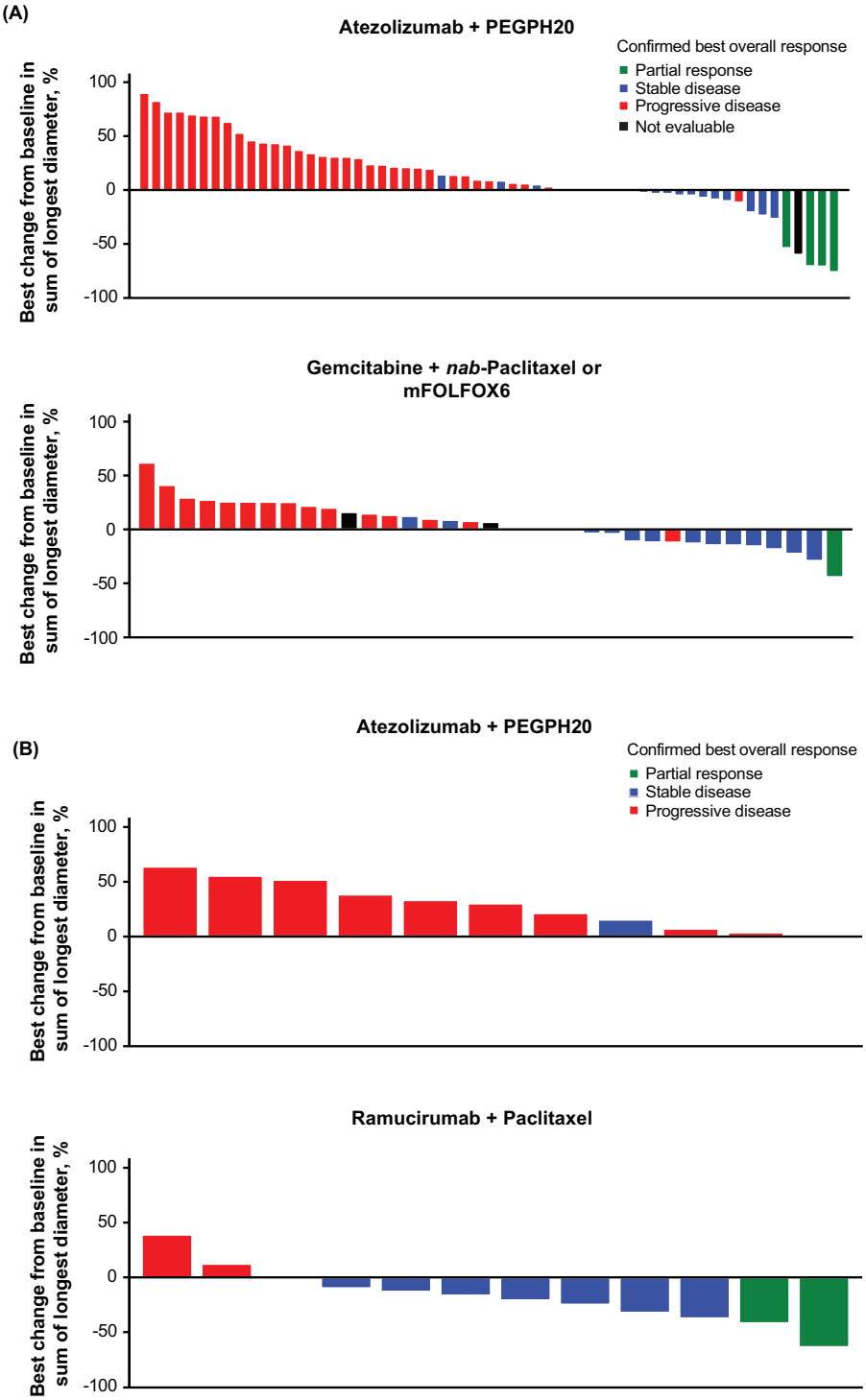

Figure 2. Waterfall plots of confirmed best overall response by treatment in (A) MORPHEUS-PDAC and (B) MORPHEUS-GC. mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; PEGPH20, PEGylated recombinant human hyaluronidase.

