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Global, multicenter, randomized, phase II trial of gemcitabine and gemcitabine plus AGS-1C4D4 in patients with previously untreated, metastatic pancreatic cancer†

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Background: We evaluated AGS-1C4D4, a fully human monoclonal antibody to prostate stem cell antigen (PSCA), with gemcitabine in a randomized, phase II study of metastatic pancreatic cancer.
Patients and methods: Patients with Eastern Cooperative Oncology Group (ECOG) performance status 0/1 and previously untreated, metastatic pancreatic adenocarcinoma were randomly assigned 1:2 to gemcitabine (1000 mg/m^2

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weekly seven times, 1 week rest, weekly three times q4weeks) or gemcitabine plus AGS-1C4D4 (48 mg/kg loading dose, then 24 mg/kg q3weeks IV). The primary end point was 6-month survival rate (SR). Archived tumor samples were collected for pre-planned analyses by PSCA expression.

Results: Between April 2009 and May 2010, 196 patients were randomly assigned to gemcitabine ($n = 63$) or gemcitabine plus AGS-1C4D4 ($n = 133$). The 6-month SR was 44.4% (95% CI, 31.9–57.5) in the gemcitabine arm and 60.9% (95% CI, 52.1–69.2) in the gemcitabine plus AGS-1C4D4 arm ($P = 0.03$), while the median survival was 5.5 versus 7.6 months and the response rate was 13.1% versus 21.6% in the two arms, respectively. The 6-month SR was 57.1% in the gemcitabine arm versus 79.5% in the gemcitabine plus AGS-1C4D4 arm among the PSCA-positive subgroup and 31.6% versus 46.2% among the PSCA-negative subgroup.

Conclusions: This randomized, phase II study achieved its primary end point, demonstrating an improved 6-month SR with addition of AGS-1C4D4 to gemcitabine among patients with previously untreated, metastatic pancreatic adenocarcinoma.

ClinicalTrials.gov identifier: NCT00902291.

Key words: chemotherapy, clinical trial, gemcitabine, metastatic disease, pancreatic cancer, prostate stem cell antigen

introduction

Pancreatic cancer is a major cause of cancer-related death worldwide and 5-year overall survival (OS) is <5% [1, 2]. For patients with metastatic disease, treatment with weekly gemcitabine results in median OS of ~6 months [3]. Multiple studies have attempted to improve upon the efficacy of gemcitabine by the addition of a second cytotoxic chemotherapy or targeted therapy, but these studies have largely failed to improve survival in these patients [4–12]. Recently, a combination regimen of fluorouracil, folinic acid, irinotecan, and oxaliplatin (FOLFIRINOX) has demonstrated improved efficacy in comparison to gemcitabine [13]; however, this regimen has greater toxicity and can be difficult to administer in several populations, including those with poorer performance status, older age, and elevated liver function tests [14, 15]. Therefore, the delineation of further treatment options remains critical to improving quality of life and survival of patients with pancreatic adenocarcinoma.

Prostate stem cell antigen (PSCA) is a glycosylphosphatidylinositol (GPI)-linked cell surface protein initially identified due to overexpression in prostate cancer [16]. Although it shares 30% homology with stem cell antigen type-2, a surface marker on immature lymphocytes, it is predominantly expressed on differentiated tissues of the gastrointestinal and genitourinary tracts [17]. Furthermore, PSCA is expressed on several cancers, including those arising from the prostate, bladder, and pancreas [18–20], with 60%–80% of pancreatic tumors expressing PSCA in prior studies [19, 21, 22]. Although the cellular function of PSCA remains poorly understood, preclinical studies have shown that targeting PSCA can be a successful anti-tumor strategy, including for pancreatic cancer [21–25]. Interestingly, a germline missense single-nucleotide polymorphism (SNP) in the first exon of *PSCA* has been identified as a predisposing factor to development of stomach and bladder cancers in large genome wide association studies (GWASs) [26–29].

AGS-1C4D4 is a fully human IgG1k anti-PSCA monoclonal antibody that has undergone phase I testing in patients with prostate cancer [30, 31]. No dose-limiting toxicity was noted in these studies. Therefore, AGS-1C4D4 at 48 mg/kg loading dose followed by 24 mg/kg every 3 weeks intravenously was selected for further investigation based on pharmacokinetic properties, rather than toxicity. To evaluate efficacy and toxicity of AGS-1C4D4 in patients with previously untreated, metastatic pancreatic cancer, we conducted an open-label, randomized, two-arm phase II study of gemcitabine alone and gemcitabine plus AGS-1C4D4, with primary end point of 6-month survival rate (SR).

methods

patients

This multicenter, open-label, randomized, phase II trial included patients aged ≥18 years with Eastern Cooperative Oncology Group (ECOG) performance status 0/1 and pathologically confirmed metastatic pancreatic adenocarcinoma. Patients with unresectable, locally advanced disease were ineligible. Measureable and non-measureable diseases by RECIST v1.1 were allowed. Prior chemotherapy for metastatic disease was not permitted. Prior treatment with gemcitabine for local or locally advanced disease was allowed if treatment was completed >6 months before enrollment. Prior chemotherapy other than gemcitabine and/or radiotherapy for local or locally advanced disease was allowed if treatment was completed >4 weeks before enrollment.

