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PAREXEL International

Halozyme, Inc.

HALO-109-301

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) in Combination with nab-Paclitaxel Plus Gemcitabine Compared with Placebo Plus nab-Paclitaxel and Gemcitabine in Subjects with Hyaluronan-High Stage IV Previously Untreated Pancreatic Ductal Adenocarcinoma

Statistical Analysis Plan

Version Number: 4.0 (Amendment 3)

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Approved by:

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Date

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LIST OF ABBREVIATIONS

ADI	Actual Dose Intensity
AE	Adverse events
AG	NAB plus GEM treatment
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BILI	Bilirubin
BLQ	Below the Limit of Quantitation
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA19-9	Cancer Antigen 19-9
CI	Confidence Interval
CIV	Central Imaging Vendor
CMH	Cochran-Mantel-Haenszel
CP	Conditional Power
CR	Complete Response
CRP	C-Reactive Protein
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DOR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30
EQ-5D	European Quality of Life – 5 Dimension Scale
FDA	Food and Drug Administration
GEM	Gemcitabine
HA	Hyaluronan
HR	Hazard Ratio
KM	Kaplan–Meier
IA	Interim Analysis
INR	International Normalized Ratio
iSAP	Interim Statistical Analysis Plan
ITT	Intent-to-treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging

MSE	Musculoskeletal Events
NAB	nab-Paclitaxel
NEC	Not Elsewhere Classified
NCI	National Cancer Institute
NRS	Numerical Rating Scale
ORR	Objective Response Rate
OS	Overall Survival
PAD	Planned Adjusted Dose
PAG	PEGPH20 plus NAB plus GEM Treatment
PDA	Pancreatic Ductal Adenocarcinoma
PEGPH20	PEGylated Recombinant Human Hyaluronidase
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient Reported Outcome
PT	Prothrombin Time
PTT	Partial Prothrombin Time
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TE	Thromboembolic Event
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal Range
ULQ	Upper Limit of Quantification

SUMMARY OF CHANGES FROM VERSION 3.0 TO VERSION 4.0

The statistical analysis plan is amended for the following two changes:

Clarification of Data Cut-off for Final Analysis

The sponsor's intention was to conduct the final OS analysis after 330 OS events have been observed and all subjects have been at least 8.5 months post randomization, as referred to in the FDA minutes from the teleconference on November 13, 2018 (FDA Reference ID: 4350039). Given the last subject was randomized on December 26, 2018, the data cut-off date for final OS analysis would need to be September 10, 2019 so that all subjects will be at least 8.5 months post randomization.

When it became apparent that the calendar date for obtaining 330 OS events would be several months in advance of September 10, 2019, the sponsor proposed to the FDA that the primary analysis be conducted at this later time. However, the FDA considered the pre-specified primary analysis to be at the calendar date when 330 OS events had occurred per FDA advice on August 15, 2019 (FDA reference ID: 4477738), as shown below:

- In general, the timing of efficacy analyses for time-to-event endpoints should be event-driven. Additionally, there was no adaptive design plan in place and we do not agree with changing the number of events for the final analysis at this point in the trial. Therefore, we will consider the analysis of overall survival (OS) based upon the prespecified number of the events (330 deaths) to be the final primary efficacy analysis in support a future Biologics Licensing Application (BLA) submission.

- Halozyme may provide an updated OS analysis based upon the proposed additional follow-up time; these results will be considered as supportive information.

Per the FDA advice above, two OS analyses will be conducted, one at 330 deaths and the other at the data cut-off date on September 10, 2019. The OS analysis at 330 deaths will be considered as the primary analysis, and the OS analysis at the data cut-off date on September 10, 2019 will be considered supportive.

Section 4.2.4 is added to specify the data cut-off criteria for the final analysis and the additional supportive OS analysis as follows.

The final analysis will be based on the pre-specified 330 OS events (deaths):

- All data up to the date when the 330th death occurred will be entered, cleaned, locked, and included as the source data for future BLA submission.
- All final analyses will be conducted using the locked data based on the data cut-off date when the 330th death occurred.

In addition, a supportive OS analysis will be conducted using the data based on the data cut-off date of September 10, 2019. All data up to September 10, 2019 will be entered and cleaned for this supportive OS analysis.

Addition of Subgroup Analysis

Per FDA preliminary meeting comments on July 19, 2019 (FDA Reference ID: 4465249), the FDA requested to assess results in subgroups enrolled based on impacted and based on non-impacted lots of the HA Detection Kit (OptiView DAB IHC Detection Kit) to assess potential differences in treatment effects in these two subgroups, although the Agency stated that enrollment based on results of impacted lots of the HA Detection Kit is unlikely to affect the interpretability of data. Thus, the following subgroup analysis is added:

- Subjects enrolled using impacted lots due to potential leaking and sticking of reagent dispensers of the HA Detection Kit (OptiView DAB IHC Detection Kit): Yes and No

SUMMARY OF CHANGES FROM VERSION 2.0 TO VERSION 3.0

The statistical analysis plan is amended to reflect changes made to protocol amendment 5 (January 10, 2019). The major changes include revising progressive free survival (PFS) from a primary endpoint to a secondary endpoint, removal of the interim efficacy analysis, and conduct of the final overall survival (OS) analysis after 330 deaths have occurred. Accordingly, the overall Type I error control is modified.

- Overall Type I error control
    - The 2-sided alpha of 0.05 is assigned to OS.
    - PFS will be tested at the 2-sided significance level of 0.05 only if OS is statistically significant.
    - ORR will be tested at the 2-sided significance level of 0.05 only if both OS and PFS are statistically significant.

In addition, the following changes or clarifications are made:

- Clarify that deaths within 14 days of randomization without disease progression are considered as PFS events.
- Clarify that deaths within 14 days of last dose of study treatment or randomization are considered as events in duration of response analysis.
- Add language for excluding study data from all analyses for study sites closed with cause due to serious GCP compliance issues.
- Clarify the treatment assignment in the Safety Population for subjects who received both PAG (PEGPH20 combined with NAB plus gemcitabine) and AG (NAB plus gemcitabine) treatments.
- Simply calculation for the average dose intensity and relative dose intensity.
- Add and modify analyses for some safety parameters.

SUMMARY OF CHANGES FROM VERSION 1.0 TO VERSION 2.0

The statistical analysis plan is amended to reflect changes made in protocol amendment 3 (February 27, 2017).

