NCT #: NCT02563548

STATISTICAL ANALYSIS PLAN

A Phase 1b Open-Label Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) Combined with Pembrolizumab in Subjects with Selected Hyaluronan-High Solid Tumors

Investigational Product: PEGPH20
Protocol Number: HALO-107-101

Sponsor:
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Version Number: 1.0
Date: 19 April, 2019

CONFIDENTIAL

SIGNATURE PAGE

Protocol Title and Protocol Number

We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

Signature Date

[redacted] 22 APR 2019

Medpace, Inc.

[redacted] 26 Apr 2019

Medpace, Inc.

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Halozyme, Inc.

[redacted] 06 MAY 2019

Halozyme, Inc.

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VERSION HISTORY

Version	Date	Description
1.0	19 April 2019	Original final version

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine transferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area-under-the-concentration time curve
BUN	blood urea nitrogen
CIV	central imaging vendor
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCE-MRI	dynamic contrast-enhanced magnetic resonance imaging
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HA	Hyaluronan
HA-high	hyaluronan high
irRC	immune-related response criteria
INR	international normalized ratio

MedDRA	Medical Dictionary of Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	maximum tolerated dose
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	Pharmacodynamics
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1
PEGPEM	PEGylated recombinant human hyaluronidase combined with pembrolizumab
PEGPH20	PEGylated recombinant human hyaluronidase
PET	positron emission tomography
PFS	progression free survival
PK	Pharmacokinetics
PR	partial response
PT	prothrombin time
PTT	partial prothrombin time
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
$T_{1/2}$	terminal half-life
TB	total bilirubin

TEAE	treatment emergent adverse event
T_{max}	time to maximum concentration
TME	tumor microenvironment
ULN	upper limit of normal

1 INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented in the analysis of data collected in the study HALO-107-101 conducted by Halozyme, Inc. This document is based on the Protocol HALO-107-101 Amendment 4 entitled "A Phase 1b Open-Label Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) Combined with Pembrolizumab in Subjects with Selected Hyaluronan-High Solid Tumors" and dated 6 November 2017.

2 STUDY OBJECTIVES

The study has two portions, namely, a Dose Escalation portion and a Dose Expansion portion. The objectives for each portion are as follows.

2.1 Dose Escalation

Primary:

- To assess the safety and tolerability of PEGylated recombinant human hyaluronidase (PEGPH20) combined with pembrolizumab (Keytruda®) (PEGPEM) in subjects with relapsed/refractory non-small cell lung cancer (NSCLC) and relapsed/refractory gastric adenocarcinoma.
- To determine the recommended phase 2 dose (RP2D) of PEGPH20 when administered with pembrolizumab in subjects with relapsed/refractory NSCLC or relapsed/refractory gastric adenocarcinoma.

Secondary:

- To assess the pharmacokinetics (PK) of PEGPH20 when given in combination with pembrolizumab in subjects with relapsed/refractory NSCLC or relapsed/refractory gastric adenocarcinoma.
- To obtain an early assessment of the antitumor activity of PEGPEM, as assessed by objective response rate (ORR), duration of response (DOR), disease control rate (DCR) and progression free survival (PFS) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and overall survival (OS) in subjects with relapsed/refractory NSCLC or relapsed/refractory gastric adenocarcinoma.

Exploratory:

- To assess the PK of pembrolizumab when given in combination with PEGPH20 in subjects with relapsed/refractory NSCLC or relapsed/refractory gastric adenocarcinoma.

2.2 Dose Expansion

The objectives described below will be evaluated in hyaluronan-high (HA-high) subjects with relapsed/refractory NSCLC and HA-high subjects with relapsed/refractory gastric adenocarcinoma.

Primary:

- To evaluate the efficacy of PEGPEM as assessed by ORR based on RECIST v1.1.

Secondary:

- To evaluate the efficacy of PEGPEM as assessed by DOR, DCR, and PFS based on RECIST v1.1, and OS.
- To evaluate the efficacy of PEGPEM as assessed by ORR, DOR, DCR, and PFS based on immune-related response criteria (irRC).
- To characterize the PK of PEGPH20 when given in combination with pembrolizumab.
- To evaluate the safety and tolerability profile of PEGPEM.

Exploratory:

- To evaluate the efficacy of PEGPEM, as assessed by ORR, DOR, DCR and PFS based on RECISIT v1.1 criteria and irRC, by programmed death-ligand 1 (PD-L1) expression levels.
- To assess the treatment effect of PEGPEM as follows:
  - Based on HA levels in plasma and tumors, or other potential biomarkers.
  - Based on tumor blood flow and metabolic activity as assessed by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and positron emission tomography (PET)/computed tomography (CT) scans, respectively.
- To assess the PK of pembrolizumab when given in combination with PEGPH20.

3 STUDY OVERVIEW

3.1 Study Design

This Phase 1b study of PEGPEM consists of 2 portions:

- A Dose Escalation portion in subjects with relapsed/refractory Stage IIIB or IV NSCLC after failing at least 1 previous platinum-based chemotherapy regimen (refer to Inclusion Criterion #2 in the protocol) and subjects with relapsed/refractory locally advanced or metastatic gastric adenocarcinoma after failing at least 1 previous chemotherapy regimen for locally advanced or metastatic disease.
- Followed by a Dose Expansion portion in:
  - Previously untreated, hyaluronan-high (HA-high) subjects with Stage IIIB or IV NSCLC
  - Previously treated, HA-high subjects with relapsed/refractory Stage IIIB or IV NSCLC having failed no more than 1 previous platinum-based chemotherapy regimen (refer to Inclusion Criterion #3 in the protocol) for locally advanced or metastatic disease

- HA-high subjects with relapsed/refractory locally advanced or metastatic gastric adenocarcinoma having failed no more than 2 previous chemotherapy regimens for locally advanced or metastatic disease

Since PEGPH20 has not been evaluated in clinical studies in combination with pembrolizumab, this study will have a Dose Escalation portion to evaluate the safety and tolerability of PEGPEM treatment before the Dose Expansion portion is initiated. The Dose Escalation portion will also be used to determine the dose of PEGPH20 to be evaluated in the Dose Expansion portion.