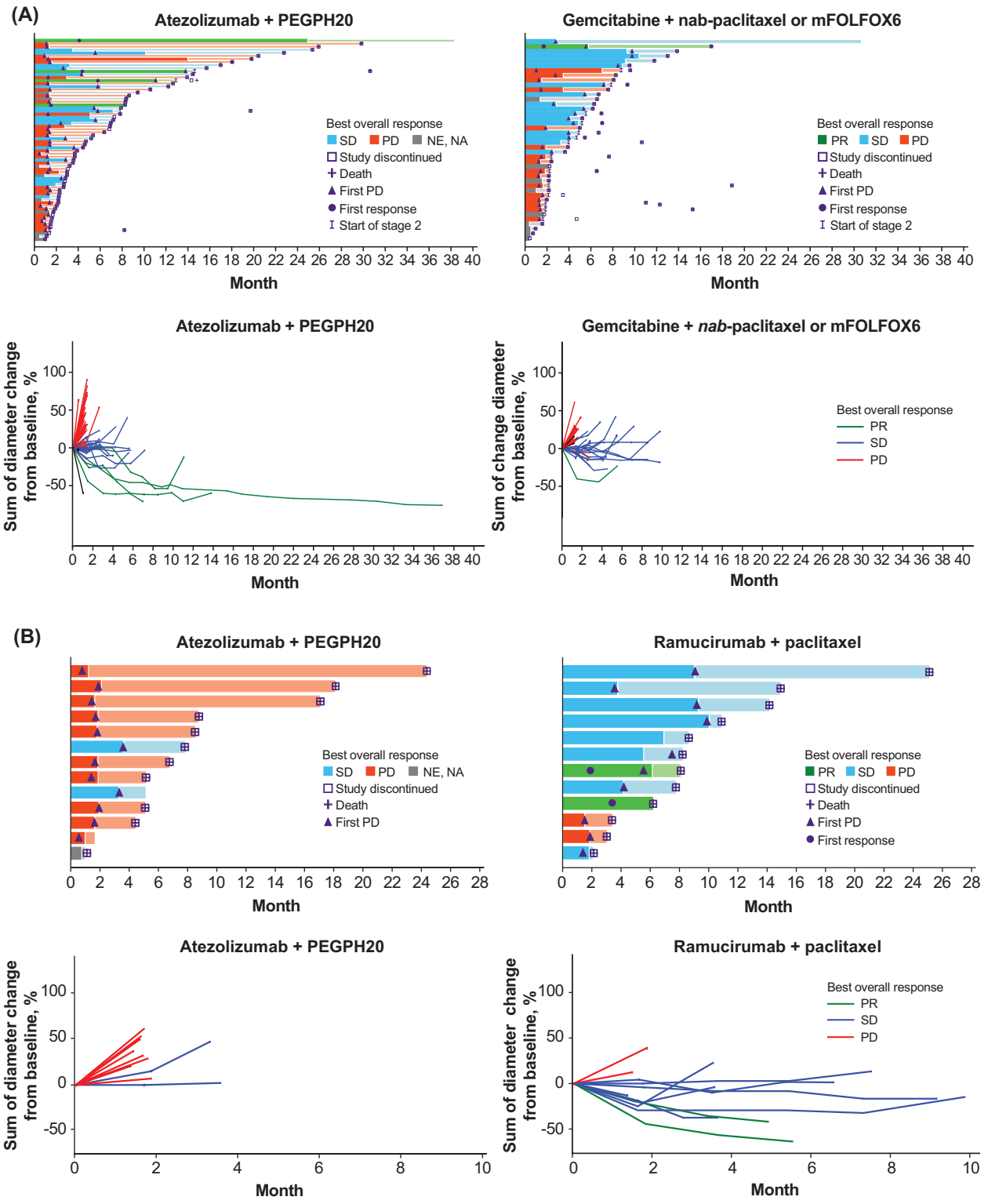

Figure 3. Swimlane plots of confirmed best overall responses in (A) MORPHEUS-PDAC and (B) MORPHEUS-GC. Darker colored bars, treatment period; lighter colored bars, follow-up. mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; NA, not assessed; NE, not evaluable, PD, progressive disease; PEGPH20, PEGylated recombinant human hyaluronidase; PR, partial response; SD, stable disease.

