original reports

Randomized Phase III Trial of Pegvorhyaluronidase Alfa With Nab-Paclitaxel Plus Gemcitabine for Patients With Hyaluronan-High Metastatic Pancreatic Adenocarcinoma

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abstract

PURPOSE To evaluate the efficacy and safety of pegvorhyaluronidase alfa (PEGPH20) plus nab-paclitaxel/gemcitabine (AG) in patients with hyaluronan-high metastatic pancreatic ductal adenocarcinoma (PDA).

PATIENTS AND METHODS HALO 109-301 was a phase III, randomized, double-blind, placebo-controlled study. Patients ≥ 18 years of age with untreated, metastatic, hyaluronan-high PDA were randomly assigned 2:1 to PEGPH20 plus AG or placebo plus AG. Treatment was administered intravenously in 4-week cycles (3 weeks on, 1 week off) until progression or intolerable adverse events: PEGPH20 3.0 μg/kg twice per week for cycle 1 and once per week thereafter; nab-paclitaxel 125 mg/m^2 once per week; and gemcitabine 1,000 mg/m^2 once per week. The primary end point was overall survival (OS); secondary end points included progression-free survival (PFS), objective response rate (ORR), and safety. Response was independently assessed per RECIST v1.1.

RESULTS At data cutoff, 494 patients were randomly assigned, with 492 (327 for PEGPH20 and 165 for placebo) included in intention-to-treat analyses. Baseline characteristics were balanced for PEGPH20 plus AG versus placebo plus AG. There were 330 deaths, with a median OS of 11.2 months for PEGPH20 plus AG versus 11.5 months for placebo plus AG (hazard ratio [HR], 1.00; 95% CI, 0.80 to 1.27; $P = .97$); median PFS was 7.1 months versus 7.1 months (HR, 0.97 [95% CI, 0.75 to 1.26]); ORR was 47% versus 36% (ORR ratio, 1.29 [95% CI, 1.03 to 1.63]). Grade ≥ 3 adverse events with a ≥ 2% higher rate with PEGPH20 plus AG than with placebo plus AG included fatigue (16.0% *v* 9.6%), muscle spasms (6.5% *v* 0.6%), and hyponatremia (8.0% *v* 3.8%).

CONCLUSION The addition of PEGPH20 to AG increased the ORR but did not improve OS or PFS. The safety profile of PEGPH20 plus AG was consistent with that found in previous studies. These results do not support additional development of PEGPH20 in metastatic PDA.

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ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Pancreatic cancer remains one of the deadliest cancers. Although survival has improved for patients with early-stage disease, more than one half of patients are diagnosed after the disease has become metastatic.[1-3] For patients with metastatic disease, the 5-year survival rate is only 3%.[1] The most common type of pancreatic cancer is pancreatic ductal adenocarcinoma (PDA), which accounts for > 85% of pancreatic neoplasms.[4] Studies of systemic therapies in metastatic PDA have shown limited benefit, reporting a median overall survival (OS) of 6 to 15 months.[5]

Efficient delivery of systemic therapies to pancreatic tumors has proven to be a major challenge. In PDA, a dense fibrotic stroma (ie, desmoplasia) surrounds the growing tumor mass, which can compress tumor vasculature within the microenvironment and increase interstitial pressure, impeding perfusion and delivery of systemic agents.[6-9] Recent treatment strategies have focused on stroma remodeling to facilitate the

CONTEXT

Key Objectives

This phase 3, randomized, double-blind, placebo-controlled study was designed to determine if the addition of pegvorhyaluronidase alfa (PEGPH20) to nab-paclitaxel/gemcitabine (AG) could improve overall survival (OS) in patients with hyaluronan-high metastatic pancreatic ductal adenocarcinoma (PDA).

Knowledge Generated

The addition of PEGPH20 to nab-paclitaxel/gemcitabine did not improve the primary endpoint of overall survival. There was an increase in the rates of some adverse events with PEGPH20 plus AG versus placebo plus AG, but safety and tolerability were manageable.