3.1.1 Phase 1b Dose Escalation Portion

This portion of the study is a single-arm, dose escalation study of PEGPH20 in combination with pembrolizumab. Using a standard 3+3 dose escalation design, approximately 3 to 6 subjects in each cohort will receive PEGPH20 + pembrolizumab. PEGPH20 will be administered on Day 1, Day 8 and Day 15 of each 21-day cycle to consecutive cohorts in increasing dose levels (1.6, 2.2, 2.6, 3.0, and 4.0 µg/kg). Pembrolizumab will be administered on Day 1 of each cycle, 4-6 hours after the dose of PEGPH20. If the maximum tolerated dose (MTD) is not reached at 4.0 µg/kg, higher doses may be evaluated. If ≥2 subjects experience a dose limiting toxicity (DLT) at the 1.6 µg/kg dose level, Cohort -1 will be opened and subjects will be dosed at 1.0 µg/kg on Day 1, Day 8, and Day 15 of each 21-day cycle. The RP2D of PEGPH20 will be the MTD determined in Dose Escalation or the Sponsor may decide to choose a dose lower than the MTD and which has completed evaluation in Dose Escalation and is found to be safe and tolerable to evaluate in Dose Expansion.

The number of cohorts studied and number of subjects exposed to a given dose level will depend on the doses tested. It is anticipated that up to 5 dose levels will be studied for a total of approximately 30 subjects exposed to study medication. The dose allocation for 5 cohorts of subjects assigned to the 5 preselected dose levels and the -1 cohort assigned to the preselected dose of 1.0 µg/kg (if ≥2 subjects experience a DLT at 1.6 µg/kg dose level) is shown as an example in Table 1. Study medication dosing and treatment schedule is shown in Table 2.

Table 1: Dose Allocation and Cohort Schedule - Dose Escalation Portion

Cohort	PEGPH20 µg/kg	Pembrolizumab mg/kg
-1	1.0	2
1	1.6	2
2	2.2	2
3	2.6	2
4	3.0	2
5	4.0[a]	2

Abbreviations: PEGPH20 = PEGylated Recombinant Human Hyaluronidase
Note: Each treatment cycle is 21 days. Dose interruption and modifications are permitted.
[a] If the MTD is not reached at 4.0 µg/kg, higher doses may be evaluated.

Safety data from all subjects dosed will be reviewed to determine the RP2D. Dose escalation will be guided by safety data from each subject during the 21 days following their first dose of

PEGPH20. Intra-subject dose escalation to the next PEGPH20 dose studied may be allowed if the Investigator deems it in the best interest of the subject and after discussion with the Sponsor and provided the next PEGPH20 dose studied has been determined not to have exceeded the MTD.

- If none of initial 3 subjects in a given cohort experience a DLT within 21 days of starting treatment, enrollment and dosing may proceed at the next planned dose level.
- If 1 of 3 initial subjects at a given dose level experiences a DLT within the first 21 days of treatment, 3 additional subjects will be enrolled and dosed at the same dose level. If ≤1 of 6 subjects experiences a DLT, dose escalation may continue to the next planned higher dose.
- If ≥2 subjects at a given dose level experience a DLT within the first 21 days of treatment, that dose level will be considered to have exceeded the MTD and dose escalation will be stopped. If the previous dose level did not already have 6 subjects treated with ≤1 DLT, enrollment and dosing will then resume in the previous dose level with additional subjects up to a total of 6 subjects. The highest dose level at which no more than 1 of 6 evaluable subjects has experienced a DLT in the first 3 weeks of treatment will be considered the MTD for the PEGPEM combination. The RP2D will be based on the overall safety profile.
- If ≥2 subjects at the 1.6 µg/kg dose level experience a DLT within the first 21 days of treatment, Cohort -1 will be opened at a lower dose level of 1.0 µg/kg.

Note: Additional subjects may be enrolled in each cohort to further assess the tolerability of PEGPEM and determine an acceptable safety profile prior to the enrollment in the next dose level and Dose Expansion portion of the study.

3.1.2 Phase 1b Dose Expansion Portion

Approximately 51 HA-high subjects will be studied in the Dose Expansion portion at the RP2D identified in the Dose Escalation portion:

- Approximately 30 subjects with Stage IIIB or IV NSCLC, previously untreated or treated and having failed no more than 1 previous platinum-based chemotherapy (refer to Inclusion Criterion #3)
- Approximately 21 subjects with relapsed/refractory gastric adenocarcinoma having failed no more than 2 previous chemotherapy regimens.

In Dose Expansion, PEGPH20 will be administered on Day 1, Day 8, and Day 15 of each 21-day cycle (i.e., 3 doses / cycle) and pembrolizumab (200 mg every 21 days) on Day 1 of each cycle (i.e., 1 dose / cycle), 4-6 hours after the completion of PEGPH20 administration. The dosing schedule is shown in Table 2.

If a dose of PEGPH20 is missed on Day 1 of Cycle 2 or beyond, the cycle will continue as scheduled. If it is known that pembrolizumab will be missed or held on Day 1, PEGPH20 should also be held and the cycle will not start until the first dose of pembrolizumab is administered. This will require planning such that the dose of PEGPH20 can be given before the pembrolizumab dose is set to resume.