Further eligibility criteria included: adequate bone marrow (neutrophils ≥1500/μl, platelets ≥100 000/μl), renal (creatinine ≤2.0 mg/dl), and hepatic function [total bilirubin ≤2 × upper limit of normal (ULN), ALT/AST ≤2.5×ULN or ≤5×ULN if known liver metastases]; and INR <1.3 or ≤3 if on warfarin for therapeutic anticoagulation. The exclusion criteria included: known brain or leptomeningeal disease; major surgery within 28 days of enrollment; clinically significant cardiovascular disease; known chronic infection with HIV, HBV or HCV; and women pregnant or lactating. The protocol was reviewed by institutional review boards of each participating center and all patients provided written informed consent.

randomization and treatment

Patients were randomly assigned 1:2 to gemcitabine alone or gemcitabine plus AGS-1C4D4 (Agensys, Inc.). Randomization was stratified by geographic region (study centers in the United States/Canada versus Europe/Russia). Gemcitabine 1000 mg/m^2 was administered over 30 min by intravenous infusion weekly for 7 weeks, followed by a 1-week rest, followed by weekly infusions for 3 of every 4 weeks. In the gemcitabine

plus AGS-1C4D4 arm, the same schedule of gemcitabine was used with the addition of AGS-1C4D4 48 mg/kg loading dose, then 24 mg/kg q3weeks administered over 60 min intravenously. Dose modifications in AGS-1C4D4 were not allowed. If a dose of AGS-1C4D4 was skipped, it could be administered 2 weeks later with resumption of a new every 3-week dosing schedule. Dose modifications of gemcitabine were as per the package insert and institutional practice. Treatment was discontinued for progressive disease, unacceptable toxicity, or withdrawal of consent.

assessments

Pretreatment evaluations included medical history and physical examination, complete blood count (CBC), chemistry panel, INR, carbohydrate antigen 19-9 (CA19-9), pregnancy test (in women of childbearing potential), evaluation of serum anti-AGS-1C4D4 antibodies, electrocardiogram, and computed tomography scan or magnetic resonance imaging of the chest, abdomen, and pelvis. Physical examination, CBC, INR, chemistry panel, and serum CA19-9 were mandated at least every 3 weeks during treatment. Evaluation of serum anti-AGS-1C4D4 antibodies and imaging studies were carried out every 8 weeks. From patients who provided informed consent, archival tumor tissue was requested for analysis of PSCA cell surface staining.

Patients were evaluated for response according to RECIST criteria v1.1 every 8 weeks. Toxicity was assessed throughout the treatment period and until 4 weeks after the last treatment administration according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Investigators assessed the causal relationship between adverse events and study treatment by the yes/no question, 'Is there a reasonable possibility that the event may have been caused by the investigational product?'

tumor PSCA immunohistochemistry (IHC) and scoring

Archival formalin-fixed, paraffin-embedded tumor tissue was received for 140 of 196 (71%) patients. Among these 140 patients, 123 had adequate tissue for IHC analysis. Four micron thick sections were dewaxed and hydrated for antigen retrieval in proteinase K (Dako, Carpenteria, California), and then treated with 3% hydrogen peroxide. Sections were incubated in either MC1-4.117 (specific anti-PSCA antibody comprised of human variable domains linked to murine IgG1 Fc domain, generated at Agensys, Inc.) at 1.5 μg/ml, or murine IgG1 isotype control antibody (Dako) at the same concentration, for 1 h using an automated instrument (Dako Autostainer, Carpenteria, California). Samples were incubated in the Envision + System-HRP Dual Link reagent (Dako) and then in DAB (Dako) as the chromogen. Sections were counterstained with hematoxylin, dehydrated, and coverslipped. The results of tumor staining for PSCA were expressed using a semi-quantitative H-score [32] by a certified pathologist blinded to patient identifiers and treatment assignment (Quest Laboratories, Van Nuys, CA). The intensity of IHC staining (0, negative; 1+, weak; 2+, moderate; 3+, strong) was multiplied by the percentage of stained cells with that intensity [H-score = (% at 1+) × 1 + (% at 2 +) × 2 + (% at 3+)×3], resulting in an H-score ranging from 0 to 300. *A priori*, PSCA positivity was defined as an H-score of ≥100 [32].

statistical analyses and study design

The primary end point was 6-month SR, defined as a proportion of patients alive at 6 months from the date of randomization. Based on a comparison of two proportions with the chi-square test and 1:2 randomization scheme, a sample size of 185 patients was needed to detect a 20% increase in 6-month SR from 45% to 65% with 90% power and one-sided alpha of 0.10. Therefore, target enrollment was 60 patients in the gemcitabine arm and 125 patients in the gemcitabine plus AGS-1C4D4 arm. The primary efficacy and safety analysis population was defined as all patients who received ≥1 dose of treatment on study.