Relevance

These results do not support additional development of PEGPH20 in metastatic PDA.

distribution of systemic agents within the tumor microenvironment (TME). Tumor stroma is composed of vasculature, fibroblasts, immune cells, and extracellular matrix (ECM).[10,11] Hyaluronan, a hydrophilic glycosaminoglycan, is a major component of ECM and has been shown to accumulate in the TME of PDA.[12-16] Preclinical and clinical data indicate that accumulation of hyaluronan in the TME is associated with aggressive metastatic disease, drug resistance, and poor prognosis.[13-17]

The metabolism of hyaluronan is dynamic and rapid, with degradation controlled primarily by hyaluronidases.[12,18] Pegvorhyaluronidase alfa (PEGPH20) is a novel PEGylated recombinant human hyaluronidase developed as an anticancer therapy for use in combination with other systemic therapies to facilitate their delivery to the TME. PEGPH20 degrades tumor hyaluronan, thereby remodeling the TME. In PDA and other tumor models, PEGPH20 has shown independent antitumor activity and increased delivery of systemic therapies to the TME with improved efficacy.[13,16,19-25]

Results from early clinical trials with PEGPH20 in patients with advanced solid tumors, including PDA, were consistent with preclinical findings and supported additional clinical development.[26,27] In HALO 109-202 (HALO-202), an open-label, phase II trial, patients with untreated metastatic PDA were randomly assigned to nab-paclitaxel/gemcitabine (AG), a standard of care,[28] with or without PEGPH20.[29] A numeric imbalance in the number of thromboembolic events was noted in the PEGPH20 arm in the early stages of the study, prompting a clinical hold. The trial restarted after protocol amendments to exclude patients at high risk of thromboembolic events and to implement enoxaparin prophylaxis, and the rate of thromboembolic events was reduced in both treatment arms. Analysis performed after ≥ 95% of enrolled patients discontinued treatment showed a significant improvement in progression-free survival (PFS) with the addition of PEGPH20. A retrospective analysis demonstrated a notable PFS benefit in the subset of patients with hyaluronan-high tumor samples, defined as ≥ 50% hyaluronan staining in the ECM of tumor samples, supporting hyaluronan as a biomarker for patient selection. Here, we report results from HALO 109-301 (HALO-301), a placebo-controlled, phase III trial to evaluate PEGPH20 in combination with AG in a population of patients with previously untreated metastatic PDA and hyaluronan-high tumors.

PATIENTS AND METHODS

Patients and Study Design

HALO-301 was a phase III, international, randomized, double-blind, placebo-controlled study. Patients with stage IV PDA with at least 1 measurable metastasis were eligible for enrollment provided they were ≥ 18 years of age and had an Eastern Cooperative Oncology Group performance status score of 0 or 1, a life expectancy of ≥ 3 months, adequate organ and bone marrow function, and fresh or archived core tumor samples obtained after metastatic disease documentation. Patients were required to have hyaluronan-high tumors, defined as ≥ 50% hyaluronan staining in the ECM of tumor samples, which were analyzed centrally with a hyaluronan affinity histochemistry assay (Ventana HA RxDx Assay; Roche, Tucson, AZ; Data Supplement).[29,30] Prior neoadjuvant or adjuvant treatment was allowed, as was prior treatment of locally advanced disease, provided that recurrence or progression was at least 6 months after completion of the last treatment dose. Prior radiotherapy, surgery, chemotherapy, or investigational therapy for metastatic disease was not permitted, with the exception of palliative radiotherapy for pain associated with bone metastases. Other key exclusion criteria included the presence of thromboembolic events at screening, metastases to the CNS, and contraindications to study drugs or heparin. Patients with New York Heart Association class III or IV cardiac disease, myocardial infarction within 12 months, or a history of cerebrovascular accident or transient ischemic attack were not eligible. Complete eligibility criteria are detailed in the study protocol. Patients were

randomly assigned 2:1 to treatment with PEGPH20 or placebo (normal saline solution) in combination with AG. Random assignment was stratified by geographic region (North America, Europe, and other). Treatment was continued until disease progression or unacceptable toxicity.

The trial was conducted in accordance with US Food and Drug Administration regulations and guidelines, the Declaration of Helsinki, and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. The study protocol and all protocol amendments were approved by the institutional review boards or ethical committees of the participating centers. Safety data were reviewed periodically by an independent Data Monitoring Committee. All patients provided written informed consent. The trial is registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02715804).

Study Treatment

Patients received treatment in 4-week cycles: 3 weeks receiving treatment and 1 week not receiving treatment. All study drugs were administered by intravenous infusion at doses of 3.0 μg/kg for PEGPH20, 125 mg/m^2 for nab-paclitaxel, and 1,000 mg/m^2 for gemcitabine. For cycle 1, PEGPH20 and placebo were administered twice per week (days 1, 4, 8, 11, 15, and 18), and AG was administered once per week (days 2, 8, and 15). For all subsequent cycles, all study drugs were administered once per week (days 1, 8, and 15). On concurrent dosing days, AG was administered 2 to 4 hours after PEGPH20 or placebo.

