PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY

Statistical Analysis Plan for

Protocol Number: PICI0002

Protocol Title: Open-label, Multicenter, Phase 1b/2 Clinical Study to Evaluate the Safety and Efficacy of CD40 Agonistic Monoclonal Antibody (APX005M) Administered Together with Gemcitabine and nab-Paclitaxel with or without PD-1 Blocking Antibody (Nivolumab) in Patients with Previously Untreated Metastatic Pancreatic Adenocarcinoma

IND Number:	132683
Name of Products:	APX005M (experimental) Nivolumab (experimental) Gemcitabine (standard of care) nab-Paclitaxel (standard of care)
Phase of Development:	1b/2
Indication:	Previously untreated metastatic pancreatic cancer
Sponsor:	Parker Institute for Cancer Immunotherapy 1 Letterman Drive Suite D3500 San Francisco, CA 94129
Date Final:	Version 1: 26 Sep 2019 Version 2: 14 Feb 2020

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1 STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Version 2: 14 Feb 2020

The Statistical Analysis Plan was amended to add details about a second interim analysis of the Phase 2 portion of the study. Additional minor changes were made to improve clarity and consistency. No changes to the study endpoints, population definitions, or statistical methods were made.

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3 INTRODUCTION

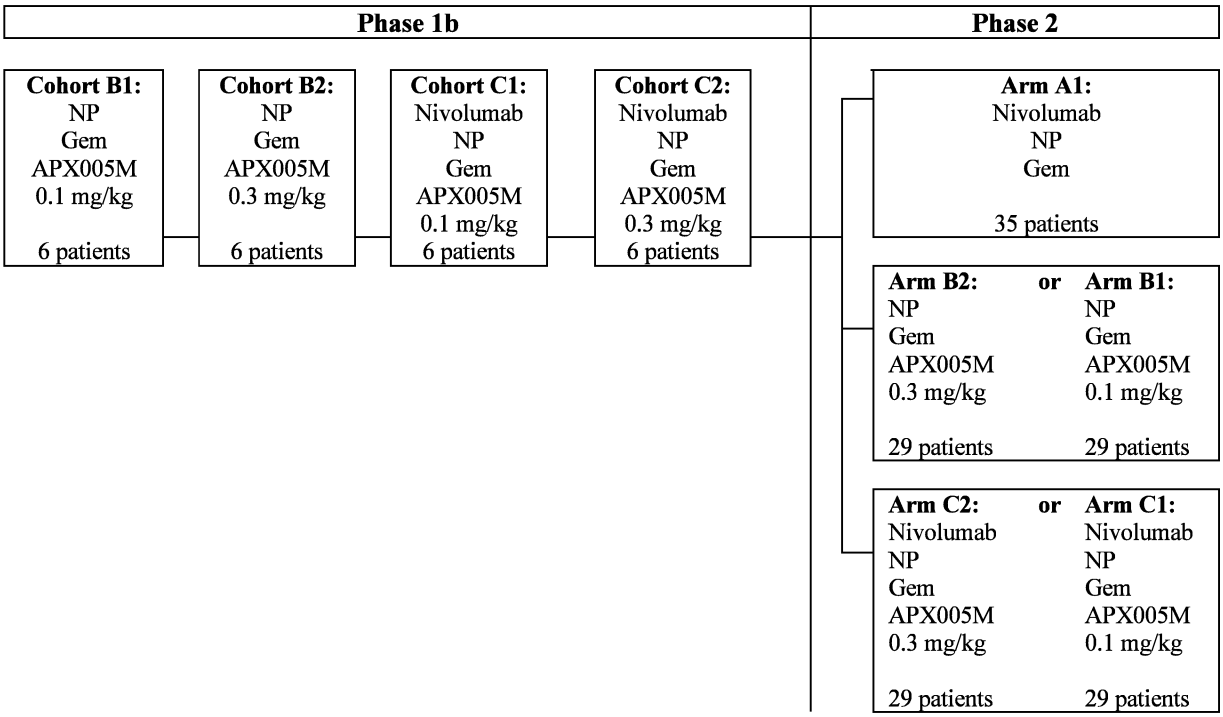
The purpose of this document is to provide details of the planned analyses for Protocol PICI0002. The analyses specified in this document supersede the high-level analysis plan described in the protocol. Statistical analyses will be performed consistent with the principles of the ICH/FDA Guidance for Industry E9 Statistical Principles for Clinical Trials.