Sample Size

The following changes are made based on the relatively lower progression-free survival (PFS) event rate observed in the Phase 2 study, HALO-109-202.

- Added language allowing enrollment to continue beyond 420 subjects up to a maximum of 570 total subjects before completion of interim efficacy analysis.
- Removed the projected timeline for target number of PFS and overall survival (OS) events.

Type I Error Control

According to the US Food and Drug Administration (FDA) Guidance for Industry on Multiple Endpoints in Clinical Trials (January 2017), the overall type I error control for two primary efficacy endpoints, PFS and OS, was modified.

- If the final PFS at the interim is significant at the alpha level of 0.01, the alpha of 0.01 assigned to the final PFS at the interim will be passed to the final OS based on the fallback method so that the final OS analysis will be conducted at the significance level of 0.05; otherwise, the final OS analysis will be conducted at the significance level of 0.04.

Analysis Population

- Because the number of subjects who are randomized but do not receive any study medication is expected to be small in this double-blinded study, the modified Intent-to-Treat population, which excludes subjects who do not receive any study medication, was removed.

Statistical Analyses

- Efron's method of handling ties is added to pre-specify the details for hazard ratio and 95% CI estimation in the Cox proportional hazard model for PFS and OS analyses.
- More details are added to the sensitivity analysis for PFS.
- Subgroup analyses for PFS and OS are added
- Data listing for subjects who met Hy's law criteria are added
- Treatment exposure analyses are clarified.
- More analyses on ECG are added.

1 INTRODUCTION

HALO-109-301 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of the PEGylated Recombinant Human Hyaluronidase (PEGPH20) in combination with nab-Paclitaxel (NAB) plus Gemcitabine (GEM) compared with placebo plus NAB and GEM in subjects with Hyaluronan (HA)-High stage IV previously untreated pancreatic ductal adenocarcinoma (PDA). This statistical analysis plan (SAP) details the planned analyses required for a clinical study report based on the protocol HALO-109-301 amendment 5 dated 10 January 2019.

The addition of PEGPH20 to AG therapy in subjects with HA-high tumors will be evaluated with overall survival (OS) as the primary endpoint in this registrational Phase 3 study.

This statistical analysis plan (SAP) outlines the final analyses that will be performed after 330 deaths have been reached. Analysis populations, data handling rules, statistical methods, and formats for data presentation are provided.

An independent Data Monitoring Committee (DMC) is responsible for periodically reviewing safety data to protect subject welfare and identify potential safety signals. Operational and logistical details are provided in the HALO-109-301 DMC charter. No interim efficacy analysis will be conducted.

The statistical analyses and summary tabulations described in this SAP provide the basis for the reporting of results for the final analysis of safety and efficacy for this trial.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

- To determine the OS benefit of PEGPH20 combined with NAB plus gemcitabine (GEM) (PAG treatment), compared with placebo plus NAB/GEM (AG treatment), in subjects with HA-high Stage IV previously untreated PDA.

2.1.2 Secondary Objectives

- To determine the PFS benefit of PAG treatment, compared with AG treatment, in subjects with HA-high Stage IV previously untreated PDA.
- To determine the ORR and DOR of PAG treatment, compared with AG treatment, in subjects with HA-high Stage IV previously untreated PDA.
- To assess the safety and tolerability of PAG treatment in subjects with HA-high Stage IV previously untreated PDA.

2.1.3 Exploratory Objectives

- To assess the treatment effect of PAG on serum levels of cancer antigen 19-9 (CA19-9).
- To assess the treatment effect of PAG on HA levels and other potential biomarkers in plasma and tumor biopsies (when available).
- To assess the pharmacokinetics (PK) of PEGPH20 in combination with NAB plus GEM.

- To assess the potential effect of PEGPH20 on the PK of NAB and GEM.
- To assess the impact of PAG treatment on patient-reported outcomes (PROs) including health-related quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30); other health outcomes using the European Quality of Life-5 Dimension Scale (EQ-5D); and symptoms related to pancreatic cancer and to treatment-associated toxicities using a Numerical Rating Scale (NRS).

2.2 Study Endpoints

2.2.1 Primary Endpoint

- OS

2.2.2 Secondary Endpoints

- PFS
- ORR
- DOR
- Incidence of AEs, changes in clinical safety laboratory values, and changes in cardiovascular parameters (ECG and vital signs)

2.2.3 Exploratory Endpoints

- Change in serum CA19-9 levels
- Change in plasma and tumor biopsy(when available) HA levels and other potential biomarkers
- Pharmacokinetics of PEGPH20 in combination with NAB plus GEM
- Pharmacokinetics of NAB and GEM in the PAG group versus the AG group
- Patient-reported outcome measures including the EORTC QLQ-C30, EQ-5D, and NRS

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter study to compare the efficacy and safety of PAG versus AG treatment in subjects with Stage IV previously untreated PDA whose tumors are HA-high. For the purposes of this study, randomized study medication is defined as PEGPH20 or placebo; and study medications are defined as PEGPH20, placebo, NAB, and GEM.

This study involves a Screening Period to assess eligibility and eligible subjects will be randomized in a double blinded fashion to two treatment groups in a 2:1 ratio:

- PAG Group: PEGPH20 (3.0 μg/kg) + NAB (125 mg/m^2) + GEM (1000 mg/m^2)
- AG Group: Placebo + NAB (125 mg/m^2) + GEM (1000 mg/m^2)

Randomization will be stratified by geographic region (North America, Europe, and Other). This study plans to randomize approximately 500 HA-high subjects with previously untreated Stage IV Pancreatic cancer at study sites globally.

The Treatment Period will consist of 4-week treatment cycles (28 days); Week 4 of every cycle will be a rest week (i.e., no treatment will be given). All study medications will be administered via intravenous (IV) infusion. During the first cycle, randomized study medication will be administered twice weekly in Week 1, Week 2, and Week 3. From Cycle 2 and beyond, randomized study medication will be administered once weekly in Week 1, Week 2, and Week 3. For all treatment cycles, NAB and GEM will be administered weekly in Week 1, Week 2 and Week 3.

Treatment will continue until disease progression, unacceptable toxicity, death, or withdrawal of consent. Subjects should return to the study site for an End of Treatment Visit within approximately 7 days after determination of disease progression or after treatment discontinuation for other reasons.