To mitigate and manage adverse events (AEs), the study protocol outlined prophylactic and supportive care measures. On dosing days of PEGPH20 and placebo, patients were administered prophylactic dexamethasone 8 mg orally before and after infusion to mitigate musculoskeletal

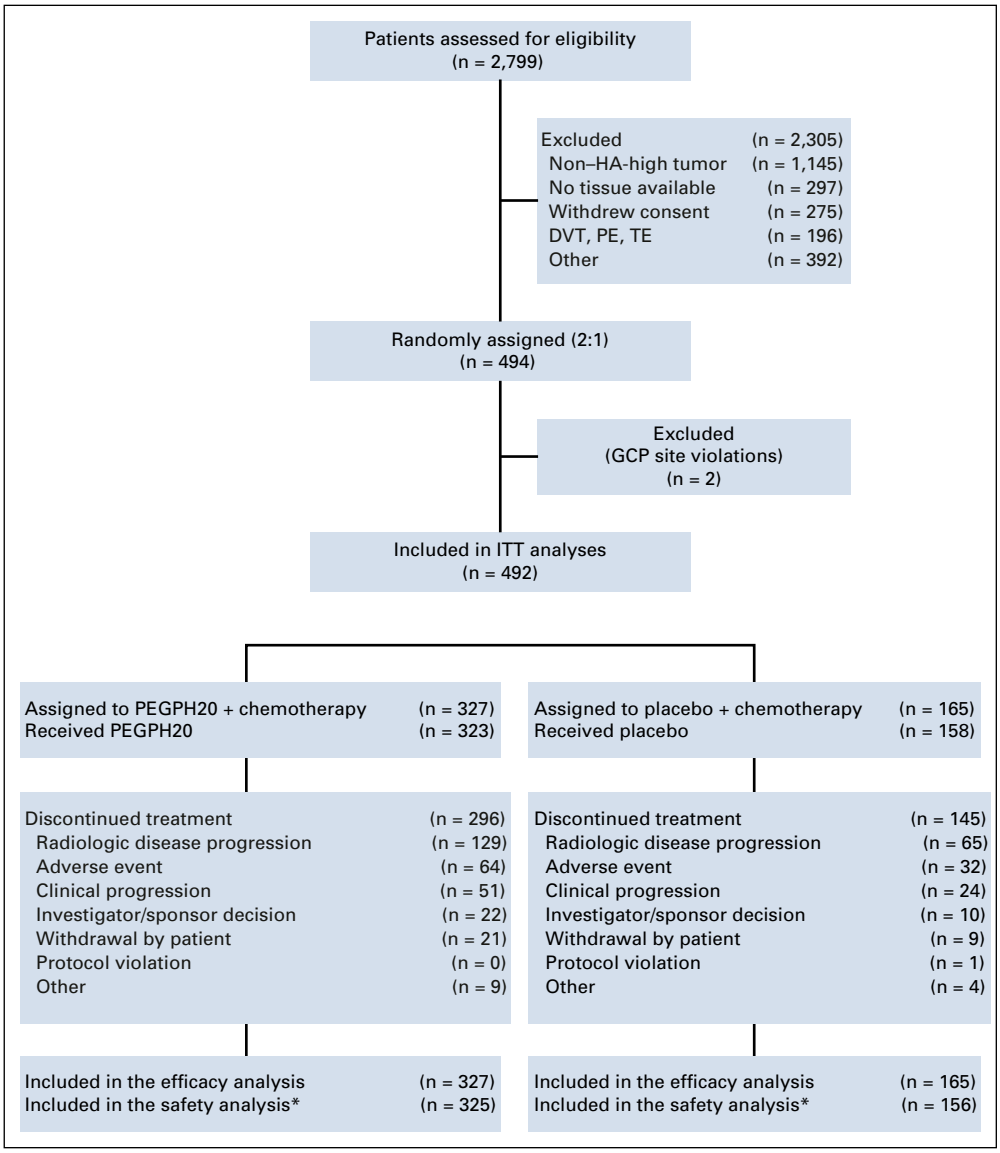

FIG 1. Patient disposition. (*)1 patient randomly assigned to pegvorhyaluronidase alfa (PEGPH20) did not receive PEGPH20; 3 patients randomly assigned to placebo received at least 1 dose of PEGPH20. DVT, deep vein thrombosis; GCP, Good Clinical Practice; HA, hyaluronan; ITT, intention-to-treat; PE, pulmonary embolism; TE, thromboembolism.

events associated with PEGPH20.[26,27,29,31] Prophylactic enoxaparin was self-administered subcutaneously at a dose of 1 mg/kg/d by all patients to mitigate thromboembolic risk.[29,31] Patients who discontinued enoxaparin were required to discontinue PEGPH20 or placebo. Dose holds and reductions to help manage AEs were specified in the study protocol and included standard dosing guidelines for AG.