Table 2: Study Medication Dosing and Treatment Schedule – Dose Escalation and Dose Expansion

Time point	PEGPEM Treatment by Treatment Group
Subjects with NSCLC	
Cycle 1 and Beyond (Each Cycle 21 Days)	
Week 1	
Day 1	PEGPH20 Pembrolizumab (4-6 hours after PEGPH20)
Week 2	
Day 8	PEGPH20
Week 3	
Day 15	PEGPH20
Subjects with Gastric Adenocarcinoma	
Cycle 1 and Beyond (Each Cycle 21 Days)	
Week 1	
Day 1	PEGPH20 Pembrolizumab (4-6 hours after PEGPH20)
Week 2	
Day 8	PEGPH20
Week 3	
Day 15	PEGPH20

Abbreviations: PEGPEM = PEGPH20 in combination with pembrolizumab; PEGPH20 = PEGylated Recombinant Human Hyaluronidase; NSCLC = non-small cell lung cancer
Notes: Dose interruption and modifications are permitted.
Subjects with NSCLC will be studied first, followed by subjects with gastric adenocarcinoma.
Visit window is ±2 days of the specified times.

3.2 Discontinuation of Treatment

Treatment in both portions of the study will continue until death, withdrawal of consent from the study, disease progression, or unacceptable toxicity; however, subjects with asymptomatic disease progression will be allowed to continue study treatment at the Investigator's discretion despite evidence of increasing tumor burden or appearance of new lesions for up to 6 weeks if the subject is "clinically stable". Clinically stable is defined as:

- Absence of symptoms and signs indicating clinically significant PD (including worsening of laboratory values) indicating disease progression and
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status and
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Dose interruptions and modifications of study treatment are permitted. Investigators may also discontinue study treatment if it is no longer in the best interest of the subject.

3.3 Study Centers

Both portions of the study will be conducted at multiple centers.

3.4 Randomization and Blinding

This is a multi-center, open-label, non-randomized study.

3.5 Study Duration

The study will consist of an optional prescreening period for HA-testing in Dose Expansion (per Protocol Amendment 4), a screening period of up to 28 days, a treatment period (21-day cycles), a 30-day post-treatment period (after last dose) for collection of AEs and a long-term follow-up. Subjects who discontinue treatment with PEGPH20 and pembrolizumab will be followed every 12 weeks for survival until death, withdrawal of consent, or lost to follow-up.

3.6 Tumor Response and Disease Progression Assessment

In both portions of the study, tumor response and progression will be assessed by the Investigator at the end of Cycle 2, Cycle 4 and then at the end of every fourth treatment cycle thereafter (i.e., Week 3 of Cycles 2, 4, 8, 12, 16 and beyond) based on RECIST v1.1 criteria (Eisenhauer 2009; see Appendix C of the protocol). In the dose expansion portion, tumor response and progression will also be assessed by the Investigator at the end of above mentioned cycles using a modified unidimensional version of the irRC criteria (Nishino 2013, Nishino 2014; see Appendix E of the protocol) first introduced by Wolchok (2009). Tumor assessment scans (CT/MRI of chest, abdomen, pelvis, and other areas of known or newly suspected disease) should be performed at Screening (within 28 days prior to first dose of study drugs) and obtained any time on or after Day 15 (of Cycles 2, 4, 8, 12, 16 and every fourth treatment cycle thereafter) to allow enough time for the scan to be reviewed locally prior to the subject's next scheduled dosing visit.

Additionally, tumor images associated with NSCLC cancer type will be assessed by an independent reviewer from a third-party vendor, Imaging Endpoints. Efficacy analyses related to NSCLC cancer type using RECIST v1.1 will also be performed based on the tumor assessments from Imaging Endpoints.

A CT/MRI brain scan must be performed at Screening (within 28 days prior to first dose of study drugs), to assess potential central nervous system disease and/or metastases.

For the duration of the study (i.e., post-baseline), CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a complete response (CR). For NSCLC subjects with a history of treated brain metastases, brain scans will be performed at tumor assessment time points.

For a confirmed best response of CR or partial response (PR) based on RECIST v1.1 and irRC, a confirmatory scan must be performed no sooner than 28 days after the initial scan that showed a PR or a CR. A confirmatory scan should also be performed to confirm disease progression (PD) based on irRC no sooner than 28 days after the initial scan that showed progression.

3.7 Disease Progression Criteria

Disease progression will be defined by the presence of 1 or both of the following, based on the Investigator's assessment:

- Disease progression documented by CT scan/MRI scan based on RECIST v1.1.
- Clinical tumor-related progression that is well documented in the absence of scans demonstrating radiographic disease progression.

4 STATISTICAL METHODS

4.1 General Considerations

In general, continuous variables will be summarized using descriptive statistics (N, mean, standard deviation [SD], median, minimum [min], maximum [max], and quartiles). Categorical variables will be summarized using frequencies and percentages. In each summary table, figure or data listing, analysis population considered will be included in the title.

PEGPH20 and pembrolizumab are referred to as study drugs.

Study day 1 for a subject is defined as the first day that any study treatment is administered to the subject. The day before the study day 1 is referred to as study day −1. Unless otherwise indicated, the baseline value of a parameter is defined as the latest non-missing value taken prior to the administration of any study drug.

Statistical analyses will be performed and related outputs will be produced using the SAS® software Version 9.3 or higher. All tables, figures, and data listings will be independently checked for accuracy, consistency, and integrity in accordance with Medpace standard operating procedures or work instructions.

4.2 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-responders.

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 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 of Concomitant Medication

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 event are
    - on or after the month and year of the date of the first dose of study medication

      AND
    - on or before the month and year of the date of the last dose of study medication plus 30 days.
- 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 event is
    - on or after the year of the date of the first dose of study medication

      AND
    - on or before the year of the date of the last dose of study medication plus 30 days.

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

Missing/Partial Dates of Initial Diagnosis

Dates of initial diagnosis that are partially missing will be imputed as follows:

- If month and year are present but day is missing, 15 will be used to impute the missing day.
- If only year is present but day and month are missing, the 01JUL will be used to impute the missing day and month.

If this imputation rule yields a date of initial diagnosis after enrollment date, then the partial date of the initial diagnosis will be imputed as 01JAN when only year is provided and the first day of the month when only month and year are provided.

4.3 Study Endpoints

All PK related analyses of endpoints described below will done independently under a separate PK analysis plan and such analyses are not covered under this analysis plan.