After the End of Treatment Visit, subjects will enter a long-term follow-up, during which information on the subject's survival status and subsequent anticancer therapies will be obtained by the site monthly until the subject dies, is lost to follow-up, or withdraws consent. Information may be collected by chart review, phone calls, clinic visits, or other means as appropriate. Long-term follow-up will continue until the subject dies, is lost to follow-up, or withdraws consent.

Refer to the study protocol for details of study procedures and assessments.

3.2 Efficacy and Safety Variables

Efficacy will be assessed through the primary and secondary endpoints of OS, PFS, ORR and DOR. Safety and tolerability will be assessed via incidence of AEs and changes in clinical safety laboratory values.

Tumor response will be assessed using RECIST version 1.1 criteria (Appendix A). Imaging assessments will be conducted by an independent, blinded Central Imaging Vendor (CIV). Tumor assessments will be performed at the end of Cycle 2 and at the end of every subsequent second treatment cycle after the last dose or the following week (i.e., Days 15 to 28 of Cycles 2, 4, 6, 8, and beyond), to allow time for reading of the scans by the CIV prior to the start of subsequent cycles. At the End of Treatment Visit, a CT scan will be obtained if radiologic disease progression was not documented in the previous CT scan unless the latter was performed within the last 14 days.

Toxicities will be graded by the Investigator using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (at time of study initiation).

Safety parameters monitored and recorded during this study include adverse events (AEs); serious adverse events (SAEs); medical history; concomitant medications; immunogenicity (PEGPH20 ADA), hematology, blood chemistry, coagulation, and urinalysis results; physical examination findings; vital signs; ECG results; pregnancy test results; and ECOG Performance Status (Appendix B).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings will be independently checked for accuracy, consistency, and integrity in accordance with standard PAREXEL procedures.

An audit may be performed at any time by Halozyme personnel or their designees, Food and Drug Administration (FDA), or other regulatory agencies. All study-related documentations must be made available to the designated auditors.

The study protocol, each step of the data recording process, and data handling, as well as any study reports or publications, will be subject to independent review by Halozyme or its representatives.

4.2 General Statistical Considerations

4.2.1 General Presentation

In general, continuous variables will be summarized using descriptive statistics (N, mean, standard deviation (SD), median, minimum (min), maximum (max), and quartiles). The mean, median and quartiles will be presented to 1 decimal place greater than the original data; the standard deviation will be presented to 2 decimal places greater than the original data; and the minimum and maximum will have the same number of decimal places as the original data. Categorical variables will be summarized using frequencies and percentages. Percentages will be rounded to 1 decimal place except for 100%, which will have no decimal place. Results will be displayed for the two treatment groups as well as the two groups combined (total).

All statistical analyses will be performed using SAS® Statistical software Version 9.3 or higher.

4.2.2 Baseline Definition

Baseline is defined as the last measurement prior to dosing on Day 1 of Cycle 1. If parameters are not measured prior to dosing on Day 1 in Cycle 1, then the most recently measured values prior to Cycle 1 Day 1 will be considered baseline. For subjects who are randomized but not dosed after randomization, the baseline is defined as the last measurement on or prior to the date of randomization.

4.2.3 Missing Data

Time to event parameters will be censored for all subjects who do not experience the event of interest (progressive disease or death). In ORR analysis, subjects with no tumor response assessment will be treated as non-responder.

All available efficacy and safety data will be included in data listings and tabulations. In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified. Missing dates will be presented without any imputation in all data listings.

Missing/Partial Dates in Adverse Events

AE stop dates that are partially missing will be imputed as follows:

- If month and year are present but day is missing, the last day of the month will be used to impute the missing day.
- If only year is present but day and month are missing, the 31DEC will be used to impute the missing day and month.

After the imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used instead.

If the AE stop date is completely missing, it will remain missing.

AE start dates that are partially missing will be imputed as follows:

- If month and year are present but day is missing, the first day of the month will be used to impute the missing day unless the month and year are the same as month and year of first dose date. In that case, day of first dose date will be used to impute the missing day.
- If only year is present but day and month are missing, first dose date will be used to impute if the year is same as the year of first dose date, otherwise 01JAN will be used to impute the missing day and month.

If the imputed date is later than the stop date, then the stop date will be used instead.

If AE start date is completely missing, then the first dose date will be used.

Missing/Partial Dates Concomitant Medication and Subsequent Therapies

Concomitant medications with start dates that are partially missing will be analyzed as follows:

If the start date has month and year but day is missing, the medication will be included in the summary table if:

- The month and year of the start date of the medication are on or before the month and year of the date of the last dose of study medication plus 30 days.
- The partial or complete medication end date is on or after the first dose date of study medication.

If the start date has year, but day and month are missing, the medication will be included in the summary table if:

- The year of the start date of the medication is on or before the year of the date of the last dose of study medication plus 30 days.
- The partial or complete medication end date is on or after the first dose date of study medication.

If the start date of a medication is completely missing, then the medication will be included in the summary table unless a partial or complete end date is before the first dose date.

Subsequent therapies with start dates that are partially missing will be analyzed as follows:

When month and year are present but the day is missing,

- If the onset month and year are the same as the month and year of last dose of study medication, the day of last dose + 1 will be used to impute the missing day.

- If the onset month and year are not the same as the month and year of last dose of study medication, the first day of the month will be used to impute the missing day.

When only a year is present but month and day are missing,

- If the onset year is the same as the year of last dose with study medication, the date of last dose + 1 will be imputed.
- If the onset year is not the same as the year of last dose with study medication, the first day of the year is imputed.

If the start date of subsequent therapy is completely missing, then the date of last dose + 1 will be used to impute the missing start date.

4.2.4 Data Cut-off Criteria for Final Analysis

Two OS analyses will be conducted, one at 330 deaths and the other at the data cut-off date on September 10, 2019, when all subjects have been at least 8.5 months post randomization. The OS analysis at 330 deaths will be considered as the primary analysis, and the OS analysis at the data cut-off date on September 10, 2019 will be considered supportive.

Therefore, the final analysis will be based on the pre-specified 330 OS events (deaths):

- All data up to the date when the 330th death occurred will be entered, cleaned, locked, and included as the source data for future BLA submission.
- All final analyses will be conducted using the locked data based on the data cut-off date when the 330th death occurred.

In addition, a supportive OS analysis will be conducted using the data based on the data cut-off date of September 10, 2019. All data up to September 10, 2019 will be entered and cleaned for this supportive OS analysis.