Outcomes and Assessments

The primary end point was OS (time from random assignment to death from any cause). Secondary end points included PFS (time from random assignment to progression or death from any cause during the treatment period), objective response rate (ORR), duration of response, safety, and tolerability.

Tumor response and progression were assessed with computed tomography or magnetic resonance imaging scans every 2 treatment cycles by blinded independent centralized review using RECIST version 1.1.[32] Patients were assessed routinely for AEs by investigators during treatment and up to 30 days after the last dose of study treatment, with severity graded by investigators using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Statistics

The study was statistically powered to evaluate OS as the primary end point. On the basis of historical data, a median OS of 8.5 months was assumed for the placebo arm.[33] The sample size was estimated to be approximately 500 patients, with final analysis of OS after 330 deaths. A hazard ratio (HR) of 0.67 favoring PEGPH20 over placebo would have a statistical power of 93% at a significance level of 0.05 using a 2-sided log-rank test. This would correspond to an approximately 50% increase in the median OS to

TABLE 1. Baseline Characteristics and Demographics

Characteristic/Demographic	PEGPH20 Plus AG (N = 327)	Placebo Plus AG (N = 165)
Age, years, mean (SD)	63.8 (9.62)	62.3 (9.50)
Sex, No. (%)		
Female	147 (45.0)	85 (51.5)
Male	180 (55.0)	80 (48.5)
Geographic region, No. (%)		
North America	126 (38.5)	63 (38.2)
Europe	141 (43.1)	72 (43.6)
Other	60 (18.3)	30 (18.2)
Race/ethnicity, No. (%)		
White	266 (81.3)	126 (76.4)
Asian	33 (10.1)	24 (14.5)
Other/unknown	28 (8.6)	15 (9.1)
Weight, kg, mean (SD)	71.3 (17.11)	68.1 (15.55)
Body surface area, m^2, mean (SD)	1.8 (0.24)	1.8 (0.22)
ECOG performance status, No. (%)		
0	160 (48.9)	79 (47.9)
1	167 (51.1)	86 (52.1)
No. of metastatic sites, No. (%)		
1	206 (63.0)	92 (55.8)
2	71 (21.7)	38 (23.0)
≥ 3	50 (15.3)	35 (21.2)
Liver metastasis, No. (%)	254 (77.7)	124 (75.2)
Biopsy location, primary tumor, No. (%)	117 (35.8)	70 (42.4)
Serum level of CA19-9, U/mL, mean (SD)	16,012 (47,295)	21,775 (57,806)
Prior PDA (stage I-III) diagnosis, No. (%)	39 (11.9)	14 (8.5)
Time to metastatic PDA diagnosis, years, mean (SD)	1.5 (0.85)	1.6 (1.76)
Prior cancer medication, No. (%)	26 (8.0)	9 (5.5)

Abbreviations: AG, nab-paclitaxel/gemcitabine; ECOG, Eastern Cooperative Oncology Group; PDA, pancreatic ductal adenocarcinoma; PEGPH20, pegvorhyaluronidase alfa; SD, standard deviation.

12.7 months under the exponential survival distribution assumption.

Efficacy analyses were conducted with the intention-to-treat (ITT) population (all randomly assigned patients), and safety analyses were conducted with the safety population (all patients who received any study medication). Median OS and PFS were estimated for each treatment arm by the Kaplan-Meier method, with treatment differences tested using the log-rank test stratified by geographic region. HRs and 95% CIs were estimated with Cox proportional-hazard models stratified by geographic region. ORR was estimated for each treatment arm and was compared with a Cochran-Mantel-Haenszel test stratified by geographic region. Significance testing of primary and secondary efficacy end points was conducted at a 2-sided alpha level of 0.05 following a hierarchical procedure (OS, PFS, and then ORR). Safety end points were summarized with descriptive statistics. Statistical analyses were performed with SAS version 9.3 (Cary, NC).

RESULTS

A total of 494 patients were randomly assigned between March 14, 2016, and December 26, 2018 (Fig 1). One study site was closed with cause because of Good Clinical Practice violations, and because the site data could not be verified, the 2 patients enrolled at this site were excluded from all analyses as prespecified in the statistical analysis plan. The ITT population included 327 patients randomly assigned to PEGPH20 plus AG and 165 patients randomly assigned to placebo plus AG, and the safety population included 325 patients who received at least 1 dose of PEGPH20 and 156 who received at least 1 dose of placebo. At data cutoff (May 20, 2019), 296 patients in the PEGPH20 plus AG arm and 145 patients in the placebo plus AG arm had discontinued treatment. The most common reason for treatment discontinuation was radiologic disease progression (43.6% for PEGPH20 plus AG and 44.8% for placebo plus AG). Baseline demographics and patient characteristics were balanced between treatment arms (Table 1). The most common metastatic site was the liver (77.7% for PEGPH20 plus AG and 75.2% for placebo plus AG).