4.3.1 Dose Escalation

Primary:

- Dose-limiting toxicity, MTD, and RP2D.

Secondary:

- PK parameters of PEGPH20: maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), terminal elimination half-life ($T_{1/2}$), area-under-the-concentration time curve (AUC), volume of distribution (V_D) and clearance (CL).
- ORR, DOR, DCR, and PFS based on RECIST v1.1.
- OS.

Exploratory:

- PK parameters of pembrolizumab: C_{max}, C_{min}, $T_{1/2}$, AUC, V_D and CL.

4.3.2 Dose Expansion

Primary:

- ORR based on RECIST v1.1.

Secondary:

- DOR, DCR and PFS based on RECIST v1.1, and OS.
- ORR, DOR, DCR, and PFS based on irRC.
- PK parameters of PEGPH20: C_{max}, C_{min}, $T_{1/2}$, AUC, V_D and CL.
- Incidence of AEs.
- Changes in clinical safety laboratory values.
- Changes in cardiovascular parameters (electrocardiogram [ECG]) and vital signs.

Exploratory:

- ORR, DOR, DCR, and PFS based on RECIST v1.1 criteria and irRC by PD-L1 expression levels.
- Changes from pre-treatment in plasma HA and tumor HA (when available).
- Correlation between plasma HA levels pre-dose, post-dose and any pharmacodynamic response.

- Changes in tumor blood flow as measured by DCE-MRI.
- Changes in tumor metabolism as measured by PET/CT.
- Correlation of biomarkers in plasma and tumor biopsy to study endpoints.
- PK parameters of pembrolizumab: C_{max}, C_{min}, $T_{1/2}$, AUC, V_D and CL.

4.4 Analysis Populations

4.4.1 Enrolled Population

The Enrolled Population is defined as all subjects who were enrolled (i.e., subjects who sign the informed consent form at the screening and are enrolled in a cohort) in the study. Subjects will be analyzed according to the initial cohort actually assigned.

4.4.2 Safety Population

The Safety Population analysis set is defined as all enrolled subjects in either Dose Escalation or Dose Expansion portion of the study, who receive at least 1 dose of any study medication (PEGPH20 or pembrolizumab). The Safety Population will be used for drug exposure, demographics and safety analyses, including AE, labs, and deaths. Subjects will be analyzed according to the initial cohort actually assigned.

4.4.3 DLT Evaluable Population

The DLT Evaluable Population is defined as all subjects enrolled in the Dose Escalation portion who receive at least 1 of the 3 full planned doses of PEGPH20 and 1 complete dose of pembrolizumab in Cycle 1 and have been followed for the first 21 days of treatment or have experienced a DLT during the initial 21 days (Cycle 1) of the study. DLTs will be assessed for each subject during the 21 days of Cycle 1 following their first PEGPH20 dose. The DLT Evaluable Population will be used for DLT analysis.

4.4.4 PK Analysis Population

This analysis plan does not cover PK analysis. As appropriate, a description of PK analysis will be provided in a separate PK analysis plan.

4.4.5 Efficacy Evaluable Population

All HA-high subjects who receive at least 1 dose of the RP2D of PEGPH20 and at least 1 dose of pembrolizumab in the Dose Expansion portion and all subjects who receive at least 1 dose of PEGPH20 and at least 1 dose of pembrolizumab in the Dose Escalation portion. The Efficacy Evaluable Population will be used for all efficacy analyses, except for tumor response related analyses.

4.4.6 Tumor Response Evaluable Population

Subjects in the Efficacy Evaluable Population who have at least one post-baseline tumor assessment on or post Cycle 2. Tumor Response Evaluable Population will be used for all tumor response related analyses.

4.5 Subject Enrollment and Disposition

For subjects who discontinued from study treatment phase and discontinued from study, the primary reason for discontinuation will be summarized for all enrolled subjects by cancer type and in total. Further, the number of subjects included in each analysis population will be tabulated.

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. Examples of possible major protocol deviations include, but are not limited to:

a. Violation of eligibility criteria
b. Dosing error of study drugs
c. Excluded concomitant medication
d. Subject withdrawal
e. Study visits and procedures

The number and percentage of subjects with major protocol deviations by type of deviation will be summarized by cancer type and in total.

4.6 Demographics and Other Baseline Data

Demographics and other baseline data will be summarized by cancer type and using the Safety Population and by cancer type using the Efficacy Evaluable Population.

4.6.1 Demographics

Age at Screening (years), height at Screening (cm), weight at Screening (kg), and body surface area (BSA; m^2) at Screening will be summarized descriptively (N, mean, standard deviation [SD], median, minimum [min], maximum [max], and quartiles). Age category at Screening (< 65 versus ≥ 65 years), sex, race, and ethnicity will be summarized by frequency counts and percentages.

Age at Screening will be calculated as follows:

$$\text{Age at Screening} = \text{Integer} \leq [(\text{Date of Screening} - \text{Date of birth} + 1) / 365.25].$$

BSA at Screening will be calculated using DuBois formula as follows:

$$\text{BSA at Screening} = 0.007184 * W^{0.425} * H^{0.725}$$

4.6.2 Baseline Disease Characteristics

A descriptive summary of baseline disease characteristics of the subjects in the Safety Population and Efficacy Population by cancer type and in total will be produced for the following: initial disease stage, time from initial diagnosis to enrollment, current disease stage (months), time from current diagnosis to enrollment (months), significant past medical history or ongoing (yes, no), tobacco usage status (current, former, or never), alcohol usage status (current, former, or never), number of cancer therapy lines, prior cancer therapies/medications (yes, no), prior cancer resections (yes, no), prior cancer radiation (yes, no), PD-L1 expression level in tumor tissues on tumor cells assessed by NeoGenomics for subjects with gastric adenocarcinoma cancer type and

Ventana for subjects with NSCLC cancer type at Baseline along with positive and negative status, and ECOG performance status at Screening and on study day 1.