4.3 Study Subjects

4.3.1 Disposition of Subjects

Subject disposition data (including analysis populations) will be summarized for each treatment group and overall for all randomized subjects.

Subject disposition will be tabulated for number of subjects randomized, receiving any study treatment, on study treatment, discontinuation from treatment, reasons for discontinuing treatment, on long-term follow-up, and discontinuation from study and reason for discontinuing study.

Enrollment by country and center and the number of subjects randomized to each stratum will also be summarized.

In addition, the screening information (overall) will be displayed, including number of subjects screened, subjects with screening failure, and reasons of screening failure.

4.3.2 Protocol Deviations

Protocol deviations will be identified on an ongoing basis by the clinical study team based on the Protocol Deviation Specification (PDS) document and assessed as “minor” or “major” in consultation with the Sponsor.

Major protocol deviations are defined as those deviations from the study protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for analysis.

Written documentation of all major protocol deviations must be kept in the study site file and provided to Halozyme. For this study, Halozyme major protocol deviations are as follows:

a. Violation of eligibility criteria
b. Dosing errors of study medication(s)
c. Receiving excluded concomitant medications
d. Developed withdrawal criteria but not withdrawn from study treatment
e. Others reasons, as outlined in the most recent version of the PDS document

Details on major and minor protocol deviations, along with actions to be taken for analysis, can be found in the PDS. All protocol deviations will be reviewed and confirmed in blind fashion prior to study unblinding.

A summary of the number and percentage of subjects with major protocol deviations by treatment group and overall and by type of deviation will also be provided. A by-subject listing of major protocol deviations will be provided.

4.4 Analysis Populations

If a study site is closed with cause due to serious GCP compliance issues and the study data cannot be verified, all subjects enrolled in such a study site will be excluded from all analysis populations and all analyses for both efficacy and safety. Halozyme will notify relevant IRB/EC and health authorities of the site's serious non-compliance and the plan for closure of such a study site.

4.4.1 Intent-to-Treat (ITT) Population

All randomized subjects will be included in the ITT Population. The ITT population will be analyzed by treatment randomized. This population will be used for all efficacy analyses as well as for analyses of subject disposition, protocol deviations, and demographic and baseline characteristics.

4.4.2 Safety Population

All subjects who receive any study medication will be included in the Safety Population. The Safety population will be analyzed by treatment received. Subjects who received both PAG and AG treatments will be assigned to the PAG treatment.

This population will be used for all safety analyses as well as for demographic and baseline characteristics.

4.4.3 PK Analysis Population

The PK population includes all subjects who receive any part of a dose of PEGPH20 and have at least 1 measurable PEGPH20 concentration. This population will be used for all PK Analysis of PEGPH20.

All subjects who receive any part of a dose of NAB and GEM in both treatment groups (PAG and AG) and have at least 1 measurable NAB and GEM concentration will be included in the PK Analysis Population for the PK analysis of NAB and GEM.

Blood samples for the aforementioned analyses deemed to be below the limit of quantitation (BLQ) will be included in the PK analyses, and the BLQ value will be handled accordingly by the modeling software.

4.5 Demographic and Other Baseline Characteristics

4.5.1 Demographics

Demographics and baseline characteristics will be summarized using both ITT and Safety Populations. The following demographic and baseline characteristics will be summarized by treatment group: age, age group (<65 and >=65; <75 and >=75), sex, race, ethnicity, geographic region, country, height, weight, BSA, and ECOG performance status.

A listing of demographic and baseline characteristics will be provided

4.5.2 Medical History

Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT) using frequencies and percentages on the ITT population. A listing of medical history will be provided.

4.5.3 Pancreatic History

Pancreatic cancer history will be summarized using descriptive statistics on the ITT population. The summary will include time from Stage IV diagnosis to randomization, sites of metastasis, primary tumor location within pancreas, biliary stents, and previous history of pancreatic cancer stage I-III. A listing of pancreatic cancer history will be provided.

4.5.4 Prior Cancer Treatment

All prior cancer treatments will be summarized using the ITT population.

Prior cancer therapies/medications will be summarized by type of treatment, WHO Drug standard medication preferred name. Prior cancer surgeries will be summarized by SOC and PT using frequencies and percentages. Prior cancer radiation treatments will be summarized by tumor location and total dose received. Prior cancer treatments will be listed.

4.6 Efficacy Evaluation

All efficacy analyses will be conducted using the ITT population.

4.6.1 Analysis and Data Conventions

This study is designed to test for superiority. The null hypothesis for the treatment comparison will be that there is no difference between PAG and AG treatment for the primary endpoint. The alternative hypothesis will be that there is a difference. The null (H_0) and alternative (H_A) hypotheses for the primary endpoint are expressed as follow:

- H_0: The OS of PAG vs. AG in subjects with Stage IV previously untreated PDA is equal.
- H_A: The OS of PAG vs. AG in subjects with Stage IV previously untreated PDA is not equal.

The OS comparisons of the 2 treatment groups above will be based on the stratified log-rank test stratified by the randomization stratification factor (i.e., geographic location) at the 2-sided significance level of 0.05.

4.6.2 Multi-center Studies

Each study center is expected to enroll an average of fewer than five patients. Analysis of data by study center would be unlikely to be informative; thus data from all participating centers will be pooled for analysis. However, subgroup analysis by region (North America, Europe, and other) will be conducted for the primary efficacy endpoint to assess any potential treatment difference by region.

4.6.3 Adjustments for Covariates

The primary and secondary efficacy analyses of OS, PFS, and ORR will be stratified by the randomization stratification factor, i.e., geographic region (North America, Europe, and Other).

No adjustments will be made for covariates.

4.6.4 Handling of Dropouts or Missing Data

Unless otherwise indicated in Section 4.2.3, missing data will not be imputed in the analysis.

4.6.5 Multiple Comparisons/Multiplicity

The overall family-wise type I error for the superiority tests of OS, PFS and ORR will be controlled at 2-sided 0.05 level using the following fixed sequence method (US FDA Guidance, January 2017):

- The 2-sided alpha of 0.05 is assigned to OS.
- PFS will be tested at the 2-sided significance level of 0.05 only if OS is statistically significant.
- ORR will be tested at the 2-sided significance level of 0.05 only if both OS and PFS are statistically significant.