4 STUDY DESIGN

PICI0002 is a multi-center, open label, Phase 1b/2 study of the immunotherapy agents APX005M and nivolumab, in combination with Gemcitabine (Gem) and nab-Paclitaxel (NP) in patients with previously untreated metastatic pancreatic adenocarcinoma.

Phase 1b will involve 4 sequential treatment cohorts, and Phase 2 will involve randomization to 3 treatment arms, as shown in Figure 1.

Figure 1 Study Flow Chart



Phase 1b

In the Phase 1b portion of the study, 4 treatment cohorts will be evaluated sequentially for feasibility and safety. Each cohort of the study will have 6 DLT-evaluable patients, defined as patients who experienced a Dose-Limiting Toxicity (DLT) or who completed the DLT observation period, i.e. received at least 2 doses of NP/Gem and 1 dose of APX005M during

Cycle 1. Patients who do not experience a DLT and who do not complete the DLT observation period will be replaced.

In general, a DLT is defined as: (1) any Grade 3 or higher non-hematologic or Grade 4 hematologic toxicity occurring during the DLT observation period that is considered to be at least possibly related to APX005M and/or nivolumab, or (2) an exacerbation of known NP/Gem toxicity that is at least possibly related to APX005M and/or nivolumab. A more comprehensive definition of a DLT can be found in the protocol. The DLT observation period is defined as the time of first administration of investigational agents until Cycle 2 Day 1.

Dose escalation will proceed if 1 or fewer DLT-evaluable patients experience a DLT during this observation period. Dose escalation will cease if 2 or more DLT-evaluable patients in a cohort experience a DLT.

On the basis of discussions among the site PIs, Sponsor, and other stakeholders, concerning feasibility, safety, clinical and immune pharmacodynamic (PD) effects (totality of available data), the recommended Phase 2 dose is defined by the highest APX00M dose with < 2 DLT in 6 DLT-evaluable patients, unless the totality of available data suggests a lower APX005M dose.

Randomized Phase 2

Once the recommended Phase 2 dose (RP2D) of APX005M in combination with nivolumab from Cohort C in the Phase 1b portion of the study is determined, the randomized Phase 2 portion will commence. Patients will be randomized to Arm A1, Arm B2, or Arm C2, or to Arm A1, Arm B1, or Arm C1, if Cohort B2 and/or C2 are deemed unsafe in Phase 1b. Note that the APX005M dose must be the same in Arms B and C, regardless of whether a higher APX005M dose was determined to be safe in Arm B. For each regimen, efficacy will be evaluated by comparing the 1-year overall survival (OS) rate to the historical value for NP/Gem. A total of approximately 93 patients will be randomized in Phase 2 (35 Arm A1, 29 Arm B2, 29 Arm C2).

All patients will be followed up for survival status until death or a maximum of 5 years. Once a patient is in follow-up, follow up can be obtained with a clinic visit or a phone call approximately every 6 months.

It is common for randomized Phase 2 studies that test the addition of an experimental agent to a standard of care regimen to include the standard of care arm. However, the setting for this study is unique. NP/Gem, the standard of care regimen, was reported recently in a very similar patient population, and the 1-year OS rate was estimated with extremely high precision (i.e., 1-year OS rate was 35% with 95% CI 30%-39%) based on 431 treated patients (Von Hoff et al.). With hundreds of pancreatic patients treated with NP/Gem since that report, experts in this

field agree that the 1-year OS rate estimate appears to be very robust. Thus, this study will not include a standard of care arm.

The 12 DLT-evaluable patients who were enrolled in Phase 1b at the recommended Phase 2 doses (6 on Arm B and 6 on Arm C) will be included in the efficacy evaluation and 93 additional patients will be randomized in Phase 2, for a total sample size of 105 patients (35 per treatment arm).

4.1 Protocol Synopsis

The Protocol Synopsis is provided in Section 9.1.

4.2 Study Objectives

This study will be conducted in two phases, each with its own objectives.

4.2.1 Phase 1b

Primary Objectives:

1. To determine the feasibility, safety, and DLTs of each treatment cohort.
2. To determine the recommended Phase 2 dose of APX005M when combined with NP/Gem.
3. To determine the recommended Phase 2 dose of APX005M when combined with nivolumab/NP/Gem.