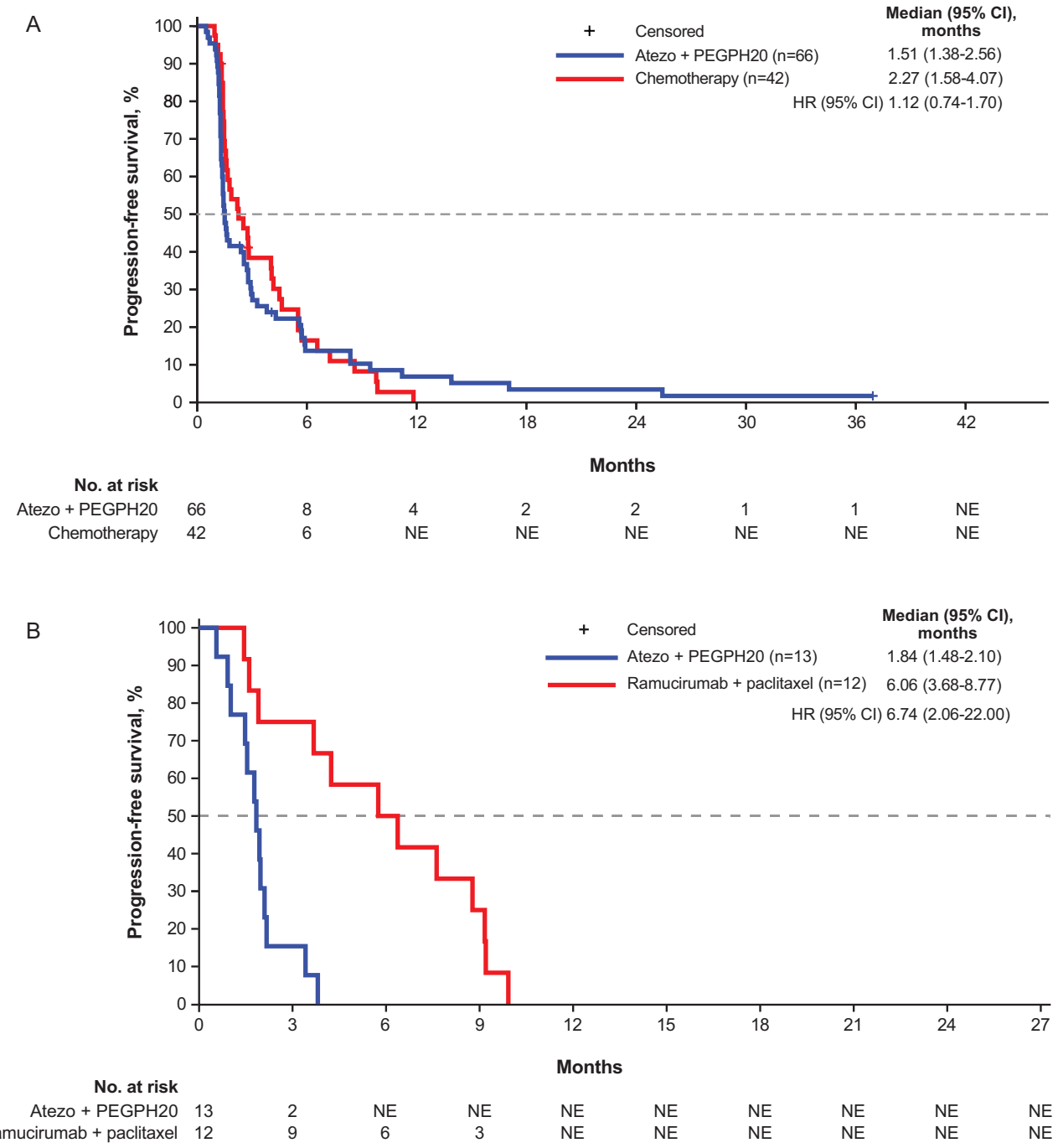

Figure 4. Kaplan-Meier plot of investigator-assessed progression-free survival per Response Evaluation Criteria in Solid Tumors version 1.1 in (A) MORPHEUS-PDAC and (B) MORPHEUS-GC. Atezo, atezolizumab; HR, hazard ratio; NE, not evaluable; PEGPH20, PEGylated recombinant human hyaluronidase.