4.6.6 Interim Analysis

No interim efficacy analysis will be conducted.

Interim safety data will be analyzed and evaluated periodically by an independent data monitoring committee (DMC), as described in the DMC charter.

4.6.7 Primary Efficacy Endpoint

The primary efficacy endpoint is overall survival (OS).

OS is defined as the time from randomization until death at any time from any cause. Subjects who are alive at the time of analysis will be censored for OS at the time of the last "known alive" contact date on or prior to data cut-off date if applicable. OS (in months) is calculated as:

$$(\text{Death date or censoring date} - \text{Date of randomization} + 1)/30.44$$

Kaplan-Meier (KM) method will be used to estimate the survival distribution function of OS and will be used to estimate the median OS and its 2-sided 95% CI, the first and third

quartiles, and survival rates at Months 6, 9, 12, 18, and 24 by treatment group. Estimated KM survival curves of OS of the two treatment groups will be displayed graphically.

The OS comparisons of the two treatment groups will be conducted using a 2-sided log-rank test stratified by the geographic region (North America, Europe, and Other). The OS superiority test will be conducted at the 2-sided significance level of 0.05.

The hazard ratio (HR) and its 95% CI for the treatment effect will be estimated using the stratified Cox proportional hazards regression model with Efron's method of handling ties, stratified by the geographic region.

Two OS analyses will be conducted, one at 330 deaths and the other at the data cut-off date on September 10, 2019. The OS analysis at 330 deaths will be considered as the primary analysis, and the OS analysis at the data cut-off date on September 10, 2019 will be considered supportive.

4.6.7.1 Subgroup Analysis

The primary efficacy endpoint of OS will be analyzed for the following subgroups:

- Geographic region: North America, Europe, and Other
- Age: <65 years and ≥65 years; <75 years and ≥75 years
- Sex: Male and Female
- Race: White, Asian, and Other
- Baseline Eastern Cooperative Oncology Group (ECOG) Performance Status: 0 and 1
- Presence of liver metastases: Yes and No
- Subjects enrolled using impacted lots due to potential leaking and sticking of reagent dispensers of the HA Detection Kit (OptiView DAB IHC Detection Kit): Yes and No

The same statistical methods as for the primary analysis will be used for all subgroup analyses. The treatment effect for each subgroup will be presented with the hazard ratio and 95% CI using a forest plot.

4.6.7.2 Subsequent Anticancer Therapy

Subsequent anticancer therapies received after discontinuation of study treatment will be summarized using the ITT population.

Subsequent anticancer therapies/medications will be summarized by WHO Drug standard medication preferred name and best overall response. Subsequent anticancer surgeries will be summarized SOC and PT using frequencies and percentages. Subsequent anticancer radiation treatments will be summarized by tumor location and total dose received. All subsequent anticancer treatments will be listed.

4.6.8 Secondary Efficacy Endpoints

The secondary efficacy endpoints are progression-free survival, objective response rate, and duration of response.

4.6.8.1 Progression-Free Survival (PFS)

PFS is defined as the time from randomization until the earliest occurrence of radiological disease progression as determined by the blinded CIV based on RECIST version 1.1 criteria,

or death from any cause during the treatment period. Subjects with no PFS event by the analysis cut-off date will have their PFS censored at the last evaluable post-baseline tumor assessment day or on Day 1 if they have no post-baseline tumor assessments. PFS (in months) will be calculated as:

(Event date or censoring date - randomization date +1)/30.44

Because the dosing interval between cycles is 14 days (from Day 15 to Day 28 of each cycle), the treatment period will include 14 days after last dose date. Thus, subjects who are not radiologically progressed, but die within 14 days of last dose or randomization (for subjects not dosed) will be considered as having PFS events. Table 1 below describes the scheme of events and censoring for PFS.

Table 1:SCHEME OF EVENTS AND CENSORING FOR PFS

Outcome	Situation	Date of Progression or Censoring
PFS Event	Radiological disease progression (determined by CIV based on RECIST 1.1) at scheduled or unscheduled visits or at end of treatment visit	First date of radiological disease progression
	Radiological disease progression after any missed scheduled visit	
	Death within 14 days of last dose or randomization (for subjects not dosed) with radiological disease progression	
	Death within 14 days of last dose or randomization (for subjects not dosed) without radiological disease progression	Death date
Censoring for PFS (If no PFS Event)	No radiological disease progression by CIV and do not die within 14 days of last dose or randomization (for subjects not dosed).	Date of last adequate tumor assessment
	Discontinuation of treatment due to reasons other than radiological disease progression by CIV	
	Clinical disease progression determined by investigator with no radiological disease progression by CIV	
	Death after 14 days of last dose or randomization (for subjects not dosed).	
	No adequate tumor assessment by CIV at Baseline	Randomization Date
	No adequate tumor assessment by CIV at post-Baseline	

Deaths after 14 days of last dose or randomization (for subjects not dosed) without radiological progression will not be considered as PFS events in the primary PFS analysis.

A sensitivity analysis will be conducted to evaluate the robustness of the PFS endpoint according to the PFS censoring rules described in Table C1 of Appendix C in US FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (US FDA Guidance, April 2015). In this sensitivity analysis, all deaths within 16 weeks (interval for two tumor response assessments) of last tumor response assessment before initiation of new anti-cancer chemotherapy will be treated as PFS events. In addition, subjects who have radiological progression or die after two or more consecutive missing tumor response assessments will be censored at the last tumor assessment date when the subject was documented to be progression free. For subjects with no post-baseline tumor response assessment, deaths within 8 weeks after randomization (before first post-baseline tumor response assessment) will be treated as PFS events.

Kaplan Meier (KM) method will be used to estimate the survival distribution function of PFS and will be used to estimate the median PFS and its 2-sided 95% confidence interval (CI), 1st and 3rd quartiles, and survival rates at Months 6, 9, 12, 18, and 24 by treatment group. Estimated KM survival curves of PFS of the two treatment groups will be displayed graphically.

The PFS comparisons of the two treatment groups will be based on a 2-sided stratified log-rank test stratified by the geographic region (North America, Europe, and Other). The PFS superiority test will be conducted at the 2-sided significance level of 0.05 only if the superiority test for OS is statistically significant.

The hazard ratio (HR) and 95% CI for the treatment effect will be estimated using the stratified Cox proportional hazards regression model with Efron's method of handling ties, stratified by the geographic region.