The secondary end points included OS (time between randomization and death), progression-free survival (PFS; time between randomization and death or disease progression), response rate [RR; proportion of patients with complete response (CR) or partial response (PR) by RECIST v1.1], disease control rate [proportion of patients with CR, PR, or stable disease (SD) by RECIST v1.1], and tolerability. Exploratory analysis was planned for efficacy end points by tumor PSCA expression and for incidence of anti-AGS-1C4D4 antibodies. Data analysis was planned for after 165 deaths. Although statistical hypothesis tests were pre-planned as one-sided tests, they are reported as two-sided in this paper.

Interim safety evaluations were carried out by an independent Data Safety Monitoring Committee (DSMC) established for this study. No formal statistical stopping rules were predetermined; however, the DSMC was chartered to recommend stopping the trial at any time if a concerning safety signal was identified.

The comparison of 6-month SR between treatment groups is reported with a two-sided Cochran–Mantel–Haenszel (CMH) chi-square test stratified for geographic region [33], and the Clopper–Pearson method for 95% confidence intervals [34]. Stratified Cox proportional hazards models were used to compare treatment arms for OS and PFS; survival probability estimates were calculated using the Kaplan–Meier method and compared with two-sided log-rank tests [35]. Similar analyses were carried out in subgroups defined by PSCA staining. The data-cut off was 8 August 2011.

To investigate whether a possible imbalance in patient characteristics between arms may have influenced the survival results, a Cox regression model was fitted with covariates whose individual univariate log-rank *P* values were ≤0.10. Covariates evaluated in univariate models included age (continuous), sex (male, female), ECOG performance status (0, 1), geographic region (North America, Europe/Russia), location of primary tumor (head, other site), liver metastases (yes, no), prior chemotherapy with gemcitabine (yes, no), prior receipt of radiotherapy (yes, no), and baseline serum CA19-9 (above/below the median). All analyses were carried out with SAS v9.1.3 (SAS Institute, Cary, NC).

results

patients

Between April 2009 and May 2010, 205 patients with metastatic pancreatic adenocarcinoma from 43 clinical centers were randomly assigned to gemcitabine (68 patients) or gemcitabine plus AGS-1C4D4 (137 patients). Five patients randomly assigned to gemcitabine and four patients randomly assigned to gemcitabine plus AGS-1C4D4 did not receive the allocated intervention. Therefore, efficacy and safety analyses included 63 patients randomly assigned to gemcitabine and 133 patients randomly assigned to gemcitabine plus AGS-1C4D4 (CONSORT Diagram). Patient characteristics are described in Table 1.

efficacy

At the time of analysis, 167 of 196 (85.2%) patients had died, and 5 patients remained on treatment (1 patient on the gemcitabine arm and 4 patients on the gemcitabine plus AGS-1C4D4 arm). The study met its primary end point of improvement in 6-month SR. The 6-month SR was 44.4% (95% CI, 31.9–57.5) in the gemcitabine arm and 60.9% (95%