Secondary Objectives:

1. To determine objective response rate (ORR) and duration of responses (DOR) of each treatment cohort.

Exploratory Objectives:

1. To assess the pharmacokinetics (PK) of APX005M in Cycles 1 to 4.
2. To assess immune pharmacodynamic effects of each treatment cohort, in both blood and tumor tissue.

4.2.2 Phase 2

Primary Objectives:

1. To estimate the OS of each treatment arm.
2. To compare 1-year OS rate of each treatment arm to the historical rate for NP/Gem.

Secondary Objectives:

1. To determine the ORR, disease control rate (DCR), DOR, and progression-free survival (PFS) of each treatment arm.
2. To further characterize the feasibility and safety of each treatment arm.

Exploratory Objectives:

1. To assess the PK of APX005M in Cycles 1 to 4 (Arms B and C).
2. To assess immune pharmacodynamic effects of each treatment arm, in both blood and tumor tissue.
3. To assess associations between immune biomarkers and clinical outcomes.
4. To evaluate baseline and on-treatment microbiome profiles.
5. To construct multivariable linear models to dissect the pharmacodynamic effects of APX005M and nivolumab on immune biomarkers.

4.3 Study Endpoints

The study endpoints are listed in the Protocol Synopsis (Section 9.1).

4.4 Determination of Sample Size

4.4.1 Phase 1b

Assuming 4 treatment cohorts will be evaluated sequentially for feasibility, safety, and dose-limiting toxicities, 24 DLT-evaluable patients will be enrolled (6 per cohort). Patients who do not experience a DLT and who do not complete the DLT observation period will be replaced.

The Phase 1b sample size was determined by practical considerations and was not based on statistical power calculations. Six patients dosed in each group was deemed sufficient to characterize the feasibility, safety, and DLTs of each cohort. Based on this sample size, Table 1 provides the probability of failing to accept a cohort as safe, defined as ≥ 2 DLTs in 6 treated patients, assuming different DLT rates.

Table 1 Probability of Failing to Accept a Dose Level at Different Event Rates

DLT Event Rate	1%	10%	20%	25%	33%	50%
Probability [a]	0.001	0.11	0.34	0.47	0.64	0.89

DLT = dose-limiting toxicity

[a] Assumes $P(X \geq 2)$ where X is a binomial random variable with sample size n = 6 and p = DLT event rate.

4.4.2 Phase 2

The 12 DLT-evaluable patients who were enrolled in Phase 1b at the recommended Phase 2 doses (6 on Arm B and 6 on Arm C) will be included in the efficacy evaluation and approximately 93 additional patients will be randomized in Phase 2, for a total sample size of 105 patients (35 per treatment arm). This is a screening study, such that for each treatment arm, the 1-year OS rate will be estimated and compared with a historical value of 35% for NP/Gem (Von Hoff et al.). The study is not powered to detect a meaningful difference in OS among the 3 arms, since these are novel experimental arms and OS is unknown.

The null hypothesis is a 1-year OS rate of 35% and the alternative hypothesis is a 1-year OS rate of 58%. The 1-year OS rate is estimated by the Kaplan-Meier method. A sample size of 35 patients on each arm provides 88% power to test this hypothesis, using a 1-sided one-sample Z test with 5% type I error rate, assuming a minimum of 1 year of follow-up for each patient. Moreover, the sample size of 35 patients on each arm, provides 81% power to statistically test the null hypothesis versus a slightly more conservative alternative hypothesis that the 1-year OS rate is 55%, given the same design assumptions.

These calculations assume that 105 patients (35 patients x 3 arms) will be enrolled. There is no assumption about the duration of patient enrollment, only that there will be a minimum of 1 year of follow-up for each patient.

4.5 Analysis Timing

The database lock for analysis of the Phase 2 primary endpoint of 1-year overall survival (OS) rate will occur approximately one year after the last patient is randomized. No changes to the SAP will be allowed at the time of or subsequent to database lock.

Analysis of the Phase 1b endpoints may be performed prior to the time of primary analysis. These results may be presented and/or published prior to the primary analysis.

The study will formally end once all patients have been followed for survival status until death or a maximum of 5 years, withdrawal of consent, or loss to follow-up. A survival analysis of long-term follow-up may be performed after the primary analysis has been completed.