4.6.8.2 Objective Response Rate (ORR)

Tumor response will be assessed by the blinded CIV based on RECIST version 1.1 criteria during the study. In determining the best overall response, the following hierarchical order for tumor response will be followed: complete response (CR), partial response (PR), stable disease (SD), non-CR/non-PD, progressive disease (PD), not evaluable (NE), and unknown. For an SD to qualify for the best overall response, the assessment day must be at least 42 days from the randomization date. Subject with a best overall response of CR or PR is considered an objective responder.

ORR is defined as the percentage of subjects with a CR or PR as determined by the blinded CIV based on RECIST version 1.1 criteria. ORR and its exact binomial 95% confidence interval will be calculated for each treatment group. Treatment group differences in ORR will be analyzed using the Cochran-Mantel-Haenszel test stratified by the geographic region. Common relative risk across three regions and its 95% CI will also be presented. Additionally, a descriptive summary of best overall response will also be tabulated by treatment group.

The superiority test for ORR will be conducted at the 2-sided significance level of 0.05 only if the superiority tests for both OS and PFS are statistically significant.

Subjects with confirmed CR or PR are those with at least one pair of CR, one pair of PR, or one pair of CR/PR that has a minimum of 4 week interval between the pair. Confirmed PR should has no PD between the pair of PRs or CR/PR. Confirmed CR could have only CR and NE between the pair. Confirmed ORR is defined as the percentage of subjects with confirmed CR or PR. Confirmed ORR will be analyzed in the same way as ORR as a supportive analysis for ORR.

4.6.8.3 Duration of Response (DOR)

DOR is defined as the time from the first objective response of CR/PR until the earliest date of radiological disease progression determined by CIV or death within 14 days of last dose or randomization (for subjects not dosed). Subjects with no PFS event will be censored at the last evaluable disease assessment date on or before the data cut-off date if applicable. The DOR (in months) will be calculated as:

(Progression date or censoring date – first date of CR or PR + 1)/30.44.

The DOR data will be summarized descriptively using Kaplan-Meier method for the subset of subjects who showed an objective response (CR or PR). Median DOR and its 95% CI and 1st and 3rd quartiles will be estimated using the KM method.

4.7 Safety Evaluation

Safety data will be periodically reviewed by an independent DMC to protect subject welfare and identify potential safety signals. All safety data will be summarized descriptively by treatment group and overall using the Safety Population. No inferential statistical tests will be conducted for safety parameters.

4.7.1 Extent of Exposure

Extent of exposure will be summarized for treatment duration, number of cycles initiated, number of doses administered, dose reductions, dose delay, cumulative dose, weight or BSA based cumulative dose, average dose intensity, and relative dose intensity.

An overall summary of drug exposure will be presented for the number of cycles initiated with any study medication and duration of treatment for all study medications. Duration of treatment is defined as the time from first dose date of any study medication to the last dose date of any study medication. Overall drug exposure will be summarized using descriptive statistics. The frequency count and percentages will also be presented for subjects who had initiated ≥2, ≥4, etc. treatment cycles.

For each study medication (PEGPH20/placebo, NAB, and Gem), exposure will be summarized using descriptive statistics for the following parameters across all cycles. In addition, for PEGPH20/placebo, the following parameters, except for number of cycles initiated, will also be summarized for Cycle 1 only.

- Number of cycles initiated
- Number of dose administered
- Frequency and percentage of subjects with at least one dose omitted

  For subjects with at least one dose omitted:

  – Total number of expected doses up to the last dose received, including doses omitted

  – Frequency and percentage of doses omitted

  – Frequency and percentage of dose omission by reason, including PEGPH20/Placebo toxicity, chemotherapy toxicity, other adverse event, schedule of conflict, and other
- Frequency and percentage of subjects with at least one dose reduction

  For subjects with at least one dose reduction:

  – Total number of doses administrated

  – Frequency and percentage of doses with dose reduction

- Frequency and percentage of subjects with at least one dose delay. A treatment cycle is considered delayed if the first dose date of the cycle is greater than 35 days after the first dose date of the preceding cycle.

  For subjects with at least one dose cycle delay:

  – Total number of cycles initiated

  – Frequency and percentage of cycles with dose delay

- Frequency and percentage of subjects with at least one dose interruption

  For subjects with at least one dose interruption:

  – Total number of doses administrated

  – Frequency and percentage of doses with dose interruption

  – Frequency and percentage of interrupted doses restarted.

- Weight-based or BSA-based cumulative dose, defined as cumulative dose divided by screening weight for PEGPH20 or Placebo and screening BSA for NAB and GEM. Cumulative dose is defined as the sum of administered doses.

- Average dose intensity per cycle is defined as the weight-based or BSA-based cumulative dose divided by number of adjusted treatment cycles. Number of adjusted treatment cycles will be calculated as follows:

  (End date of last cycle - first dose date + 1) / 28

  The end date of last cycle is defined as last dose date plus 10 days for PEGPH20 at first cycle and last dose date plus 13 days for PEGPH20 at Cycle 2 and beyond. For GEM and NAB at all treatment cycles, the end date of last cycle is defined as last dose date plus 13 days.

- Relative dose intensity (RDI) is defined as the average dose intensity per cycle divided by the planned dose intensity per cycle. The planned dose intensity per cycle will be 375 mg/m^2 for NAB and 3000 mg/m^2 for GEM. For PEGPH20, the planned dose intensity per cycle will be 18 ug/kg if adjusted treatment cycle is ≤1, otherwise, will be calculated as follows:

  [18 + (adjusted treatment cycles – 1) x 9 µg/kg] / adjusted treatment cycles

  In addition to descriptive summary of relative dose intensity, the frequency and percentage of subjects will be presented for the following relative dose intensity categories: ≥90%, 80% to <90%, 70% to <80%, 60% to <70%, 50% to <60%, and <50%.

4.7.2 Adverse Events

An AE is any unfavorable or unintended sign, symptom, or disease temporarily associated with the use of a pharmaceutical product (i.e., study medication), whether or not considered related to the pharmaceutical product. All summaries of adverse events (AEs) will include only treatment emergent adverse events (TEAEs). TEAEs are defined as new events occurring on or after the first dose of study treatment or events worsening from pre-treatment to post-

treatment. An AE will be considered treatment-emergent if it occurs on or after the first dose of the study treatment up to 30 days after the last dose of study treatment. In addition, any AE considered to be related, probably related, or possibly related to any study medication will also be considered TEAE regardless of the onset date.