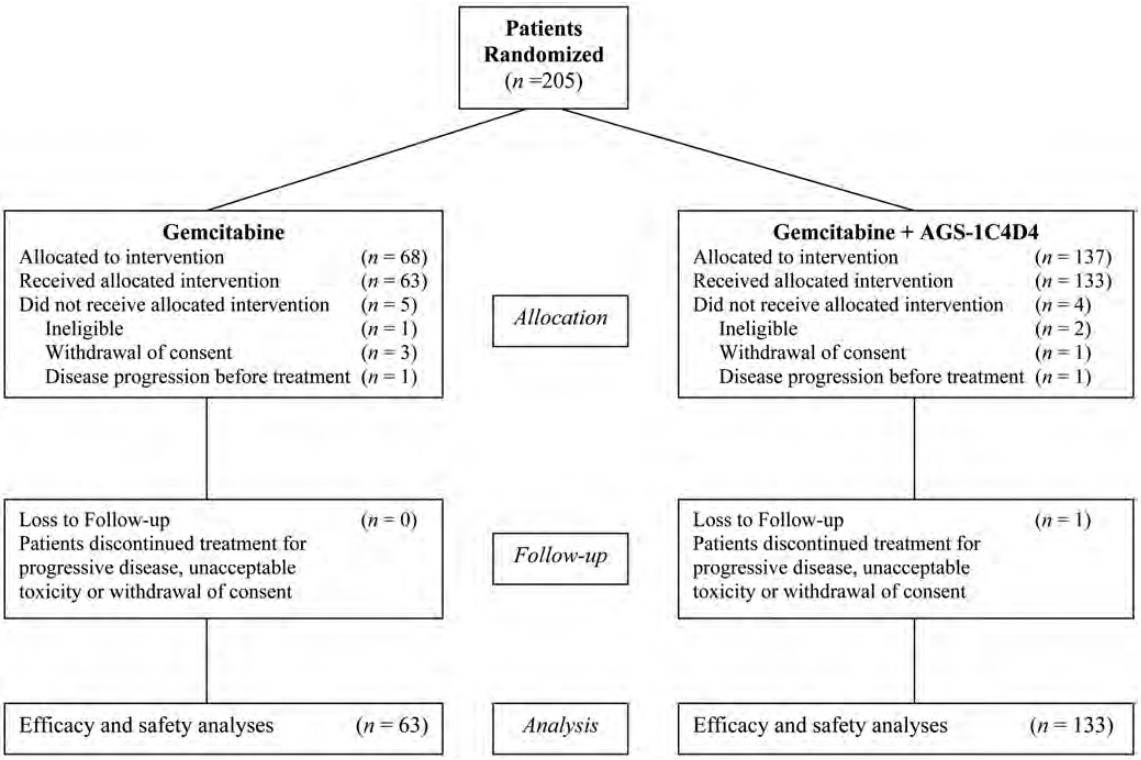

Table 1. Patient demographic and clinical characteristics

Characteristic	Gemcitabine ($n = 63$)		Gemcitabine + AGS-1C4D4 ($n = 133$)	
	No.	%	No.	%
Age (years)				
Median	63		62	
Range	37–89		40–88	
Female sex	38	60.3	59	44.4
ECOG PS at screening				
0	11	17.5	35	26.5
1	52	82.5	97	73.5
White race/ethnicity	59	93.7	130	97.7
Geographic region				
United States/Canada	38	60.3	82	61.7
France/Russia/Spain	25	39.7	51	38.3
Location of primary tumor				
Head	36	57.1	66	49.6
Body	10	15.9	30	22.6
Tail	8	12.7	20	15.0
Other/Unknown	9	14.3	17	12.8
Location of metastases				
Lung	17	27.0	30	22.6
Liver	48	76.2	93	69.9
Lymph nodes	25	39.7	62	46.6
Prior treatments				
Pancreatectomy	12	19.0	22	16.5
Chemotherapy	7	11.1	18	13.5
5-Fluorouracil	3	4.8	9	6.8
Gemcitabine	3	4.8	12	9.0
Radiotherapy	6	9.5	17	12.8
Baseline serum CA19–9 (U/ml)				
Median range	2445.0 (4–266 984)		2771.5 (4–1 750 000)	

ECOG PS, Eastern Cooperative Oncology Group performance status

Table 2. Six-month survival rate by treatment arm and tumor PSCA expression

Population	Gemcitabine	Gemcitabine + AGS-1C4D4	*P* value[b]
Primary end point			
All patients			
No. of patients	63	133	
Six-month SR (95% CI)	44.4% (31.9–57.5)	60.9% (52.1–69.2)	0.03
Tumor PSCA expression[a]			
PSCA-positive			
No. of patients	21	44	
Six-month SR (95% CI)	57.1% (34.0–78.2)	79.5% (64.7–90.2)	0.06
PSCA-negative			
No. of patients	19	39	
Six-month SR (95% CI)	31.6% (12.6–56.6)	46.2% (30.1–62.8)	0.29
PSCA unknown			
No. of patients	23	50	
Six-month SR (95% CI)	43.5% (23.2–65.5)	56.0% (41.3–70.0)	0.32

6-month SR (95% CI), 6-month survival rate (95% confidence intervals).

[a]Tumor staining for PSCA evaluated by immunohistochemistry (IHC) and described using a semi-quantitative H-score. Tumors with an H-score of ≥100 were defined as PSCA-positive.

[b]Two-sided *P* value by a Cochran–Mantel–Haenszel chi-square test stratified by geographic region.

PSCA, prostate stem cell antigen.