5 STUDY CONDUCT

5.1 Randomization Details

In Phase 1b, patients will be enrolled sequentially into 4 cohorts (B1, B2, C1, and C2) as summarized in Table 2. The Phase 1b portion of the study is non-randomized. Enrollment in Cohorts B2 and C1 may occur concurrently.

Table 2 Phase 1b Treatment Assignment

Arm	Regimen	Number of DLT-Evaluable Patients
B1	NP/Gem/APX005M 0.1 mg/kg	6
B2	NP/Gem/APX005M 0.3 mg/kg	6
C1	Nivolumab/NP/Gem/APX005M 0.1 mg/kg	6
C2	Nivolumab/NP/Gem/APX005M 0.3 mg/kg	6

DLT = dose-limiting toxicity; Gem = gemcitabine; NP = nab-paclitaxel

Once the RP2D of APX005M in combination with nivolumab from Cohort C in the Phase 1b portion of the study is determined, the randomized Phase 2 portion will commence. Patients will be randomized to Arm A1, Arm B2, or Arm C2, or to Arm A1, Arm B1, or Arm C1, if Cohort B2 and/or C2 are deemed unsafe in Phase 1b. Note that the APX005M dose must be the same in Arms B and C, regardless of whether a higher APX005M dose was determined to be safe in Arm B.

A total of 105 patients will be evaluated in the Phase 2 portion of the study, including 12 DLT-evaluable patients from Phase 1b (i.e., 6 patients on B1 and 6 patients on C1 or 6 patients on B2 and 6 patients on C2). The remaining 93 patients will be randomized and treated only in Phase 2. In step 1 of randomization, 12 of the 93 new patients will be randomized to the 3 arms in a 4:1:1 ratio in Arms A1, B2, and C2 (or A1, B1, and C1), to achieve balance in the total number of patients enrolled on the arms (since Arm A1 does not accrue in Phase 1b, more patients need to be enrolled in Arm A1). In step 2 of randomization, 81 patients will be randomized to Arms A1, B2, and C2 (or A1, B1, and C1) in a 1:1:1 allocation. The randomization design is outlined in Table 3.

Table 3 Phase 2 Design

Arm	Regimen	Phase 1b	Phase 2		Total
			Step 1	Step 2	
		Number of patients	Number of patients	Number of patients	Number of patients
A1	Nivolumab/NP/Gem	0	8	27	35
B2 [a]	NP/Gem/APX005M 0.3 mg/kg	6	2	27	35
C2 [a]	Nivolumab/NP/Gem/APX005M 0.3 mg/kg	6	2	27	35

[a] Or B1 and C1, if either B2 or C2 is not tolerable.
Gem = gemcitabine; NP = nab-paclitaxel

Randomization will be managed by the Parker Institute for Cancer Immunotherapy (PICI), using an interactive voice response system (IVRS). The randomization is not stratified by baseline patient or tumor characteristics.

5.2 Blinding

This is an open-label study with no blinding.

5.3 Data Monitoring

The study will be closely monitored, and data will be reviewed on an ongoing basis. In order to ensure the safety and well-being of participating patients, as well as the validity of data during the study, a Data Review Team (DRT) will review the safety and further emerging data on a regular basis. The DRT consists of members from the Sponsor, the overall Principal Investigator (PI), the lead statistician, and all active PIs. The DRT will adjudicate DLTs relevant for the treatment and will decide by consensus on dose escalation, dose de-escalation, prolongation of the DLT observation period, suspension of enrollment based on safety, PK, or possibly pharmacodynamic data, and will recommend the dose level for the Phase 2 portion.

5.3.1 Early Termination Rules for Unacceptable Toxicity in Phase 2

A Bayesian rule will be employed to monitor toxicity during Phase 2. A minimally informative beta (0.5, 2.5) prior has been assumed, which is information that is equivalent to ½ the weight of 1 DLT in 6 patients treated, the definition of a safe dose in Phase 1b. For each treatment arm, if the number of patients with an unacceptable toxicity (defined the Section 6.1 of the study protocol) is greater than or equal to the number in Table 4, then termination of that particular treatment arm will be considered, as it is likely that the toxicity rate is >30%, as noted by the Bayesian posterior probabilities. This rule is intentionally conservative early in the enrollment phase.