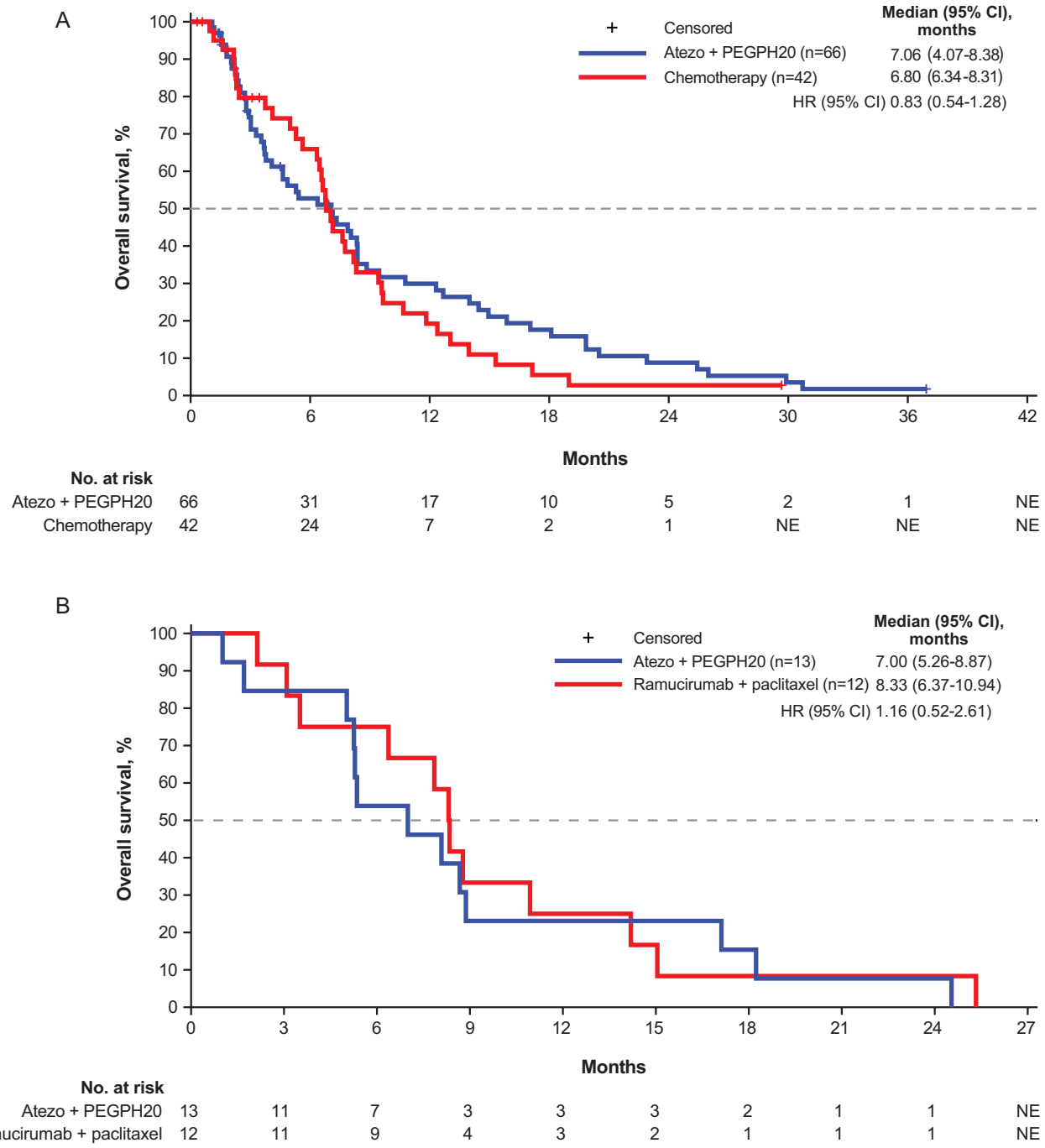

Figure 5. Kaplan-Meier curve of overall survival in (A) MORPHEUS-PDAC and (B) MORPHEUS-GC. Atezo, atezolizumab; HR, hazard ratio; NE, not evaluable; PEGPH20, PEGylated recombinant human hyaluronidase.

