Name of Sponsor:	Agensys, Inc.
Name of Finished Product:	AGS-1C4D4
Name of Active Ingredient:	Human $IgG_1\kappa$ monoclonal antibody to human prostate stem cell antigen
Title of Study:	A Global, Multicenter, Open-label, Phase 2 Study of AGS-1C4D4 Given in Combination with Gemcitabine in Subjects with Metastatic Pancreatic Cancer
Investigators and Study Centers:	This was an international multicenter study in which 42 investigational sites participated.
Publication(s):	Wolpin BM, O'Reilly EM, Ko YJ, et al. Global, multicenter, open-label, randomized phase II trial of gemcitabine and gemcitabine plus AGS-1C4D4 in patients with previously untreated, metastatic pancreatic cancer. Ann Oncol 2013 (in press)
Study Period:	27 April 2009 (first subject dosed) through 23 April 2012 (last subject visit)
Development Phase:	Phase 2

Objectives:

The primary objective of this study was to evaluate the 6-month survival rate of subjects with metastatic pancreatic cancer who were treated with AGS-1C4D4 plus gemcitabine compared with subjects given gemcitabine alone. Secondary objectives were to evaluate standard efficacy and safety variables including overall survival and progression-free survival, objective response rate, disease control, changes in the serum marker CA19-9, the effects of PSCA expression on efficacy outcomes, and the immunogenicity of AGS-1C4D4.

Methodology:

Multicenter, open-label, randomized, comparative Phase 2 study in subjects with metastatic pancreatic cancer. Subjects were randomized in a 1:2 ratio to receive either gemcitabine alone (Arm 1) or gemcitabine plus AGS-1C4D4 (Arm 2), stratified by geographic region

Subjects Planned:	185
Subjects Randomized:	205 (196 were treated: 63 in Arm 1 and 133 in Arm 2)
Sex:	50.5% male, 49.5% female
Mean (Range) Age:	62 (37, 89) years
Ethnicity (Race):	96.4% white, 1.5% black, 1.0% Asian, 1.0% other

Diagnosis and Main Criteria for Eligibility:

Pathologically confirmed measurable or nonmeasurable metastatic adenocarcinoma of the pancreas (AJCC Stage IV) other than islet cell neoplasms; ECOG performance status of 0 or 1;

adequate hematologic, renal, and hepatic function; no prior systemic therapy for metastatic pancreatic cancer (chemotherapy for locally advanced or adjuvant treatment prior to metastatic disease was allowed)

Test Product, Dose and Mode of Administration, Manufacturing Batch Number:

AGS-1C4D4 was supplied as a [colorless liquid in 10 mL vials at a concentration of 10 mg/mL. The total dose of AGS-1C4D4 was diluted in saline and administered as an IV infusion over 60 to 120 minutes. Batch numbers used were [redacted].

Dosage of AGS-1C4D4 consisted of a loading dose of 48 mg/kg as an IV infusion over 60 minutes in Week 1, followed by 24 mg/kg thereafter every 3 weeks (ie, Weeks 4, 7, 10, etc) for the duration of treatment.

Duration of Treatment:

Planned treatment was at least 8 weeks, continuing until disease progression, unacceptable toxicity, or other reasons for treatment discontinuation.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:

Commercial gemcitabine dosed at 1000 mg/m^2 as an IV infusion over 30 minutes once weekly for 7 weeks followed by 1 week of rest, after which dosing was the same dose once weekly for 3 weeks followed by 1 week of rest for the duration of treatment.

Primary endpoint:	Survival rate at 6 months
Secondary endpoints:	Overall survival, progression-free survival, objective tumor response rate (PR or better), disease control rate (stable disease or better), change in CA19-9, standard safety variables

Statistical Methods:

All data were presented by randomized treatment assignment. Subject demographics, disease history, other baseline characteristics, and cumulative drug exposure were summarized using conventional descriptive statistics (mean, standard deviation or standard error as appropriate, median, and range). Number of subjects completing planned treatment and reasons for discontinuation were tabulated.

Efficacy analyses were performed on the Full Analysis Set according to randomized treatment assignment. Six-month survival rate was estimated based on the crude proportion of randomized subjects alive at 6 months from randomization. A confidence interval (CI) for the proportion was calculated using the method of Clopper and Pearson. An inferential comparison between treatment groups was made using a 1-sided Cochran-Mantel-Haenszel chi-square test at the 5% significance level, stratified by geographic region. Relative risks and their CI were estimated using the Mantel-Haenszel method.

Median overall survival, PFS, and duration of response were estimated using the Kaplan-Meier method. Best overall response to treatment was determined for each subject using the RECIST criteria version 1.1. Response rate was calculated as the crude proportion of subjects with a CR or PR. Exact CIs were calculated using the Clopper and Pearson method.