Table 4 Bayesian Termination Rules

Rules for Unacceptable Toxicity Rate >30%					
Patients treated on an arm	10	15	20	25	30
Patients with unacceptable toxicity	4	6	9	11	13
Posterior Probability [toxicity rate >30%]	0.61	0.69	0.87	0.88	0.90
Action	Consider termination of arm, re-evaluate study design.				

6 STATISTICAL METHODS

Summary statistics will be presented by treatment arm. For continuous variables, data will be summarized with the number of patients (N), mean, standard deviation, median, minimum, and maximum by treatment arm. For categorical variables, data will be tabulated with the number and proportion of patients for each category by treatment arm.

6.1 Analysis Populations

6.1.1 Safety Population

The safety population consists of all patients who received at least 1 dose of any study drug. This is the population for the analyses of safety. A subset of the safety population is the DLT-evaluable population.

For the safety analyses, patients will be analyzed according to the treatment regimen actually received. Using a conservative approach:

- Phase 1b patients who receive at least one dose of nivolumab but do not receive APX005M will be analyzed under Arm C1. Phase 2 patients who receive at least one dose of nivolumab but do not receive APX005M will be analyzed under Arm A1.
- Phase 1b patients who receive at least one dose of APX005M but do not receive nivolumab will be analyzed under Arm B1 or B2, depending on the highest dose level of APX005M received. Phase 2 patients who receive at least one dose of APX005M but do not receive nivolumab will be analyzed under Arm B2 (the dose level selected for Phase 2 enrollment).
- Phase 1b patients who receive at least one dose of both APX005M and nivolumab will be analyzed under Arm C1 or C2, depending on the highest dose level of APX005M received. Phase 2 patients who receive at least one dose of both APX005M and nivolumab will be analyzed under Arm C2 (the dose level selected for Phase 2 enrollment).
- Patients who receive at least one dose of NP/Gem but do not receive APX005M or nivolumab will be analyzed under the treatment arm assigned at enrollment (Phase 1b) or randomization (Phase 2).

6.1.2 DLT-evaluable Population

The DLT-evaluable population consists of patients who (1) were enrolled in Phase 1b, (2) received at least 2 doses of NP/Gem and 1 dose of APX005M during Cycle 1, and (3) completed the DLT observation period (i.e. from the time of first administration of study

intervention until Cycle 2 Day 1). Alternatively, patients who did not complete the DLT observation period due to a DLT event will also be considered DLT evaluable.

The DLT-evaluable population is the population for analyses of Phase 1b efficacy and DLTs. Patients will be grouped according to the treatment arm assigned at enrollment, regardless of the treatment actually received.

6.1.3 Efficacy Population

The efficacy population consists of (1) all patients who were randomized in Phase 2 and received at least 1 dose of any study drug and (2) the 12 DLT-evaluable patients (6 on Arm B and 6 on Arm C) who were enrolled in Phase 1b at the recommended Phase 2 dose. The efficacy population is the population for the primary analyses of efficacy in Phase 2. Patients will be grouped according to the treatment arm assigned at enrollment/randomization, regardless of the treatment actually received.

6.2 Analysis of Study Conduct

The number of patients enrolled in Phase 1b and randomized in Phase 2 will be tabulated by treatment arm. Patient disposition (e.g. the number of patients enrolled/randomized, receiving at least one dose of study drug) and time on study will be tabulated by treatment arm and may be represented graphically (e.g. swim lane plot). Reasons for premature discontinuation from study treatment and reasons for premature discontinuation from the study, including the 5-year follow-up period, will be summarized.

Feasibility, defined by the number of Phase 1b patients who complete the DLT observation period and receive the intended therapy without delays or dose modification, will be described for each treatment arm.

6.3 Analysis of Treatment Group Comparability

Demographic and baseline characteristics, including but not limited to age, sex, race, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status at baseline, cancer location (pancreas body, head, or tail) and cancer stage at initial diagnosis and enrollment will be summarized by treatment arm using descriptive statistics for all enrolled/randomized patients.

The baseline value of any variable will be defined as the last available value recorded prior to the first administration of study drug.

Previous and concomitant cancer therapy will also be summarized, including radiotherapy and surgery, as well as subsequent anti-cancer therapy. Previous and concurrent diseases and medications will be listed.