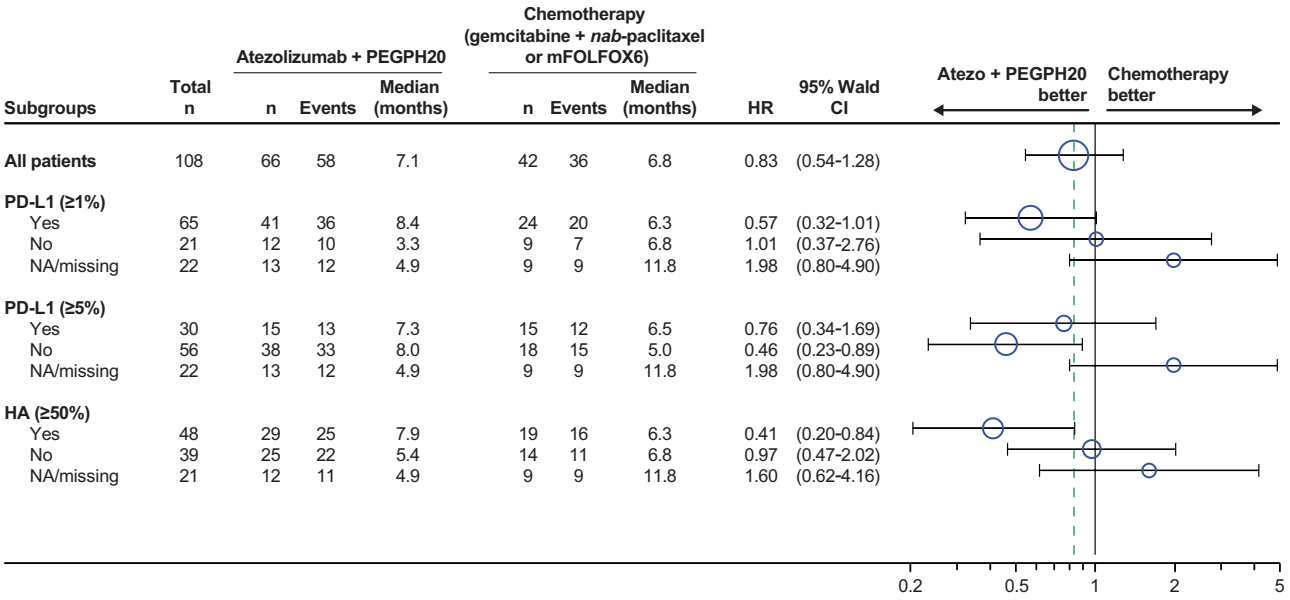

Figure 6. Overall survival by biomarker status in MORPHEUS-PDAC. Atezo, atezolizumab; HA, hyaluronic acid; HR, hazard ratio; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; NA, not assessed; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PEGPH20, PEGylated recombinant human hyaluronidase.

Table 1. Patient disposition in MORPHEUS-PDAC at clinical cutoff date.

	Atezolizumab + PEGPH20	Gemcitabine + *nab*-paclitaxel or mFOLFOX6
Disposition from study (all randomized patients), *n* (%)	*n* = 71	*n* = 46
Ongoing (long-term follow-up)	1 (1.4)	1 (2.2)
Discontinued	70 (98.6)	45 (97.8)
Death	58 (81.7)	36 (78.3)
Withdrawal by patient	9 (12.7)	5 (10.9)
Other	3 (4.2)	3 (6.5)
Lost to follow-up	0	1 (2.2)
Disposition from study treatment (patients who received ≥1 dose of study treatment), *n* (%)	*n* = 66	*n* = 42
Discontinued study treatment	66 (100)	42 (100)
Progression of disease	48 (72.7)	31 (73.8)
Physician decision	5 (7.6)	2 (4.8)
Withdrawal by patient	1 (1.5)	6 (14.3)
Symptomatic deterioration	5 (7.6)	1 (2.4)
Adverse event	2 (3.0)	1 (2.4)
Death	2 (3.0)	0
Other	2 (3.0)	0
Lost to follow-up	1 (1.5)	0
Pregnancy	0	1 (2.4)

Abbreviations: mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; PEGPH20, PEGylated recombinant human hyaluronidase.

Table 2. Baseline demographics and disease characteristics in MORPHEUS-PDAC and MORPHEUS-GC.

	MORPHEUS-PDAC[a], *n (%)*		MORPHEUS-GC[b], *n (%)*	
	Atezolizumab + PEGPH20 (*n* = 71)	**Gemcitabine + *nab*-paclitaxel or mFOLFOX6 (*n* = 46)**	**Atezolizumab + PEGPH20 (*n* = 15)**	**Ramucirumab + paclitaxel (*n* = 16)**
Age				
<65 years	49 (69.0)	28 (60.9)	9 (69.2)	9 (56.3)
≥65 years	22 (31.0)	18 (39.1)	4 (30.8)	7 (43.8)
Male	43 (60.6)	23 (50.0)	10 (76.9)	12 (75.0)
Race				
Asian	21 (29.6)	16 (34.8)	8 (53.3)	10 (62.5)
White	43 (60.6)	30 (65.2)	7 (46.7)	6 (37.5)
ECOG PS[c]				
0	26 (37.9)	19 (41.3)	4 (26.7)	4 (26.7)
1	44 (62.1)	27 (58.7)	11 (73.3)	11 (73.3)
Baseline albumin				
<3.5 g/dL	18 (25.4)	13 (28.3)	2 (13.3)	2 (12.5)
≥3.5 g/dL	53 (74.6)	33 (71.7)	13 (86.7)	14 (87.5)
Baseline CRP				
≤1.2 mg/dL	46 (66.7)	32 (69.6)	8 (72.7)	9 (69.2)
>1.2 mg/dL	23 (33.3)	14 (30.4)	3 (27.3)	4 (30.8)
Baseline LDH				
<1.5 × ULN	66 (95.7)	43 (93.5)	11 (78.6)	11 (68.8)
1.5 × ULN to <2.5 × ULN	3 (4.3)	2 (4.3)	2 (14.3)	5 (31.3)
≥2.5 × ULN	0	1 (2.2)	1 (8.3)	0
Baseline NLR				
<5	59 (83.1)	30 (65.2)	–	–
≥5	12 (16.9)	16 (34.8)	–	–
Metastatic sites at enrollment				
1-3	60 (84.5)	43 (93.5)	14 (93.3)	15 (93.8)
≥4	11 (15.5)	2 (6.5)	1 (6.7)	1 (6.3)
PD-L1 status				
PD-L1 IC/TC >1%				
Positive	42 (59.2)	25 (54.3)	NA	NA
Negative	13 (18.3)	9 (19.6)	NA	NA
NA	16 (22.5)	12 (26.1)	–	–
PD-L1 IC/TC >5%				
Positive	14 (19.7)	13 (28.3)	NA	NA
Negative	41 (57.7)	21 (45.7)	NA	NA
NA	16 (22.5)	12 (26.1)	–	–
HA status				
<50%	26 (36.6)	14 (30.4)	NA	NA
≥50%	30 (42.3)	19 (41.3)	NA	NA
NA	15 (21.1)	13 (28.3)	–	–
Prior chemotherapy				
5-FU	36 (52.2)	23 (50.0)	2 (13.3)	4 (25.0)
Gemcitabine	33 (47.8)	23 (50.0)	–	–
Prior cancer surgery	11 (15.5)	5 (15.2)	2 (13.3)	9 (56.3)
Prior radiotherapy	12 (16.9)	5 (10.9)	2 (13.3)	1 (6.3)