All TEAE summaries will include the frequency count of subjects with TEAE and the percentage by treatment group. Subjects with multiple TEAEs will be counted only once for each TEAE category.

An overall summary of TEAE will include number of subjects in the following TEAE categories:

- Any TEAE
- Any TEAE with Grade ≥ 3
- Any treatment related TEAE by study medication
- Any treatment related TEAE with Grade ≥ 3 by study medication
- Any TEAE leading to treatment discontinuation
- Any TEAE leading to dose reduction or interruption
- Any serious AE
- Any treatment related serious AE by study medication
- Any AE with outcome of death

TEAE will also be summarized by MedDRA system organ class (SOC) and preferred term (PT) for the following TEAE categories:

- Any TEAE
- TEAEs with Grade ≥ 3
- Treatment related TEAE
- Any TEAE leading to discontinuation
- Any TEAE leading to dose reduction or interruption
- Any serious AE

TEAEs experience by ≥5% subjects in either treatment arm and with ≥2% difference between treatment arms will be summarized by MedDRA preferred term. All death and SAEs will be listed.

In addition, subjects who have the following adverse events will be grouped together and summarized by MedDRA PT and treatment group as follows:

- Thromboembolic events (TEs) by Standard MedDRA Queries (SMQ) term: Embolic and thrombotic events arterial, venous, and vessel type unspecified and mixed arterial and venous
- Haemorrhage events with SMQ and sub-SMQ Haemorrhage terms excluding laboratory terms.
- Musculoskeletal events (MSE) by MedDRA high-level term: bone related signs and symptoms, joint related signs and symptoms, muscle pains, muscle related signs and symptoms NEC, muscle tone abnormalities, muscle weakness conditions,

musculoskeletal and connective tissue pain and discomfort, musculoskeletal and connective tissue signs and symptoms NEC

- Allergic events by MedDRA SMQ: anaphylactic reaction, angioedema, hypersensitivity.

The grouped adverse events above will be summarized with any severity grade and grade 3 or above separately. In addition, the incidence rate will also be adjusted the total exposure to study treatment.

The following adverse events will also be summarized by the worst outcome: muscle spasms, myalgia, arthralgia, back pain, pain in extremity, oedema peripheral, and peripheral swelling. For these adverse events, summary statistics will be presented for the duration between first dose date and onset date of the first event.

4.7.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

For the purposes of this study in subjects with Stage IV PDA, progression of the subject's underlying disease ("disease progression") is an efficacy assessment and should not be reported as an AE or SAE. However, if the Investigator determines that there is evidence suggesting a causal relationship between the event and the study medication, the event should be recorded as an AE or SAE.

Death resulting from disease progression is a study efficacy endpoint, and should not be reported as an SAE. However, if the Investigator determines that there is evidence suggesting a causal relationship between the event and the study medication, the event should be reported as an SAE.

All deaths. SAEs, and AEs of special interests (e.g. thromboembolic events) will be summarized.

4.7.4 Clinical Laboratory Evaluation

All lab values will be reported and summarized using standard international (SI) units. A list of the SI units to the laboratory parameter is provided in Appendix C. Only central lab data will be used for summarizing lab values by visit and change from baseline. All lab data from both central and local labs will be used for summarizing lab parameters with worst CTCAE grade at post-baseline visits and their shift from Baseline.

Central laboratory assessments are listed below:

- **Blood chemistry**: glucose, blood urea nitrogen (BUN), albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), electrolytes (including sodium, potassium, calcium, magnesium, chloride, and bicarbonate), creatinine, and C-reactive protein (CRP).
- **Hematology**: hemoglobin, hematocrit, red blood cell count, white blood cell count, neutrophils (absolute), lymphocytes (absolute), monocytes (absolute), eosinophils (absolute), basophil (absolute), granulocyte (absolute), mean corpuscular hemoglobin, mean corpuscular volume, and platelet count.
- **Coagulation**: prothrombin time (PT), partial prothrombin time (PTT), and international normalized ratio (INR).
- **Urinalysis**: protein, glucose, ketones, blood, specific gravity, nitrite, pH, leukocytes.

The continuous test results for each test parameter and change from baseline will be summarized by visit through Cycle 10 and at End of Treatment using descriptive statistics. Baseline is defined as the last evaluation prior to the first dose of study medication. The categorical test results for each test parameter will be summarized using frequencies and percentages.

A shift summary of baseline grade by maximum post-baseline CTCAE grade, if available, will be presented. All CTCAE grade ≥3 laboratory tests will also be listed.

For subjects who meet the lab criteria of Hy's law (ALT > 3×ULN or AST > 3×ULN, Total BILI > 2×ULN and ALP < 2×ULN) at any time point, all available laboratory values of AST, AST, ALP, and Total BILI will be listed. In addition, the frequency count and percentage of subjects for meeting the following criteria will also be summarized: ALT or AST>3x ULN, >5x ULN, >10x ULN, >20x ULN; total bilirubin >2x ULN; ALT or AST >3x ULN and total bilirubin >2x ULN.

Quantitative laboratory measurements reported as below the lower limit of quantification (BLQ) or above the upper limit of quantification (ULQ) will be converted to BLQ or ULQ respectively for the purpose of quantitative summaries.

4.7.5 Pregnancy Test

Individual pregnancy test result for each subject will be listed.

4.7.6 Vital Signs, Physical Examination, and Physical Measurements

Vital signs including blood pressure (systolic and diastolic), heart rate, respiratory rate (number of breaths/min), and body temperature will be summarized by visit using descriptive statistics.

Clinically significant findings of physical examinations at screening will be summarized using frequencies and percentages.

Height (cm), weight (kg) and body surface area (BSA; m^2) will be summarized by visit using descriptive statistics. BSA is calculated using DuBois formula as:

$$BSA = 0.007184 \times W^{0.425} \times H^{0.725}$$

For heart rate and blood pressure, the following out of range categories will be summarized with frequency count and percentage:

- Heart rate:
  <50 bpm, >120 bpm, ≥30 bpm increase from baseline, ≥30 bpm decrease from baseline
- Blood pressure:
  - Systolic: >140 mmHg and increase from baseline by > 20 mmHg; >180 mmHg, <90 mmHg and decrease from baseline by >10 mmHg.
  - Diastolic: >90 mmHg and increase from baseline by >20 mmHg, >105 mmHg, <60 mmHg and decrease from baseline by >10 mmHg.