6.4 Efficacy Analysis

Phase 2 efficacy analyses will be conducted on the efficacy population (see Section 6.1.3), with patients grouped according to the treatment assigned at randomization. Phase 1b efficacy analyses will be conducted on the DLT-evaluable population.

Efficacy summaries will include data from patients who discontinued study drug early but continued with study assessments and may include data collected at unscheduled visits, early termination visits, or follow-up visits.

6.4.1 Comparisons of Interest

The 1-year OS rate and 1-sided 95% confidence interval will be calculated for each treatment arm, to determine whether the lower bound of the confidence interval (CI) excludes the assumed historical value for NP/Gem of 35%.

This study is not powered for statistical comparisons between arms.

6.4.2 Type I Error Management

Due to the exploratory nature of this study, no control of type I error will be applied for any of the endpoints.

6.4.3 Covariate Adjustment

Unless otherwise noted, analyses of primary and secondary efficacy endpoints will not be adjusted for additional covariates.

6.4.4 Primary Efficacy Endpoint

There is no primary efficacy endpoint for Phase 1b. The Phase 2 primary efficacy endpoint is the 1-year OS rate in each treatment arm. OS is defined as the time from initiation of study therapy to date of death due to any cause. Patients who are not reported as having died at the time of analysis will be censored at their most recent contact date they were known to be alive. Patients who do not have post-baseline survival information will be censored at the date of randomization. See Section 6.6.2 for handling of missing or partial death dates.

OS will be estimated by the Kaplan-Meier method for each treatment arm. For each treatment arm, the following parameters and analyses will be provided: Kaplan-Meier product-limit estimates of the OS distribution functions, the total number of patients, the total censored, the total deaths, the OS time (median and its 95% CI; 25th and 75th percentiles), and the survival rates at monthly intervals (i.e. 3, 6, 9, 12, etc. months).

The 1-year OS rate and 1-sided 95% confidence interval will be calculated for each treatment arm, to determine whether the lower bound of the confidence interval (CI) excludes the assumed historical value for NP/Gem of 35%.

A 1-sided one-sample Z test will also be conducted. The goal is to compare the survival probability at time t to the historical value. The null hypothesis is H_0: $S(t) \leq s^*$ at time t. The alternative hypothesis is H_1: $S(t) > s^*$, a one-sided test.

The Z test is:

$$\frac{\hat{S}(t) - s^*}{\widehat{SE}(\hat{S}(t))}$$

where $\hat{S}(t)$ and $\widehat{SE}$ are sample estimates. For this study, t = 1 year, $\hat{S}(t)$ = estimated 1-year OS probability from the Kaplan-Meier analysis, $\widehat{SE}(\hat{S}(t))$ = standard error of $\hat{S}(t)$ and null hypothesis $s^* = 0.35$.

A survival follow-up analysis may be performed based on more mature data.

6.4.5 **Secondary Efficacy Endpoints**

Secondary efficacy endpoints for Phase 1b include ORR and DOR. The Phase 1b efficacy endpoints will be analyzed for the DLT-evaluable population.

Secondary efficacy endpoints for Phase 2 include ORR, DCR, DOR, and PFS. The Phase 2 efficacy endpoints will be analyzed for the efficacy population.

6.4.5.1 Objective Response Rate

ORR, on the basis of investigator assessment, is defined as the proportion of patients who attain a complete response (CR) or partial response (PR). Per RECIST v1.1, confirmation of objective response is not required for this secondary endpoint. Patients without a post-baseline tumor assessment will be considered non-responders, as well as patients with a best overall response of stable disease (SD), progressive disease (PD) or not evaluable (NE). For a patient to have a best overall response of SD, he/she must have at least one post-baseline tumor assessment of SD at least 7 weeks after treatment initiation (8 weeks minus 7-day window; study day 49).

A 95% confidence interval for the rate will be estimated for each treatment arm using the Clopper-Pearson method.

Spider plots and waterfall plots will be generated to visualize changes in the sum of target lesions.

6.4.5.2 Duration of Response

For patients who have experienced an objective response (CR or PR) during the study as assessed by the investigator, DOR is defined as the time from the first tumor assessment that documents response (CR or PR, whichever is recorded first) to first documentation of

radiographic PD per RECIST v1.1. Patients who have not progressed at the time of analysis will be censored at the last tumor assessment date prior to the start of subsequent systemic anti-cancer therapy. The Kaplan-Meier method will be used to estimate the median DOR for each treatment arm with 95% confidence limits.