Table 3. Summary of efficacy results for secondary end points

Efficacy end point	Gemcitabine ($n = 63$)		Gemcitabine + AGS-1C4D4 ($n = 133$)	
	No.	%	No.	%
Overall survival (OS)				
Median, months	5.5		7.6	
Hazard ratio (95% CI)	0.78 (0.56–1.07)			
Log-rank *P* value	0.12			
Progression-free survival (PFS)				
Median, months	3.2		3.8	
Hazard ratio (95% CI)	0.84 (0.61–1.15)			
Log-rank *P* value	0.27			
Best overall response[a]	($n = 61$)		($n = 125$)	
CR	0	0	0	0
PR	8	13.1	27	21.6
SD	28	45.9	53	42.4
PD	15	24.6	25	20.0
Clinical progression/death	6	9.8	12	9.6
Inadequate assessment[b]	4	6.6	8	6.4
Response rate (CR + PR)		13.1		21.6
Disease control rate (CR + PR + SD)		59.0		64.0

[a]Among patients with measurable disease at baseline.

[b]Includes patients who did not have objective tumor assessments and withdrew for reasons other than disease progression or death.

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

CI, 52.1–69.2) in the gemcitabine plus AGS-1C4D4 arm (CMH $P = 0.03$; Table 2).

Median OS was 5.5 months for patients receiving gemcitabine versus 7.6 months for those receiving gemcitabine plus AGS-1C4D4 [hazard ratio (HR), 0.78; 95% CI, 0.56–1.07; log-rank *P* value, 0.12; Table 3 and Figure 1A]. Median PFS was 3.2 months *versus* 3.8 months (HR, 0.84; 95% CI, 0.61–1.15; log-rank *P* value, 0.27), while RR was 13.1% *versus* 21.6% (Table 3 and Figure 1B). Our multivariable-adjusted Cox model for OS additionally included ECOG performance status, baseline serum CA19-9 and presence of liver metastases. After inclusion of these factors in the model, the HR for OS comparing the two treatment arms was 0.82 (95% CI, 0.62–1.08), favoring gemcitabine plus AGS-1C4D4. Patients