The positive and negative status for PD-L1 on tumor cells at Baseline are determined based on the following (see prescribing information of Keytruda®):

- Subjects with gastric adenocarcinoma cancer type: the PD-L1 status is provided by NeoGenomics based on Combined Positive Score (CPS) where PD-L1 status is assigned as negative if CPS = 0 and positive if CPS ≥ 1.
- Subjects with NSCLC cancer type: the PD-L1 status will be derived based on Tumor Proportion Score (TPS) from Ventana data as follows:
    - If pembrolizumab is the first-line treatment, the PD-L1 status will be considered as negative if TPS < 50 and positive if TPS ≥ 50.
    - If pembrolizumab is the second-line treatment or beyond, the PD-L1 status will be considered as negative if TPS = 0 and positive if TPS ≥ 1.

A listing of baseline disease characteristics will also be provided.

4.6.3 Medical History and Prior Cancer Treatments

Medical/surgical history and prior cancer surgeries will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) and will be listed for all subjects in the Enrolled Population.

Prior cancer treatments (medication) will be coded using the World Health Organization (WHO) Drug dictionary (WHO Drug) and will be summarized by preferred term for the Safety Population by cancer type and in total and also be listed for all subjects in the Enrolled Population.

4.6.4 Prior and Concomitant Medications

Prior medications are those the subject used prior to the first dose date. Prior medications can be discontinued before first dosing or can be ongoing during treatment phase.

Concomitant medications are defined as medications that were either initiated prior to the first dose of study drug and continued during the study treatment, or initiated on or after the date of the first dose of study drug till the end of the last dose of study drug plus 30 days. A given medication can be classified both as a prior medication and as a concomitant medication depending on the start and stop dates.

A summary showing the number and percentage of subjects who took either prior and/or concomitant medications will be coded by WHO therapeutic drug class, and summarized separately by anatomic therapeutic class (ATC) and preferred term using frequencies and percentages for subjects in the Safety Population by cancer type and in total. In these summaries, subjects taking more than one medication in the same ATC or preferred name will be counted only once under that ATC or preferred term. All prior and concomitant medications will also be listed.

4.7 Efficacy Evaluations

All efficacy endpoints regarding response (i.e., ORR, DCR, and DOR) will be analyzed by cancer type [i.e., gastric adenocarcinoma and non-small cell lung cancer (NSCLC)] using the Tumor Response Evaluable Population for subjects for the Dose Escalation portion, Dose Expansion portion, and all subjects in both portions. The median DOR with two-sided 80% confidence intervals will be estimated using the Kaplan-Meier survival analysis methods. In addition, Kaplan-Meier estimates of rate of subjects with continuing response and the corresponding two-sided 80% confidence interval will also be provided.

All other efficacy endpoints (i.e., PFS and OS) will be analyzed by cancer type using the Efficacy Evaluable Population for the Dose Escalation portion, Dose Expansion portion, and all subjects in both portions. The median PFS, the median OS and two-sided 80% confidence intervals will be estimated using the Kaplan-Meier survival analysis methods. The Kaplan-Meier estimates of percent event-free for PFS, percent alive for OS and the corresponding two-sided 80% confidence intervals will also be provided.

All efficacy endpoints will be provided in listings for both Dose Escalation and Dose Expansion portions.

4.7.1 Definitions

Objective Response Rate

Objective Response Rate (ORR) is defined as the proportion of subjects who achieve an objective response, which will be calculated as the number of subjects with a CR or PR divided by the number of subjects in the analysis population of interest (i.e., Tumor Response Evaluable Population) multiplied by 100. ORR is defined using the RECIST v1.1 and irRC by cancer type for the Dose Escalation portion, Dose Expansion portion, and all subjects in both portions.

The primary efficacy endpoint of the study in the Dose Expansion portion is PEGPEM treatment effect on ORR. A confirmed response requires a confirmatory scan showing a CR or PR at least 28 days apart from the initial observation of CR or PR. Any scans done within 28 days that show CR, PR or NE (not evaluable) cannot be used as a confirmatory scan. In addition, ORR without confirmed response (unconfirmed) will also be analyzed.

The best overall response categories (CR, PR, SD, PD, and NE) defined using the RECIST v1.1 and irRC will be analyzed in summary tables. Listings of these response categories will be provided for both Dose Escalation and Dose Expansion portions.

Disease Control Rate

Disease Control Rate (DCR) is defined as the proportion of subjects who achieve a best overall response of CR, PR, or Stable Disease (SD) and will be calculated as the number of subjects with a best overall response of CR, PR or SD divided by the number of subjects in the analysis population multiplied by 100. DCR defined using the RECIST v1.1 and irRC will be analyzed with both summary tables and listings.

Duration of Response

Duration of Response (DOR) is defined as the time from the date on which an objective response (CR or PR) is first determined until the first date on which radiographic disease progression is

determined, and will only be calculated for subjects with an objective response (both confirmed and unconfirmed) for the Dose Escalation portion, Dose Expansion portion, and all subjects in both portions. Subjects achieving an objective response who do not have radiographic disease progression will be censored at the date of the last available post-baseline evaluable tumor assessment. DOR defined using the RECIST v1.1 and irRC will be analyzed with both summary tables and listings.

Progression-free Survival per RECIST v1.1

Progression-free survival (PFS), defined as the time from the first dose date until the first occurrence of either radiographic or clinical disease progression or death from any cause during the treatment period. Subjects without 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 – First dose date + 1) / 30.4375

Because the dosing interval between cycles without a dose is 7 days (from Day 15 to Day 21 of each cycle), the treatment period will include 7 days after the last dose date. Thus, subjects who are not radiologically or clinically progressed, but died within 7 days of the last dose will be considered as having PFS events. Deaths after 7 days of last dose without radiological or documented clinical progression will not be considered as PFS events in the primary PFS analysis. Table 3 below describes the scheme of events and censoring for PFS.