Efficacy

There were 330 deaths at the data cutoff. Median OS was 11.2 months in the PEGPH20 arm compared with 11.5 months in the placebo arm (stratified HR, 1.00 [95% CI, 0.80 to 1.27]; $P = .97$; Fig 2A). The study failed to achieve its primary end point of improved OS. Use of subsequent therapies after treatment discontinuation was similar between the 2 treatment arms (Data Supplement).

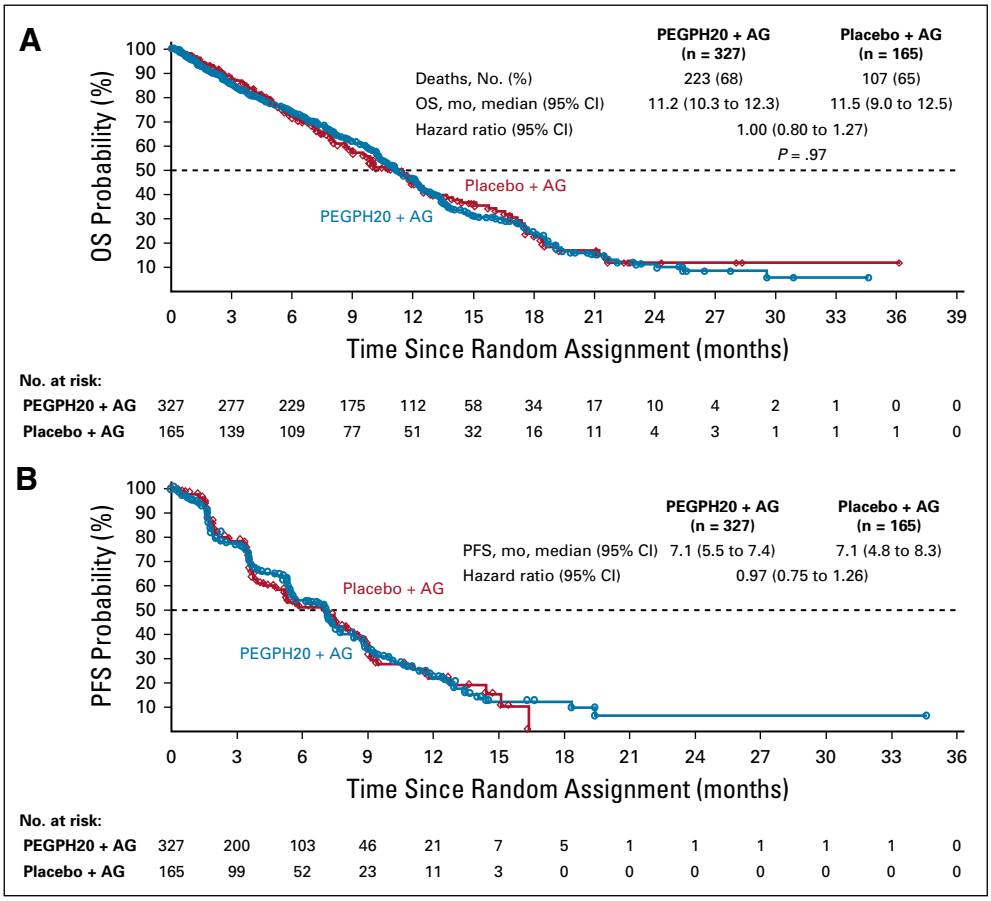

FIG 2. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival in the intention-to-treat population. AG, nab-paclitaxel/gemcitabine; OS, overall survival; PEGPH20, pegvorhyaluronidase alfa; PFS, progression-free survival.