[a]Clinical cutoff: June 25, 2021.
[b]Clinical cutoff: November 26, 2020.
[c]One patient in the atezolizumab group had an ECOG PS of 3.
Abbreviations: 5-FU, 5-fluorouracil; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; HA, hyaluronic acid; IC, immune cell; LDH, lactate dehydrogenase; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; NA, not assessed; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed cell death 1 ligand 1; PEGPH20, PEGylated recombinant human hyaluronidase; TC, tumor cell; ULN, upper limit of normal.

Table 3. Summary of efficacy in MORPHEUS-PDAC and MORPHEUS-GC.

	MORPHEUS-PDAC[a]		MORPHEUS-GC[b]	
	Atezolizumab + PEGPH20 (*n* = 66)	**Gemcitabine + *nab*-paclitaxel or mFOLFOX6 (*n* = 42)**	**Atezolizumab + PEGPH20 (*n* = 13)**	**Ramucirumab + paclitaxel (*n* = 12)**
ORR, *n* (%)[c] [95% CI]	4 (6.1) [1.7-14.8]	1 (2.4) [0.1-12.6]	0 [0.0-24.7]	2 (16.7) [2.1-48.4]
CR, *n* (%) [95% CI]	0 (0) [0.0-5.4]	0 (0) [0.0-8.4]	0 [0.0-24.7]	0 [0.0-26.5]
PR, *n* (%) [95% CI]	4 (6.1) [1.7-14.8]	1 (2.4) [0.1-12.6]	0 [0.00-24.7]	2 (16.7) [2.1-48.4]
SD, *n* (%) [95% CI]	18 (27.3) [17.0-39.6]	16 (38.1) [23.6-54.4]	2 (15.4) [1.9-45.5]	8 (66.7) [34.9-90.1]
PD, *n* (%) [95% CI]	35 (53.0) [40.3-65.4]	16 (38.1) [23.6-54.4]	10 (76.9) [46.2-95.0]	2 (16.7) [2.1-48.4]
NE, *n* (%)	2 (3.0)	2 (4.8)	0	0
Missing, *n* (%)	7 (10.6)	7 (16.7)	1 (7.7)	0
Disease control rate, *n* (%) [95% CI]	12 (18.2) [9.8-29.6]	12 (28.6) [15.7-44.6]	0 [0.0-24.7]	8 (66.7) [34.9-90.1]
Median DOR (minimum–maximum) [95% CI]	8.2 (5.3-32.8) [5.3-NE]	3.9 (3.9-3.9) [NE]	NE	3.3 [2.9-3.8]
PFS				
Patients with event, *n* (%)	62 (93.9)	38 (90.5)	13 (100)	12 (100)
Median, months (95% CI)	1.5 (1.4-2. 6)	2.3 (1.6-4.1)	1.8 (1.5-2.1)	6.1 (3.7-8.8)
HR (95% CI)	1.12 (0.74-1.70)		6.74 (2.06-22.00)	
OS				
Patients with event, *n* (%)	58 (87.9)	36 (85.7)	13 (100)	12 (100)
Median, months (95% CI)	7.1 (4.1-8.4)	6.8 (6.3-8.3)	7.0 (5.3-8.9)	8.3 (6.4-10.9)
HR (95% CI)	0.83 (0.54-1.28)		1.16 (0.52-2.61)	

[a]Clinical cutoff: June 25, 2021.
[b]Clinical cutoff: November 26, 2020.
[c]Confirmed objective responses by investigator per Response Evaluation Criteria in Solid Tumors version 1.1.
Abbrevaitions: CR, complete response; DOR, duration of response; HR, hazard ratio; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PEGPH20, PEGylated recombinant human hyaluronidase; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 4. ORR in MORPHEUS-PDAC biomarker subgroups.