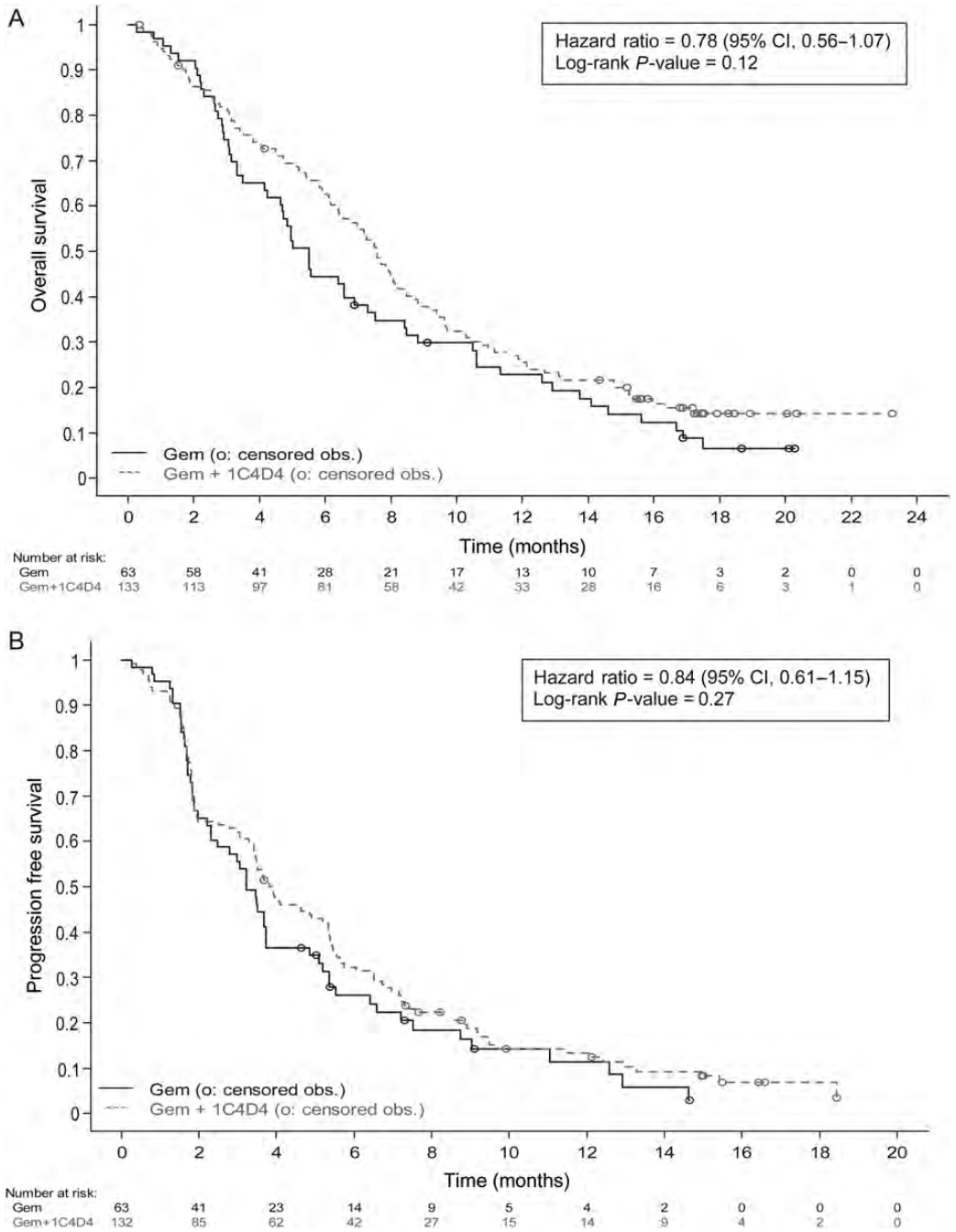

Figure 1. Duration of (A) overall survival (OS) and (B) progression-free survival (PFS) by treatment arm. (A) OS. (B) PFS.

remained on study treatment for a median of 3.6 months in the gemcitabine arm and 4.3 months in the gemcitabine plus AGS-1C4D4 arm.

tumor PSCA expression

Among 123 patients with available tumor, 65 (53%) had tumors that were positive for PSCA cell surface staining defined by an H-score of ≥100. Although patient numbers were limited for these exploratory analyses, the survival time appeared longer among patients receiving gemcitabine who had PSCA-positive tumors *versus* those who had PSCA-negative tumors (Table 2; Figure 2A), indicating a possible prognostic effect of this marker. However, the HRs for OS comparing the two treatment arms were similar in PSCA-positive (HR, 0.83; 95% CI 0.46–1.48) and PSCA-negative (HR, 0.83; 95% CI, 0.47–1.50) groups, suggesting that tumor staining for PSCA by IHC, as defined by an H-score of ≥100, may not be predictive of treatment benefit from AGS-1C4D4 (Figure 2B).

tolerability

Grade 3/4 treatment-emergent adverse events (TEAEs) are summarized in Table 4. Grade 3/4 TEAEs were seen in 40