Progression-free Survival per irRC

PFS per irRC will be defined analogous to PFS per RECIST v1.1 by replacing RECIST v1.1 progression by irRC progression (irPD). In the schema shown in Table 3, replace ‘radiological’ disease progression per RECISIT v1.1’ by irPD and ‘First date of radiological disease progression’ by ‘First date of irPD’.

Table 3: Scheme of Events and Censoring for PFS per RECIST v1.1

Outcome	Situation	Date of Progression or Censoring
PFS Event	Radiological disease progression per RECIST v1.1 at scheduled or unscheduled visits or at End of Treatment visit	The earliest date of radiological disease progression, documented clinical progression, or death
	Death within 7 days of the last dose	
	Documented clinical progression	
Censoring for PFS (If no PFS Event)	No radiological or documented clinical disease progression, do not die within 7 days of the last dose, and have adequate tumor assessment at both Baseline and post-Baseline	Date of last adequate tumor assessment
	Discontinuation of treatment due to reasons other than radiological disease progression, or documented clinical progression	
	Death after 7 days of the last dose	
	No documented clinical disease progression, do not die within 7 days of the last dose, and had no adequate tumor assessment at either Baseline or post-baseline	First dose date

Overall Survival:

Overall Survival (OS) is defined as the time from the first dose date until death from any cause. OS data from surviving subjects will be censored at date of the last contact. OS (in months) will be calculated as:

(Death or censoring date – First dose date + 1) / 30.4375

To determine the date of the last contact, the latest date of the following should be used:

- Hospitalization admission and discharge dates
- Dosing dates
- Laboratory test, vital signs test and 12-Lead Electrocardiogram (ECG) test dates
- Immunogenicity assessment dates
- AE start and stop dates (full dates)
- Cancer therapies/medications/resections/radiation start and stop dates (full dates)
- Tumor assessment dates
- Brain scan dates

- Last known alive dates collected in long-term follow-up period
- Other clinical data which can confirm the subject's survival status

4.7.2 Analysis of Unconfirmed/Confirmed ORR, DCR and DOR

The primary efficacy endpoint of the study in Dose Expansion portion is PEGPEM treatment effect on confirmed ORR based on tumor assessments from the Investigator using RECIST v1.1. The statistical hypothesis tests for the primary endpoint are as follows:

- NSCLC cancer type: H_0: ORR $\leq$ 23%; H_1: ORR > 23%
- Gastric adenocarcinoma cancer type: H_0: ORR $\leq$ 15%; H_1: ORR > 15%

The hypothesis tests will be conducted using the one-sided exact binomial test at the significance level of 0.1. Thus, confirmed ORR and its two-sided 80% exact confidence interval will be provided to test each of the hypotheses above. If the lower limit of the exact confidence interval lies above 23% or 15% for NSCLC or gastric adenocarcinoma cancer types respectively, the respective null hypothesis will be rejected concluding a statistically significant effect of PEGPEM treatment in the respective cancer type. In addition, best overall response data will be summarized in frequency and percentage format by cancer type and the two-sided, exact 80% confidence intervals for the unconfirmed ORR and DCR will also be provided. Further, median DOR and its 80% confidence interval will be calculated and reported. Unconfirmed/confirmed ORR, DCR, and DOR will also be calculated based on irRC and displayed in summary tables and listings.

Additional efficacy analyses of ORR, DCR, and DOR related to NSCLC cancer type will also be performed using RECIST v1.1 data from Imaging Endpoints.

Note: Halozyme made the decision to discontinue further enrollment into the study on 31 May 2018. At the time of the early termination, a total of 25 gastric adenocarcinoma cancer subjects and 17 NSCLC subjects have been enrolled in the Dose Expansion portion. The planned sample size in the Dose Expansion portion is approximately 51 subjects (approximately 30 with HA-high tumors in NSCLC and approximately 21 with HA-high tumors in the gastric adenocarcinoma cohort). Therefore, a caveat regarding the interpretation of the results will be provided for the NSCLC cohort which is underpowered because of the early termination.

4.7.3 Analysis of PFS and OS

The PFS based on the RECIST v1.1 and irRC, and OS will be analyzed in summary tables by cancer type for the Dose Escalation portion, Dose Expansion portion, and all subjects in both portions.

The PFS based on the RECIST v1.1 and irRC, and OS will be presented by listings for both Dose Escalation and Dose Expansion portions. KM plots will also be constructed for PFS based on the RECIST v1.1 and OS for the Dose Escalation portion, Dose Expansion portion, and all subjects in both portions.

Additional efficacy analyses of PFS related to NSCLC cancer type will also be performed using RECIST v1.1 data from Imaging Endpoints.

4.7.4 Exploratory Analyses

PD-L1 expression levels in tumor tissues, plasma HA and tumor HA will be presented in data listings. No formal analysis regarding exploratory endpoints will be conducted.

4.7.5 Adjustment for Covariates

Not applicable.

4.7.6 Multicenter Studies

The center effect will not be considered for this study.

4.7.7 Multiple Comparisons/Multiplicity

There will be no adjustment for multiple hypothesis testing.

4.8 Subgroup Analysis

No subgroup analyses are planned.

4.9 Safety Evaluations

Safety evaluations include exposure to study medications, DLTs, adverse events (AEs), serious adverse events (SAEs), ECGs, vital signs, clinical laboratory and ECOG performance status. All AEs will be coded using the MedDRA. All safety summaries will be produced by cancer type and overall using the subjects in the Safety Population. The summary of DLTs in the Dose Escalation portion will be performed by cancer type, dose level and in total based on the DLT Evaluable Population.

4.9.1 Definitions

Dose Limiting Toxicity

See the definition stated under "Definition of DLT" in Section 6.1.1 of Protocol HALO-107-101 Amendment 4 entitled "A Phase 1b Open-Label Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) Combined with Pembrolizumab in Subjects with Selected Hyaluronan-High Solid Tumors" and dated 6 November 2017.

Treatment emergent adverse event

Treatment emergent adverse event (TEAE) is defined as any adverse event with an onset date on or after the first dose of any study drug up through and including 30 days after the last dose of any study drug.