By-subject listings of vital sign, physical examination, and physical measurements will also be provided.

4.7.7 12-Lead Electrocardiogram (ECG)

Frequency and percentage of subjects who had abnormal (clinically significant or not clinically significant) ECG findings will be summarized by treatment group based on the worst ECG finding. When there are multiple ECGs taken at a visit, the worst ECG finding will be used.

QTcF value will be calculated by applying Fredericia's formula ($QTcF = \frac{QT}{\sqrt[3]{RR}}$).

When multiple ECGs are taken at a visit, the average of the calculated QTcF values will be used for all QTcF analyses. QTcF values and their changes from Baseline will be summarized with descriptive statistics by visit. In addition, QTcF values will be summarized with frequency count and percentage by visit with the following categories: ≤ 450 msec, > 450 to ≤ 480 msec, > 480 to ≤ 500 msec, and >500 msec. QTcF change from Baseline will be summarized with frequency count and percentage by visit with the following categories: <= 30 msec, > 30 to ≤ 60 msec, and > 60 msec. The maximum value of QTcF at post-baseline and change from baseline will also be summarized in the same way as the summary by visit and the QTcF categorical change from baseline to maximum post-baseline will also be presented in a shift table.

Listings of clinical significantly abnormal ECG findings will be provided. Additionally, a listing will also be provided for subjects with any calculated QTcF > 500 msec or > 60 msec increase.

4.7.8 ECOG Performance Status

Frequency and percentage of subjects for each ECOG performance status score will be displayed by visit. A shift summary of baseline score by maximum post-baseline score will also be presented. Listings of ECOG will be provided.

4.7.9 Prior and Concomitant Medications

Prior medications are those the subject used prior to the first dose date.

Concomitant medications are those the subject has taken concomitantly to any study medication including the medications taken within 30 days of last dose of any study medication.

Medications used prior to and after first dose of study drug will be considered as both prior and concomitant medications.

Medications will be coded by WHO Drug preferred name and will be summarized using frequencies and percentages on the Safety population. Subjects taking more than 1 medication in the same preferred name will be counted once. Prior medications and concomitant medications.

4.7.10 Safety Monitoring

An independent DMC will be constituted and responsible for periodically reviewing safety data to protect subject welfare and identify potential safety signals. Operational and logistical details are provided in a separate DMC charter.

4.8 Other Analyses

4.8.1 Pharmacokinetics and Pharmacodynamics Analysis

Plasma exposure levels of PEGPH20 will be evaluated in the PAG group, while GEM and NAB will be evaluated in both treatment groups. Pharmacokinetic and pharmacodynamic analyses will be provided in a separate pharmacometric analysis plan and report for this study.

4.8.2 Biomarker Analysis

Tumor, whole blood, and plasma samples will be collected for biomarker assessments including pharmacogenetic analysis. An optional tumor biopsy may be obtained upon determination of disease progression in subjects who consent to it. Samples may be analyzed for biomarkers relevant to PEGPH20 mechanism of action and/or dysregulation in tumor-relevant pathways as well as for exploratory studies to determine clinical response biomarkers.

Biomarker data will be summarized with descriptive statistics by treatment group.

4.8.3 Patient Reported Outcome (PRO) Measures

In this study, three PRO measures will be used to assess the impact of treatment on the following aspects of a subject's health status: health-related quality of life using the EORTC QLQ-C30, general health outcome using the EQ-5D; and symptoms related to pancreatic cancer and treatment-associated toxicities using a Numerical Rating Scale (NRS).

Details of PRO analysis will be provided in a separate PRO analysis plan.

4.9 Determination of Sample Size

Approximately 500 eligible subjects will be randomized to receive PAG or AG in 2:1 ratio. The analysis of final OS will be conducted after 330 deaths have occurred. The study is powered for the final OS. The statistical power and sample size calculations below are based on the comparison of treatment difference in OS between PAG and AG groups and obtained from East 6.3.1 software, Cytel Inc.

The median OS in the AG group is expected to be approximately 8.5 months (Von Hoff, 2013). If PAG therapy improves median OS by 50% from 8.5 months to 12.7 months with a HR of 0.67, the study with 330 OS events (deaths) will have 93% statistical power to show statistically significant improvement in OS at the significance level of 0.05 at the final OS analysis based on 2-sided log-rank test.

5 REFERENCES

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6 APPENDICES

6.1 APPENDIX A: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1

Target Lesion Response Evaluation:

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study thus far, nadir (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Non-Target Lesion Response Evaluation:

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions.

Overall Response Evaluation with Target (+/- Non-Target) Disease:

Target Lesion Response	Non-Target Lesion Response	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated or NA	No	PR
SD	Non-PD or not all evaluated or NA	No	SD
Not all evaluated	Non-PD or NA	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NA=Not Applicable (i.e., no non-target lesions identified at baseline); NE=Not Evaluable.			

Overall Response Evaluation with Non-Target Disease

Non-target Lesion Response	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Source: Eisenhauer 2009

6.2 APPENDIX B: ECOG PERFORMANCE STATUS

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Note: Shaded grades represent acceptable status for enrollment in Study HALO 109-301

6.3 APPENDIX C: LABORATORY STANDARD UNITS (SI)

Laboratory Parameter	SI Units
Albumin	g/L
Alkaline Phosphatase	U/L
Absolute neutrophil count	10^9/L
Basophils	10^9/L
Bicarbonate	mmol/L
Total Bilirubin	µmol/L
Blood Urea Nitrogen	mmol/L
Calcium	mmol/L
Chloride	mmol/L
Creatinine	µmol/L
Eosinophils	10^9/L
Glucose	mmol/L
Granulocytes	10^9/L
Hematocrit	frac of 1
Hemoglobin	g/L
INR	1
Lymphocytes	10^9/L
Magnesium	mmol/L
Mean Corpuscular Hemoglobin	pg
Mean Corpuscular Volume	fL
Monocytes	10^9/L
Platelets	10^9/L
Potassium	mmol/L
Total Protein	g/L
Prothrombin Time	s
Partial Thromboplastin Time	s
Red Blood Cells	10^{12}/L
Aspartate Transaminase	U/L
Alanine Transaminase	U/L
Sodium	mmol/L
White Blood Cells	10^9/L

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