6.4.5.3 Disease Control Rate

DCR is defined as the proportion of patients who achieve a best response of CR, PR, or SD. For a patient to have a best overall response of SD, he/she must have at least one post-baseline tumor assessment of SD at least 7 weeks after treatment initiation (8 weeks minus 7-day window; study day 49). Patients without a post-baseline tumor assessment will be considered non-responders, as well as patients with a best overall response of PD or NE. A 95% confidence interval for the rate will be estimated for each treatment arm using the Clopper-Pearson method.

DCR will also be estimated at 6 and 12 months. For these landmark analyses, DCR is defined as the proportion of patients who have a response of CR, PR, or SD at the first tumor assessment on or after the landmark time. Accounting for the Q8W (i.e. every 8 weeks) schedule and 7-day window for disease assessment, 6-month DCR will consider the first evaluable scan after study day 161 (24 weeks – 7 days) and 12-month DCR will consider the first evaluable scan after study day 329 (48 weeks – 7 days). Patients without an evaluable disease assessment after the landmark time will be considered non-responders.

6.4.5.4 Progression-free Survival

PFS is defined as the time from initiation of study therapy to date of first documented radiographic progression of disease or date of death due to any cause, whichever occurs first. PFS will be determined on the basis of investigator assessment of progression using RECIST v1.1. Patients who have not progressed or died at the time of analysis will be censored at the last tumor assessment date prior to the start of subsequent systemic anti-cancer therapy. Patients with no post-baseline tumor assessment will be censored at the date of study therapy initiation. The Kaplan-Meier method will be used to estimate the median PFS for each treatment arm with 95% confidence limits.

PFS will also be estimated at various landmark times (e.g. 6 and 12 months).

6.4.6 **Exploratory Efficacy Endpoints**

Exploratory endpoints defined in the protocol and listed in Section 9.1 are outside the scope of this SAP. Biomarker analyses will be detailed in a Translational Analysis Plan.

6.4.7 **Subgroup Analyses**

For each treatment arm, OS will be analyzed in the subset of patients in the efficacy population who remain on treatment for at least 3 cycles (i.e. receive at least one dose of any study drug

in Cycle 4) vs. those who remain on treatment for 3 cycles or less. This subset is in contrast to the efficacy population analyzed in the primary analysis. The 1-year OS rate and 1-sided 95% confidence interval will be calculated.

6.4.8 Sensitivity Analyses

The following sensitivity analyses will be performed:

- Efficacy analyses will be performed on the Phase 2 Efficacy Population, defined as all patients who were randomized in Phase 2 and received at least 1 dose of any study drug. This population similar to the Efficacy Population but excludes the 12 DLT-evaluable patients who were enrolled in Phase 1b at the recommended Phase 2 dose.
- If the number of patients dosed in Phase 1b does not match the DLT-evaluable population, ORR and DOR will be calculated for all patients who received at least one dose of study drug in Phase 1b (i.e. the safety population).
- If any Phase 2 patients were randomized but not dosed, Phase 2 primary and secondary efficacy endpoints may be analyzed using an intention-to-treat (ITT) approach. For these analyses, all randomized patients will be included, grouped according to the treatment assigned at randomization.
- The impact of response confirmation on ORR will be assessed by requiring confirmation of CR or PR at least 4 weeks after initial documentation.
- The effect of death on DOR will be assessed by defining DOR as the time from the first tumor assessment that documents response (CR or PR, whichever is recorded first) to first documentation of radiographic progressive disease or death, whichever occurs first. Patients who have not progressed or died at the time of analysis will be censored at the last tumor assessment date prior to the start of subsequent systemic anti-cancer therapy.

6.5 Safety Analysis

Safety will be assessed through the summary of adverse events (AEs), serious adverse events (SAEs), DLTs, laboratory test results (hematology and serum chemistry), vital signs, and physical examinations. This may include data collected at unscheduled visits, early termination visits, or follow-up visits.

The baseline value of any variable will be defined as the last available value recorded prior to the first administration of study medication. If multiple values are available at the same visit, the mean of the values will be used for analysis at that timepoint.