In addition, any adverse event deemed related (i.e., eCRF categories: related, probably related or possibly related) to any study medication by the Investigator will also be considered as TEAE irrespective of the onset date.

4.9.2 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 adjusted

cumulative dose, average dose intensity, and relative dose intensity by cancer type and in total separately for the Dose Escalation portion and the Dose Expansion portion.

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 number of treatment cycles initiated >0, ≥2, ≥4, etc.

For each study medication (PEGPH20 and pembrolizumab), exposure will be summarized using descriptive statistics by cancer type and in total for the following parameters across all cycles.

- Number of cycles initiated
- Duration of treatment
- Number of doses 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 toxicity, chemotherapy toxicity, other adverse event, scheduling conflict, discontinued PEGPH20 and other
- Frequency and percentage of subjects with at least one dose PEGPH20 reduction

  For subjects with at least one PEGPH20 dose reduction:

  – Total number of doses administered

  – 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 following cycle is greater than 28 days after the first dose date of the cycle of interest.

  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 dose interruption by reason, including adverse event and other
  - Frequency and percentage of interrupted doses restarted

- Actual dose intensity (ADI) per cycle is defined as the cumulative dose divided by number of adjusted treatment cycles.
  - The weight-adjusted cumulative dose administered for PEGPH20 (in both Dose Escalation and Dose Expansion portions) and pembrolizumab (in the Dose Escalation portion only) is the sum of the respective doses administered at a given visit, divided by the subject's weight measurement (kg) at Screening. Cumulative dose for pembrolizumab (in the Dose Expansion portion only) is defined as the sum of administered doses.
  - If the last dosed cycle is Cycle 1, then number of adjusted treatment cycles is considered to be 1. If the last dosed cycle is Cycle 2 or beyond, then the number of adjusted treatment cycles will be calculated as [(End date of last cycle – First dose date + 1) / 21], where the end date of last cycle is calculated as [First dose date of last cycle + (Number of doses received or omitted in the last cycle up to the last dose received) * 20 / 3] for PEGPH20 and (Dose date + 20) for pembrolizumab. For PEGPH20, if the day of the visit of first dose date of last cycle is not 1, then an adjustment should be made by subtracting 7 or 14 depending on whether the day is 8 or 15 respectively.
- The planned dose intensity (PDI) for PEGPH20 is calculated as follows:
  - For the Dose Escalation portion, if the number of adjusted treatment cycles is 1, then the planned dose intensity per cycle (ug/kg) for each individual dosing cohort will be calculated as [(Dose level in ug/kg) * Number of doses received or omitted up to the last dose received in Cycle 1]. Else, the planned dose intensity per cycle (ug/kg) for each individual dosing cohort will be calculated as [(Dose level in ug/kg) * 3].
  - For the Dose Expansion portion, if the number of adjusted treatment cycles is 1, the planned dose intensity per cycle (ug/kg) will be calculated as [(RP2D dose in ug/kg) * Number of doses received or omitted up to the last dose received in Cycle 1]. Else, the planned dose intensity per cycle (ug/kg) will be calculated as [(RP2D dose in ug/kg) * 3].
- The PDI for pembrolizumab is calculated as follows:
  - For the Dose Escalation portion, the planned dose intensity per cycle is 2 mg/kg.
  - For the Dose Expansion portion, the planned dose intensity per cycle is 200 mg.
- The Relative dose intensity (RDI) (percent) is defined as follows:
  - [(ADI per cycle) / (PDI per cycle)] * 100%

  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%.

4.9.3 Analysis of DLTs

Dose Limiting Toxicities (DLTs) will be assessed for each subject in the Dose Escalation portion during the 21 days following their first PEGPH20 dose. Number and percent of subjects experiencing DLTs in the Dose Escalation portion will be tabulated by cancer type, dose level and in total for the DLT Evaluable Population. A listing of DLT events will also be provided.

4.9.4 Analysis of AEs

Only TEAEs will be tabulated by system organ class or standard MedDRA query (SMQ) or high level term, and preferred term for the subjects in the Safety Population by cancer type and in total. Summary tabulations include the following:

- An overall summary of TEAEs.
- Grade 3 or higher TEAEs
- Drug-related TEAEs
- Grade 3 or higher drug-related TEAEs
- TEAEs with outcome of death
- Treatment-emergent serious AEs (SAEs)
- PEGPH20 related treatment-emergent SAEs
- Pembrolizumab related treatment-emergent SAEs
- TEAEs leading to discontinuation of study drug
- TEAEs related to PEGPH20 leading to discontinuation of PEGPH20
- TEAEs related to pembrolizumab leading to discontinuation of pembrolizumab
- Summary of Treatment-emergent thromboembolic events by standard MedDRA query (SMQ)
- Summary of Treatment-emergent serious thromboembolic events by SMQ
- Bleeding TEAEs by SMQ
- Musculoskeletal TEAEs by MedDRA high level term.

Subjects experiencing the same AE more than once will have that event counted only once within each body system, and once within each preferred term in all summary tabulations. Listings will be provided for AEs leading to death, SAEs, grade 3 and above AEs, and AEs leading to discontinuation of study drug. Additionally, by-subject listings of the AEs will be presented including, but not limited to, verbatim term, preferred term, system organ class, NCI-CTCAE grade, and relationship to study drug.

4.9.5 Vital Signs and Body Weight

Vital signs assessments will be performed pre dose on Day 1, Day 8, and Day 15 of all cycles and at the End of Treatment visit. On all other days, vital signs will be evaluated for clinically significant AEs.

Vital signs including blood pressure (systolic and diastolic), heart rate (beats/min), respiratory rate (breaths/min), body temperature (˚C) and weight (kg) will be summarized by visit and by cancer type and in total using descriptive statistics.

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:

$$BSA = 0.007184 * W^{0.425} * H^{0.725}$$

By-subject listings of vital signs and body weight will also be provided.