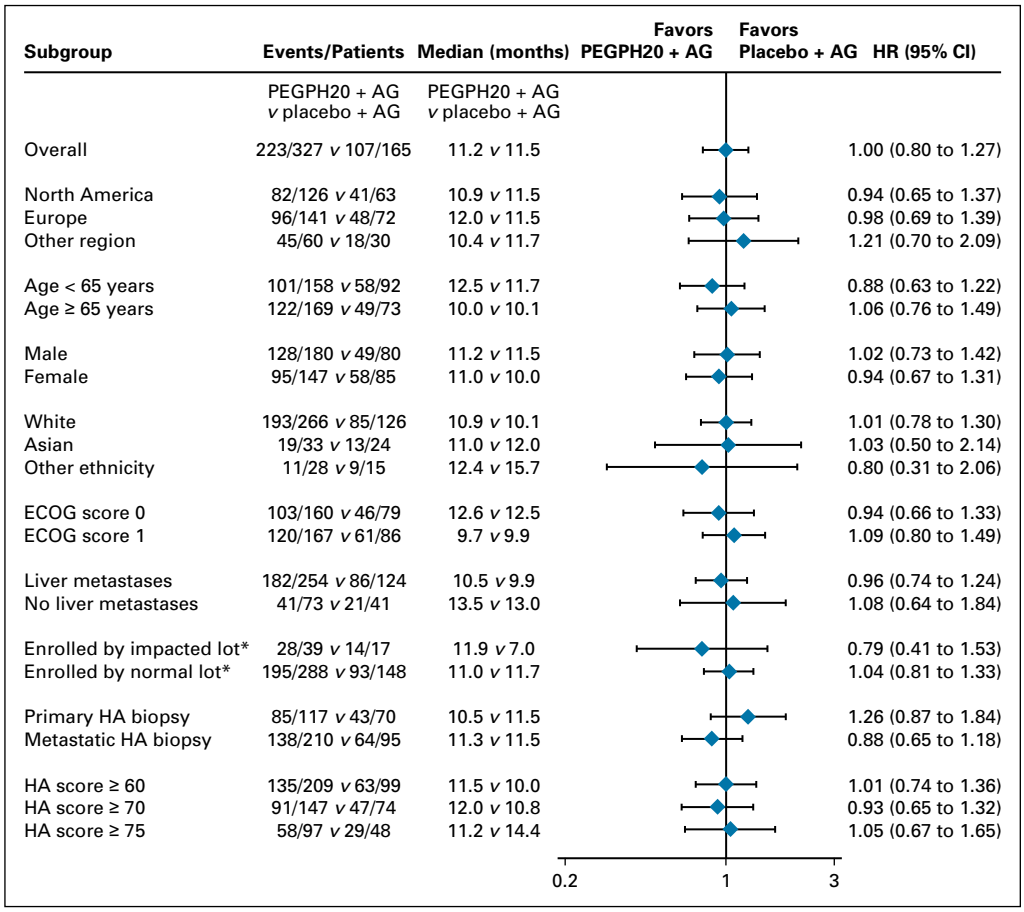

FIG 3. Forest plots of the treatment effect on overall survival in prespecified and exploratory subgroups. (*) Refers to manufacturing batch. AG, nab-paclitaxel/gemcitabine; ECOG, Eastern Cooperative Oncology Group; HA, hyaluronan; HR, hazard ratio; PEGPH20, pegvorhyaluronidase alfa.

Survival results in prespecified and exploratory subgroups were generally consistent with those of the ITT population (Fig 3). A supportive analysis of OS with longer follow-up was conducted at a data cutoff of September 10, 2019, after 363 deaths, with similar outcomes (median 11.4 *v* 11.7 months; HR, 1.02 [95% CI, 0.82 to 1.27]; $P = .85$; Data Supplement).

There was no difference in PFS between the treatment arms (Fig 2B), with a median of 7.1 months in both arms (stratified HR, 0.97 [95% CI, 0.75 to 1.26]). The proportion of patients achieving a response was higher with PEGPH20 plus AG versus placebo plus AG (ORR, 47% *v* 36%; response ratio, 1.29 [95% CI, 1.03 to 1.63]), but there was no improvement in the duration of response (median of 6.1 *v* 7.4 months; Data Supplement). PFS and response outcomes by subgroup were generally consistent with the overall study population (Data Supplement).

Safety

In the safety population, study treatment exposure and dose modifications were generally similar between the 2 arms (Data Supplement). The median number of cycles initiated was 5.0 for both treatment arms, with a median treatment duration of 4.4 months for PEGPH20 plus AG versus 4.2 months for placebo plus AG. Rates for treatment interruption related to AEs were similar between the treatment arms (77.2% *v* 74.4%), as were rates for dose reductions related to AEs (43.1% *v* 46.8%). Treatment discontinuations related to AEs occurred in 28.9% of patients with PEGPH20 plus AG and 28.8% with placebo plus AG; these included fatigue (2.8% *v* 0.6%), musculoskeletal events (2.8% *v* 0), and GI disorders (3.4% *v* 1.3%). The relative dose intensity of the individual study treatments was generally consistent between the 2 arms.