Atezolizumab + PEGPH20	**Responders, *n/N* (%)**
ITT	4/66 (6.1)
PD-L1 BEP	4/53 (7.3)
PD-L1 IC/TC ≥1%	4/41 (9.8)
PD-L1 IC/TC ≥5%	3/15 (20)
HA BEP	3/53 (5.7)
HA ≥50%	1/29 (3.4)

Abbreviations: BEP, biomarker-evaluable population; HA, hyaluronic acid; IC, immune cell; ITT, intention to treat; ORR, objective response rate; PD-L1, programmed cell death 1 ligand 1; PEGPH20, PEGylated recombinant human hyaluronidase; TC, tumor cell.

Table 5. Pharmacokinetics of atezolizumab and PEGPH20 in MORPHEUS-PDAC.

Visit/time point	Nominal sampling time (day)	*n*	Mean	CV % mean
Atezolizumab (μg/mL)				
Cycle 1, day 1/30 minutes post dose	0.06	63	367	30.9
Cycle 2, day 1/predose	21	50	69.8	31.3
Cycle 3, day 1/predose	42	28	106	38.2
Cycle 4, day 1/predose	63	24	138	39.8
Cycle 8, day 1/predose	147	10	174	21.0
PEGPH20 (ng/mL)				
Cycle 1, day 1/5 minutes post dose	0.01	59	68.8	26.1
Cycle 1, day 1/1-3 hours post dose	0.09	61	61.0	26.9
Cycle 1, day 8/predose	7	61	4.86	68.6
Cycle 1, day 15/predose	14	56	4.71	91.9
Cycle 2, day 1/predose	21	49	5.66	74.6
Cycle 2, day 1/5 minutes post dose	21.01	46	69.5	42.7
Cycle 3, day 1/predose	42	26	7.57	63.5
Cycle 4, day 1/predose	63	21	7.52	74.0
Cycle 8, day 1/predose	147	7	13.8	52.6

Abbreviations: CV, coefficient of variation; PEGPH20, PEGylated recombinant human hyaluronidase.

Table 6. Pharmacokinetics of atezolizumab and PEGPH20 in MORPHEUS-GC.

Visit/time point	Nominal sampling time (day)	*n*	Mean	CV % mean
Atezolizumab (μg/mL)				
Cycle 1, day 1/30 minutes post dose	0.06	11	384	33.9
Cycle 2, day 1/predose	21	10	66.5	24.0
Cycle 3, day 1/predose	42	8	101	34.6
Cycle 4, day 1/predose	63	1	117	NR
PEGPH20 (ng/mL)				
Cycle 1, day 1/5 minutes post dose	0.01	11	59.7	49.9
Cycle 1, day 1/1-3 hours post dose	0.09	11	46.9	44.9
Cycle 1, day 8/predose	7	12	NR	NR
Cycle 1, day 15/predose	14	11	NR	NR
Cycle 2, day 1/predose	21	10	NR	NR
Cycle 2, day 1/5 minutes post dose	21.01	9	60.1	34.3
Cycle 3, day 1/predose	42	8	5.63	72.2

Abbreviations: CV, coefficient of variation; NR, nonreportable; PEGPH20, PEGylated recombinant human hyaluronidase.

Table 7. Safety summary in MORPHEUS-PDAC and MORPHEUS-GC.

n (%)	Atezolizumab + PEGPH20 (*n* = 66)	Gemcitabine + *nab*-paclitaxel or mFOLFOX6 (*n* = 42)	Atezolizumab + PEGPH20 (*n* = 13)	Ramucirumab + paclitaxel (*n* = 12)
Total patients with ≥1 AE	65 (98.5)	41 (97.6)	13 (100)	12 (100)
Grade 5 AE	3 (4.5)[a]	1 (2.4)[b]	0	0
SAE	30 (45.5)	20 (47.6)	1 (7.7)	6 (50.0)
Related AE	62 (93.9)	36 (85.7)	13 (100)	12 (100)
Grade 3/4 AE	43 (65.2)	26 (61.9)	4 (30.8)	9 (75.0)
AE leading to dose modification/interruption[c]	30 (45.5)	30 (71.4)	5 (38.5)	11 (91.7)
AE leading to withdrawal from treatment[c]	10 (15.2)	2 (4.8)	0	1 (8.3)
AESI	23 (34.8)	15 (35.7)	6 (46.2)	5 (41.7)

[a]Cardiorespiratory arrest, myositis, and death (cause unknown).
[b]Disseminated intravascular coagulation.
[c]Any drug.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; PEGPH20, PEGylated recombinant human hyaluronidase; SAE, serious adverse event.