4.9.6 Clinical Laboratory Evaluation

Clinical laboratory evaluations will be performed at specified time points per schedule of study events in the protocol. All clinical laboratory evaluations will be performed by a central laboratory. In addition, local laboratories may be used if immediate clinical decision making is required. The following clinical laboratory tests will be performed:

- Hematology: Minimally, scheduled hematology collections should include hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count, neutrophils (ANC), lymphocytes (absolute), monocytes (absolute), eosinophils (absolute), basophils (absolute), granulocytes (absolute), mean corpuscular hemoglobin, mean corpuscular volume, and platelet count
- Serum electrolytes and chemistry: glucose, blood urea nitrogen (BUN), albumin, total bilirubin, alkaline phosphatase, AST, ALT, electrolytes (including sodium, potassium, calcium, magnesium, chloride, and bicarbonate), and creatinine
- Coagulation parameters: international normalized ratio (INR), prothrombin time (PT), and partial thromboplastin time (PTT)
- Thyroid function tests: free T3, free T4, and TSH
- Urinalysis: protein, glucose, ketones, blood, specific gravity, nitrite, pH, and leukocytes

All lab values will be reported and summarized by cancer type and in total using standard international (SI) units. Only central lab data for hematology, serum electrolytes and chemistry, coagulation, and thyroid function tests will be used for summarizing laboratory values by visit and change from baseline. All lab data for hematology, serum electrolytes and chemistry, and coagulation 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. Laboratory results will be graded using NCI CTCAE V4.03, if applicable.

All clinical laboratory data will be listed, and values deemed clinically significant will be flagged. Frequency and percentage of subjects with laboratory values of ALT, AST, BILI, and ALP who meet Hy's law criteria (ALT > 3×ULN or AST > 3×ULN, BILI ≥ 2×ULN and ALP < 2×ULN) at any time point will be summarized by cancer type and in total.

4.9.7 12-Lead Electrocardiogram (ECG)

ECGs are taken at Screening, End of Treatment visit and as needed basis when clinically indicated. Frequency and percentage of subjects who had post-baseline abnormal (clinically significant or not clinically significant) ECG findings will be summarized by cancer type and in total.

A listing will be provided for the ECG data.

4.10 ECOG Performance Status

Frequency and percentage of subjects in each ECOG performance status score will be displayed at baseline. Listings of ECOG will be provided.

4.11 Immunogenicity Assessments

A blood sample will be collected from all subjects who receive PEGPH20 and analyzed to determine if PEGPH20 is eliciting a humoral immune response. Initial anti-drug antibodies (ADA) testing will be done using a multi-tiered approach per the Guidance, and immunocompetition will be performed to confirm an initial positive response in the screening assay. Any samples confirmed as positive in the ADA assay will then be assayed for neutralizing antibodies. ADA status (positive or negative) will be tabulated at each scheduled time point and overall at post-baseline for subjects receiving PEGPH20. Number and percent of subjects with positive neutralizing antibodies will be summarized descriptively at each scheduled time point and overall at post-baseline. For each subject, overall is defined as positive if at least one post-baseline neutralization test result is positive. A listing of the ADA data will also be provided.

4.12 Sample Size Determination

In the Dose Escalating portion, there may be up to 5 dose levels for a total of approximately 30 subjects.

In the Dose Expansion portion, approximately 51 subjects with HA-high tumors will be enrolled (30 with HA-high tumors in NSCLC cohort and 21 with HA-high tumors in the gastric adenocarcinoma cohort).

KEYNOTE-001 study data presented at the American Society of Clinical Oncology 2016 (Hui 2016) showed that when treated with pembrolizumab alone, treatment naïve subjects who had evaluable PD-L1 Tumor Proportion Score (TPS) levels had an ORR of 29% and previously treated subjects who had evaluable PD-L1 TPS levels had an ORR of 21%. Under the assumption that no more than 40% of the subjects enrolled in this study will be treatment naïve, ORR in the combined NSCLC population is expected to be approximately 24% when treated with pembrolizumab alone. A 20% improvement in ORR is considered clinically meaningful when PEGPH20 is added to pembrolizumab. Under these conditions, 30 NSCLC subjects would provide approximately 80% power at the hypothesized ORR of 44% when the null hypothesis H_0: ORR $\leq$24% is tested against H_1: ORR >24% using an exact one-sided binomial test at a 10% significance level. KEYNOTE-012 study data showed that the ORR in PD-L1 positive gastric cancer subjects is about 22% (Muro 2016). Since subjects will not be selected based on PD-L1 expression levels prospectively in this study, in order to accommodate all subjects (irrespective

of PD-L1 expression levels), a conservative ORR of 15% is assumed with pembrolizumab treatment alone and it is further assumed that the addition of PEGPH20 to pembrolizumab will lead to a clinically meaningful improvement of 20% in ORR to 35%. Under these assumptions, 21 subjects will provide approximately 80% power at the hypothesized ORR of 35% when the null hypothesis H_0: ORR ≤15% tested against H_1: ORR >15% using an exact one sided binomial test at a 10% significance level.

4.13 Interim Analysis and Early Stopping Rules

No formal interim analyses are planned for this study. However, since the combination of PEGPH20 and pembrolizumab have not been studied previously, to protect safety of the subjects, a Data Monitoring Committee (DMC) will review the accumulated safety data regularly. Frequency of these data reviews are documented separately in a DMC charter.

5 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

- In the protocol, Tumor Response Evaluable Population is defined as subjects in the Efficacy Evaluable Population who have at least one post-baseline tumor assessment. However, this definition was changed to “subjects in the Efficacy Evaluable Population who have at least one post-baseline tumor assessment on or post Cycle 2”.
- The protocol states that only values derived from the central labs will be utilized for study analysis and reporting purpose. However, all lab data from both central and local labs will be used for worst CTCAE grade at post-baseline visits and their shift from Baseline.

6 REFERENCES

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3. Muro K, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol 2016; 17: 717‑26