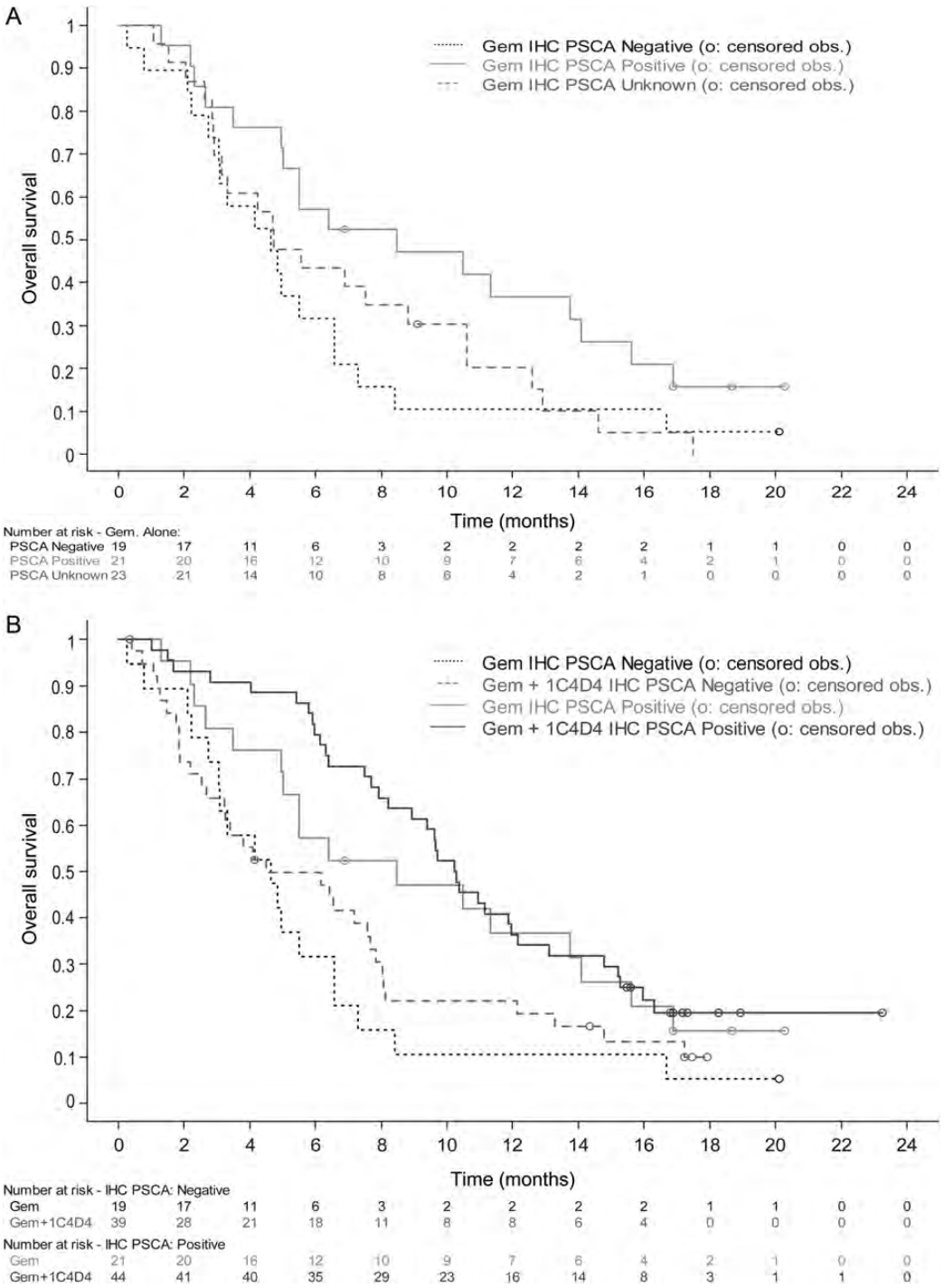

Figure 2. Overall survival (OS) of patients receiving (A) gemcitabine and (B) gemcitabine versus gemcitabine plus AGS-1C4D4 by tumor PSCA staining. (A) Gemcitabine arm only. (B) Gemcitabine arm and gemcitabine plus AGS-1C4D4 arm.

(63.5%) patients on the gemcitabine arm and 105 (78.9%) patients on the gemcitabine plus AGS-14D4 arm, although no specific toxicity signal was evident in the gemcitabine plus AGS-1C4D4 arm. Three (2.3%) patients had a grade 1 and five (3.8%) patients had a grade 2 infusion reaction attributed to AGS-1C4D4. One patient with a grade 2 infusion reaction opted to discontinue AGS-1C4D4 and remained on gemcitabine. No patients receiving AGS-1C4D4 developed antibodies to the drug.

All-cause 60-day mortality was 7.9% in the gemcitabine arm and 13.5% in the gemcitabine plus AGS-1C4D4 arm. The number of deaths that occurred during treatment or within 30 days of the last treatment was 11 (17.5%) on the gemcitabine arm and was 23 (17.3%) on the gemcitabine plus AGS-1C4D4 arm.

Table 4. Grade 3/4 treatment-emergent adverse events by treatment arm

Treatment-emergent adverse events (frequency ≥5%)	Gemcitabine ($n = 63$)		Gemcitabine + AGS-1C4D4 ($n = 133$)	
	No.	%	No.	%
Hematologic				
Anemia	2	3.2	9	6.8
Neutropenia	4	6.3	11	8.3
Thrombocytopenia	1	1.6	7	5.3
Non-hematologic				
Abdominal pain	1	1.6	13	9.8
Abdominal pain upper	5	7.9	4	3.0
Ascites	1	1.6	11	8.3
Asthenia	4	6.3	16	12.0
Bile duct obstruction	3	4.8	8	6.0
Fatigue	7	11.1	12	9.0
Hyperbilirubinemia	5	7.9	7	5.3
Hyperglycemia	1	1.6	8	6.0
Pulmonary embolism	2	3.2	8	6.0
Vomiting	4	6.3	4	3.0
Any grade 3/4 adverse event	40	63.5	105	78.9

discussion

This large, global, randomized, phase II trial evaluating the addition of AGS-1C4D4 to gemcitabine met its primary end point of improved 6-month SR in patients with previously untreated, metastatic pancreatic adenocarcinoma. Specifically, the 6-month SR was 44.4% in the gemcitabine alone arm and 60.9% in the gemcitabine plus AGS-1C4D4 arm ($P = 0.03$). Data from the study's secondary end points, including OS, PFS and RR, were also suggestive of benefit from the addition of AGS-1C4D4 to gemcitabine; however, definitive conclusions are limited in the context of a phase II study.