Table 8. TRAEs reported by ≥10% of patients in either arm in MORPHEUS-PDAC.

TRAE, *n* (%)	Atezolizumab + PEGPH20 (*n* = 66)	Gemcitabine + *nab*-paclitaxel or mFOLFOX6 (*n* = 42)
Myalgia	43 (65.2)	3 (7.1)
Edema peripheral	19 (28.8)	6 (14.3)
Fatigue	15 (22.7)	9 (21.4)
Arthralgia	15 (22.7)	1 (2.4)
Muscle spasms	11 (16.7)	0
Nausea	9 (13.6)	16 (38.1)
Decreased appetite	7 (10.6)	9 (21.4)
Pyrexia	5 (7.6)	6 (14.3)
Aspartate aminotransferase increased	4 (6.1)	5 (11.9)
Anemia	4 (6.1)	5 (11.9)
Vomiting	3 (4.5)	9 (21.4)
Stomatitis	1 (1.5)	6 (14.3)
Neutropenia	1 (1.5)	10 (23.8)
Platelet count decreased	1 (1.5)	6 (14.3)
Neuropathy peripheral	1 (1.5)	6 (14.3)
Neutrophil count decreased	0	10 (23.8)
Thrombocytopenia	0	7 (16.7)
White blood cell count decreased	0	5 (11.9)
Alopecia	0	9 (21.4)

Abbreviations: mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; PEGPH20, PEGylated recombinant human hyaluronidase; TRAE, treatment-related adverse event.

Table 9. AESIs reported by ≥5% of patients in either arm (by MedDRA preferred term) in MORPHEUS-PDAC.

AESI, *n* (%)	Atezolizumab + PEGPH20 (*n* = 66)	Gemcitabine + *nab*-paclitaxel or mFOLFOX6 (*n* = 42)
Aspartate aminotransferase increased	9 (13.6)	6 (14.3)
Alanine aminotransferase increased	7 (10.6)	5 (11.9)
Blood bilirubin increased	4 (6.1)	4 (9.5)
Infusion-related reaction	4 (6.1)	0
Ascites	3 (4.5)	3 (7.1)
Dermatitis acneiform	1 (1.5)	3 (7.1)
Rash maculo-papular	0	3 (7.1)

Abbreviations: AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; PEGPH20, PEGylated recombinant human hyaluronidase.

Table 10. TRAEs reported by ≥10% of patients in either arm in MORPHEUS-GC.

TRAE, *n* (%)	Atezolizumab + PEGPH20 (*n* = 13)	Ramucirumab + paclitaxel (*n* = 12)
Decreased appetite	3 (23.1)	2 (16.7)
Tinnitus	3 (23.1)	0
Fatigue	2 (15.4)	4 (33.3)
Dyspepsia	2 (15.4)	0
Peripheral sensory neuropathy	2 (15.4)	2 (16.7)
Vomiting	2 (15.4)	0
Edema peripheral	2 (15.4)	0
Arthralgia	2 (15.4)	0
Muscle spasms	2 (15.4)	0
Myalgia	2 (15.4)	0
Infusion-related reactions	2 (15.4)	0
Neuropathy peripheral	1 (7.7)	3 (25.0)
Constipation	1 (7.7)	2 (16.7)
Diarrhea	1 (7.7)	2 (16.7)
Neutrophil count decreased	0	6 (50.0)
Alopecia	0	4 (33.3)
Anemia	0	4 (33.3)
Epistaxis	0	4 (33.3)
Neutropenia	0	2 (16.7)
Asthenia	0	2 (16.7)
Hypertension	0	2 (16.7)

Abbreviations: PEGPH20, PEGylated recombinant human hyaluronidase; TRAE, treatment-related adverse event.

Table 11. AESIs reported by ≥10% of patients (ie, >1 patient) in either arm (by MedDRA preferred term) in MORPHEUS-GC.

AESI, *n* (%)	Atezolizumab + PEGPH20 (*n* = 13)	Paclitaxel + ramucirumab (*n* = 12)
Ascites	4 (30.8)	1 (8.3)
Infusion-related reaction	2 (15.4)	0

Abbreviations: AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; PEGPH20, PEGylated recombinant human hyaluronidase.