All patients in both treatment arms experienced at least 1 treatment-emergent AE. The most common events of any grade with a ≥ 2% higher rate in the PEGPH20 plus AG arm versus the placebo plus AG arm included peripheral edema (61.8% *v* 33.3%), muscle spasms (51.4% *v* 9.6%), myalgia (28.9% *v* 14.7%), and arthralgia (19.4% *v* 11.5%; Table 2). Grade ≥ 3 events with a ≥ 2% higher rate with PEGPH20 plus AG versus placebo plus AG included fatigue (16.0% *v* 9.6%), muscle spasms (6.5% *v* 0.6%), and hyponatremia (8.0% *v* 3.8%; Table 3). As a class,

TABLE 2. All-Cause Adverse Events of Any Grade with a > 10% Rate and a ≥ 2% Higher Rate in the PEGPH20 Arm[a]

Adverse Event	PEGPH20 Plus AG (n = 325)	Placebo Plus AG (n = 156)
Any adverse event	325 (100)	156 (100)
Peripheral edema	201 (61.8)	52 (33.3)
Fatigue	168 (51.7)	71 (45.5)
Muscle spasms	167 (51.4)	15 (9.6)
Decreased appetite	110 (33.8)	43 (27.6)
Vomiting	104 (32.0)	43 (27.6)
Thrombocytopenia/platelet count decreased	170 (52.3)	99 (44.3)
Myalgia	94 (28.9)	23 (14.7)
Arthralgia	63 (19.4)	18 (11.5)
Insomnia	61 (18.8)	17 (10.9)
Weight decreased	57 (17.5)	14 (9.0)
Dyspnea	54 (16.6)	17 (10.9)
Hypotension	49 (15.1)	20 (12.8)
Hypoalbuminemia	48 (14.8)	11 (7.1)
Dysphonia	48 (14.8)	7 (4.5)
Epistaxis	43 (13.2)	16 (10.3)
Dehydration	42 (12.9)	10 (6.4)
Hyponatremia	38 (11.7)	11 (7.1)
Stomatitis	35 (10.8)	9 (5.8)

NOTE. Data are presented as No. (%).
Abbreviations: AG, nab-paclitaxel/gemcitabine; PEGPH20, pegvorhyaluronidase alfa.
[a]Safety population.

musculoskeletal events occurred at a rate of 75.4% for PEGPH20 plus AG versus 46.2% for placebo plus AG for any grade and 13.2% versus 5.1% for grade ≥ 3. Thromboembolic events of any grade occurred in 15.1% of patients in the PEGPH20 arm and in 13.5% of patients in the placebo arm, with corresponding grade ≥ 3 rates of 6.5% and 7.1%, respectively. Grade ≥ 3 bleeding events occurred in 4.6% versus 1.9% of patients and included GI bleeding (3.6% *v* 0.6%). Serious AEs were experienced by 57.5% of patients in the PEGPH20 plus AG arm and in 51.3% in the placebo plus AG arm; these included pyrexia (7.1% *v* 5.1%) and sepsis (6.8% *v* 2.6%). Serious infections

TABLE 3. All-Cause Adverse Events of Grade ≥ 3 With a ≥ 2% Higher Rate in the PEGPH20 Arm[a]

Adverse Event	PEGPH20 Plus AG (n = 325)	Placebo Plus AG (n = 156)
Any adverse event	301 (92.6)	138 (88.5)
Thrombocytopenia/platelet count decreased	68 (20.9)	25 (16.1)
Fatigue	52 (16.0)	15 (9.6)
Asthenia	28 (8.6)	9 (5.8)
Hyponatremia	26 (8.0)	6 (3.8)
Sepsis	24 (7.4)	6 (3.8)
Muscle spasms	21 (6.5)	1 (0.6)
Myalgia	11 (3.4)	1 (0.6)
Edema peripheral	11 (3.4)	2 (1.3)
Leukocytosis	7 (2.2)	0 (0.0)
Weight decreased	7 (2.2)	0 (0.0)

NOTE. Data are presented as No. (%).
Abbreviations: AG, nab-paclitaxel/gemcitabine; PEGPH20, pegvorhyaluronidase alfa.
[a]Safety population.

occurred in 21.8% of patients receiving PEGPH20 plus AG versus 12.8% of those receiving placebo plus AG. There were 19 deaths (5.8%) related to AEs in the PEGPH20 arm and 7 deaths (4.5%) in the placebo arm, including GI bleeding (0.9% *v* 0%; Data Supplement).