Safety analyses were performed on the Safety Analysis Set (which was identical to the Full Analysis Set) according to actual treatment received. AEs were assigned a preferred term according to the MedDRA dictionary (version 10.1) and subject incidence was tabulated by system organ class, by study drug relatedness, and by CTCAE grade. AEs that were serious,

AEs that led to discontinuation of treatment, and AEs that were fatal were separately tabulated. Laboratory analytes were summarized using descriptive statistics and shift tables; additionally, listings of Grade 3 and 4 laboratory values were prepared.

Efficacy Results:

Crude 6-month survival rate was 60.9% (95% CI: 52.1, 69.2) in Arm 2 vs 44.4% (95% CI: 31.9, 57.5) in Arm 1 (p = 0.0156). The relative risk of death at 6 months for subjects in Arm 2 relative to Arm 1, was 0.70 (90% CI: 0.54, 0.91). For the subjects who were high expressers of PSCA (H-score ≥ 100), 6-month survival rate was 79.5% (95% CI: 64.7, 90.2) in Arm 2 vs 57.1% (95% CI: 34.0, 78.2) in Arm 1 (p = 0.0305). For the low PSCA expressers (H-score < 100), survival rates were shorter in both treatment groups and the between-group difference was not significant. Based on the Kaplan-Meier estimate, median survival was 7.6 months (95% CI: 6.4, 8.4) for Arm 2 vs 5.5 months (95% CI: 4.2, 7.3) for Arm 1 (p = 0.0611).

Using treatment only in a univariate Cox proportional hazards analysis of overall survival, the hazard ratio of death for Arm 2 vs Arm 1 was 0.7777. Baseline characteristics that were statistically significant predictors for death (independent of treatment) were the presence of liver metastases, ECOG score greater than 0, and high CA19-9 values. Using these baseline variables in a multivariate analysis, the hazard ratio of death for Arm 2 vs Arm 1 was 0.822 (95% CI: 0.622, 1.086).

Median PFS based on Kaplan-Meier estimate was 3.8 months for Arm 2 vs 3.2 months for Arm 1; this difference was not statistically significant. The hazard ratio of progressing for Arm 2 vs Arm 1 based on univariate Cox analysis was 0.8088, p = 0.097. For Region 1 (US and Canada), however, a treatment effect was seen in PFS, with median PFS of 3.8 months (95% CI: 3.42, 5.45) vs 3.0 months (95% CI: 1.97, 3.68) for Arms 2 vs 1, respectively (p = 0.0181).

Partial responses were attained in 22.4% of subjects in Arm 2 (95% CI: 15.4, 30.7) vs 13.1% in Arm 1 (95% CI: 5.8, 24.2); there were no complete responses. The relative risk for achieving an objective response with AGS-1C4D4 was 1.71 (90% CI: 0.93, 3.13). Duration of objective response showed little between-group difference: 3.8 weeks for Arm 2 (95% CI: 3.7, 7.3) vs 4.2 weeks for Arm 1 (95% CI: 1.7, 7.4).

Slightly more subjects in Arm 2 displayed a decrease in CA19-9 during treatment compared with Arm 1: 79.5% vs 75.0%.

Safety Results:

Median cumulative exposure to AGS-1C4D4 for subjects in Arm 2 was 10.92 g (range: 1.69, 76.8). Subjects in Arm 2 received a higher median cumulative dose of gemcitabine relative to Arm 1 (18.9 vs 16.3 g, respectively), reflecting the longer duration on treatment (14.1 vs 10.6 weeks, respectively).

Higher incidences in Arm 2 relative to Arm 1 were seen in neutropenia, dyspnea, asthenia, and nausea. Grade 3 or 4 AEs were generally uncommon; those occurring more frequently in Arm 2 were neutropenia and asthenia. AEs that were considered related to AGS-1C4D4 occurred in 65.4% of Arm 2 subjects, the most common being fatigue, nausea, anemia, and vomiting. Serious AEs occurred in approximately 49% of subjects in both treatment groups. No treatment-emergent cardiac abnormalities were apparent in the ECG data. Possible infusion reactions to AGS-1C4D4 were associated with 10 infusions among 8 subjects. One subject tested seropositive for antibodies to AGS-1C4D4. Approximately 18% of subjects in both treatment groups died on, or within 30 days of, treatment discontinuation—most a consequence of disease progression. No patterns emerged in the causes of nonprogression-related deaths.

Possible treatment-emergent adverse shifts in serum chemistries were observed for ALT, AST, glucose, and uric acid (all in the increasing direction), with a higher proportion of grade shifts and/or postbaseline Grade 3/4 values in Arm 2 relative to Arm 1. Between-group differences in

hematologic toxicity were observed in neutrophils, lymphocytes, and platelets. The proportion of subjects with postbaseline Grade 3 or 4 hematology values in Arm 2 was approximately twice that as in Arm 1, perhaps due in part to the longer duration of treatment.

Date of the Report: 29 March 2013; Conclusions and End of Text Tables /Figures removed for posting 09 May 2013