Multiple clinical trials have attempted to improve upon the efficacy of single-agent gemcitabine in patients with metastatic pancreatic cancer by the addition of a second cytotoxic chemotherapy or targeted therapy [4–12]. In many instances, preclinical data and a single-arm phase II study appeared promising, but the subsequent randomized, phase III trial did not confirm a significant improvement in survival. The current study enrolled a larger number of subjects to include a randomized, control group, which received gemcitabine alone. This study design has the advantages of reducing selection bias and allowing for the formal comparison of an intermediate end point (such as 6-month SR), with the goal of more reliably determining the appropriateness of a subsequent randomized, phase III study [36]. Furthermore, in the current study, survival of patients on the gemcitabine alone arm was comparable with that in several recent randomized, phase III trials [6, 10, 11], lowering the likelihood that patient selection was primarily responsible for the improved survival in the gemcitabine plus AGS-1C4D4 arm. Specifically, the median OS in the gemcitabine plus placebo arm was 5.9 months in NCIC CTG PA.3 [6], SWOG-S0205 [11], and CALGB 80303 [10], with 24%, 22%, and 16% of patients, respectively, on these trials having locally advanced disease. In the current study, the median OS in the gemcitabine arm was 5.5 months, with all patients required to have distant metastases.

As suggested by data from prior phase I studies in prostate cancer [30, 31], toxicity due to AGS-1C4D4 appeared modest, with similar adverse event rates in the gemcitabine and gemcitabine plus AGS-1C4D4 arms. It is believed that PSCA has limited normal tissue expression [18], which may reduce the incidence of on-target, non-tumor effects and is currently being exploited for novel imaging approaches and immune-based therapies [23, 37]. Additionally, safety data were followed during the study by an independent DSMC and no concerning toxicity signal emerged. This manageable toxicity profile is of particular importance in patients with metastatic pancreatic cancer, as they are commonly symptomatic from their disease.

The mechanisms by which PSCA may promote malignant transformation and progression remain to be defined. It is a member of the Thy-1/Ly-6 family of GPI-linked surface proteins, which have no transmembrane domain, and PSCA has no known ligand [16, 17]. Nevertheless, GPI-linked proteins appear to participate in a diverse array of cellular functions, including signal transduction, cell–cell adhesion and immune modulation [38]. Furthermore, a growing number of preclinical studies have demonstrated the ability of PSCA-targeted therapy to inhibit tumor growth and spread, including in models of pancreatic cancer [21–25].

We obtained adequate tumor specimens from 123 patients enrolled on study. Among the collected specimens, 53% were positive for PSCA cell surface staining, as defined by an H-score of ≥100. This H-score was assigned to each tumor specimen by a pathologist blinded to treatment assignment and the cut-off for a 'positive' score was determined before analysis of the data. This rate of PSCA 'positive' tumors is slightly lower than that seen in a limited number of other studies, in

which rates ranged from 60% to 80% [19, 21, 22]. However, the methods used to define PSCA positivity varied across these studies and further work is necessary to better define what constitutes a PSCA-positive tumor.

In a pre-planned exploratory analysis, we investigated tumor PSCA staining as a possible predictive marker for efficacy of AGS-1C4D4. Although patient numbers were limited for this analysis, tumor PSCA staining did not appear to select for those patients who would benefit from AGS-1C4D4, using our predefined definition of PSCA positivity. The HR of death was ~0.80 comparing the two treatment arms in both the PSCA-positive and PSCA-negative subgroups. Further studies of AGS-1C4D4 should address the utility of PSCA staining as a predictive marker by collecting diagnostic tumor specimens from a larger group of patients receiving AGS-1C4D4.

Interestingly, among patients who received gemcitabine, the 6-month SR was higher among those with PSCA-positive tumors (57.1%) versus those with PSCA-negative tumors (31.6%). These data would suggest that tumor PSCA staining may act as a prognostic marker, independent of treatment with AGS-1C4D4. However, this analysis was not pre-planned and any prognostic value of PSCA staining must be confirmed in additional populations.

A role for the PSCA in tumorigenesis has also been suggested in large studies evaluating germline genetic variants and risk of bladder and gastric cancers [26–28]. A missense SNP (rs2294008) in the first exon of *PSCA* was associated with cancer risk and functional evaluation suggested that the rs2294008 SNP modulated transcriptional activity of the *PSCA* promoter [26, 27, 29]. Whether this SNP is associated only with the risk of cancer or whether it may also impact survival of patients with cancer remains to be determined [39]. We did not collect germline DNA in the current trial, so exploratory studies of germline PSCA variants and survival were not possible. Nevertheless, this is an interesting area for further study. Of note, several GWASs of pancreatic cancer have not identified germline *PSCA* variants as related to risk, although the sample sizes of these studies have been somewhat modest [40–42].

In sum, this large, global, randomized, phase II trial evaluating the addition of AGS-1C4D4 to gemcitabine met its primary end point of improved 6-month SR in patients with previously untreated, metastatic pancreatic adenocarcinoma. These data support further research involving AGS-1C4D4 in pancreatic cancer, with the hope of improving outcomes for patients with this highly lethal malignancy.

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disclosure

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