DISCUSSION

HALO-301 was a randomized, blinded, phase III study comparing PEGPH20 plus AG versus placebo plus AG. Baseline characteristics were well balanced between the treatment arms, and the administration of study treatments and use of poststudy therapies were similar. The addition of PEGPH20 to AG did not improve the primary end point of OS, and PFS outcomes were similar between the 2 arms. The ORR was higher with PEGPH20 plus AG than with placebo plus AG, but there was no improvement in the duration of response. Safety outcomes were generally consistent with the established profiles of PEGPH20 and AG.[27,29,33] Grade ≥ 3 sepsis (7.4% *v* 3.8%) and grade ≥ 3 GI bleeds (3.6% *v* 0.6%) were reported more frequently in the PEGPH20 plus AG arm versus the placebo plus AG arm, but this did not seem to have a notable impact on the survival end point, given the absolute low incidence of AE-related deaths in both treatment arms.

Assumptions in the statistical plan for HALO-301 were based in part on results from the MPACT study. In the MPACT study, patients with untreated metastatic PDA were randomly assigned to AG (a regimen similar to the one used in the current study) or to gemcitabine monotherapy. Combination therapy with AG significantly improved OS, PFS, and ORR compared with gemcitabine monotherapy, with a median OS of 8.5 versus 6.7 months (HR, 0.72 [95% CI, 0.62 to 0.83]; $P < .001$), a median PFS of 5.5 versus 3.7 months (HR, 0.69 [95% CI, 0.58 to 0.82]; $P < .001$), and an ORR of 23% versus 7% ($P < .001$).[33] Surprisingly, the median OS in the placebo plus AG arm of HALO-301 was longer at 11.5 months than that reported in the MPACT study, indicating that HALO-301 was underpowered. However, it is doubtful that a larger study would have had a different outcome.

In HALO-301, there were no apparent safety signals that affected study treatment exposure or survival outcomes. Generally, most patients required dose reductions but were able to maintain dose intensity with PEGPH20, and similar rates of dose modifications and treatment discontinuations were reported in the PEGPH20 plus AG and placebo plus AG arms. Screening for patients at risk of thromboembolism and the use of prophylactic enoxaparin seemed to be an effective strategy for mitigating the incidence of thromboembolic events during HALO-202[29] and HALO-301. Pancreatic cancer is associated with a relatively high risk of thromboembolic events,[34,35] and strategies to identify at-risk patients and to develop prophylactic regimens are worthy of additional evaluation.[36,37]

A number of observations support the effective conduct of this study. The clear steps on the PFS Kaplan-Meier curves show that patients were being scanned at the planned intervals, without evidence of ascertainment bias. In addition, rates of radiologic and clinical progression were comparable in both arms, and rates of study discontinuation because of nonprogression (35.5% for PEGPH20 plus AG and 33.9% for placebo plus AG) were lower than the rate reported in the AG arm of the MPACT study (45.9%).

HALO-301 adds to the body of evidence of stroma remodeling in solid tumors, which collectively indicates the need to re-evaluate this treatment strategy. Although positive results were reported for HALO-202,[29] a phase Ib/II randomized study of PEGPH20 with modified FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) for patients with untreated metastatic PDA was closed early after an interim futility analysis reported a median OS of 7.7 months for PEGPH20 plus modified FOLFIRINOX versus 14.4 months for modified FOLFIRINOX (HR, 2.07 [95% CI, 1.28 to 3.34]; $P < .01$).[31] The investigators hypothesized that a high rate of dose holds and reductions in the PEGPH20 arm led to lower chemotherapy drug exposure and may have contributed to the inferior survival outcomes with PEGPH20, or there may have been unforeseen negative drug interactions.

Other agents targeting tumor desmoplasia as a treatment strategy in PDA have also failed,[38-41] but the complexity of the fibro-inflammatory infiltrate and actionable drug targets has not been fully explored. More preclinical and retrospective analyses are needed to better understand the failures of tumor stroma remodeling and whether and how it should continue to be pursued. Although studies have demonstrated that desmoplastic stroma may limit the accessibility of systemic agents to the TME, there is also evidence that stromal elements may restrain PDA progression.[38,42] In addition, the use of immunohistochemical scoring on the basis of the percentage of overall positive surface area may not be a reliable method for determining hyaluronan status with regard to prognostic significance,[43] and there are limited data on tumor stroma of metastatic sites compared with the primary tumor site.[14]

In summary, the addition of PEGPH20 to AG did not improve the primary end point of OS in patients with hyaluronan-high metastatic PDA. The safety profile was manageable and consistent with those of prior studies. These results do not support the continued clinical development of PEGPH20 in stage IV PDA without compelling evidence to refine patient selection.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase III Trial of Pegvorhyaluronidase Alfa With Nab-Paclitaxel Plus Gemcitabine for Patients With Hyaluronan-High Metastatic Pancreatic Adenocarcinoma

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