Safety outcomes will be summarized based on the safety population (see Section 6.1.1). Safety summaries will be presented by the treatment regimen actually received.

6.5.1 Exposure to Study Medication

The number of patients exposed to each study drug and the extent of exposure (as number of doses, cumulative dose received, and relative dose received) will be summarized using descriptive statistics. Relative dose received is defined as the total amount of each drug actually received divided by the amount of drug the patient would have been expected to receive had he/she received all planned doses without any dose modifications until the date of treatment discontinuation.

6.5.2 Adverse Events

All reported AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A treatment-emergent adverse event (TEAEs) is defined as any new adverse event or any worsening of an existing condition with an onset date on or after the first dose of study drug. AEs with relationship to study drug of "Possibly", "Probably", "Definitely" or unknown (missing) will be considered treatment related.

For each patient and each AE, the worst severity/grade recorded will be attributed and used in the severity summaries.

Listings for all AEs, SAEs, and TEAEs will be presented by patient. Listings will include information regarding onset day/date, end day/date, duration, relationship to study drug, severity, action taken with study drug, whether concomitant medication was administered and outcome.

Summaries of TEAEs (overall, by system organ class and preferred term and by severity) by treatment arm will be provided for each of the following categories:

- AEs
- AEs by most extreme severity
- Treatment-related AEs
- SAEs
- Treatment-related SAEs
- AEs leading to discontinuation of study treatment
- DLTs
- AEs from patients enrolled in Phase II that meet the protocol-defined unacceptable toxicity criteria

The proportion of events that are resolved at the time of analysis will be presented. In addition, patient deaths and the primary cause of death will be listed, as well as any cases of pregnancy.

6.5.3 Laboratory Data

Descriptive summaries of clinical laboratory values at each timepoint, including changes from baseline, will be generated for hematology and chemistry parameters by treatment arm. The proportion of patients with values outside the normal upper and lower limit at each visit will be displayed.

In addition, select laboratory parameters (including, but not limited to, AST, ALT, alkaline phosphatase and total bilirubin) will be summarized by grade using the CTCAE grading scale.

Missing laboratory values will not be imputed. Analysis will only occur on observed values.

6.5.4 Vital Signs

Vital signs will be summarized by treatment arm using descriptive statistics including mean values and mean change from baseline.

Missing vital signs will not be imputed. Analysis will only occur on observed values.

6.6 Missing Data

6.6.1 Missing and Partial Missing Adverse Event Dates

If the AE start date is not a complete date, the following rules will be applied to determine whether the event is treatment emergent.

- If the start date is completely missing: The AE will be assumed to be treatment-emergent unless the AE stop date is earlier than the date of first dose of study drug.
- If the day part of the AE start date is missing: If the month and year of the start date are later than or equal to the month and year of the date of first dose of study drug, then the AE will be assumed to be treatment emergent. If the month and year of the stop date are earlier than the month and year of the date of first dose of study drug, then the event will be assumed to be non-treatment emergent.
- If the day and month of the start date are missing: If the year of the start date is later than or equal to year of the date of first dose of study drug, then the AE will be assumed to be treatment emergent. If the year of the stop date is earlier than the year of the date of first dose of study drug, then the event will be assumed to non-treatment emergent.

6.6.2 Missing and Partial Missing Death Dates

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive plus 1 day, and the maximum will be considered as the death date.

- If the month or the year is missing, the death date will be imputed as the last known date alive plus 1 day.
- If the date is completely missing but the reason for death is present, the death date will be imputed as the last known date alive plus 1 day.

6.7 Interim Analyses

Given the hypothesis generating nature of this study, the Sponsor may conduct two interim analyses of safety and efficacy during the Phase 1b and Phase 2 portions of the study. These interim analyses are strictly meant to support decision making for future studies. No adaptations (e.g. sample size re-estimation, early stopping for futility or efficacy, dropping/adding arms, modifying dose levels) will be made to the study based on the interim results. The analysis will be performed and interpreted by members of the Sponsor study team and management. Full results will be shared with management of the pharmaceutical partners of this study (Apexigen and Bristol-Myers Squibb), as their input is critical for decision making and design of future studies using this treatment regimen. Safety and limited efficacy results will be shared with study Investigators because they are key contributors to the design of an in-development clinical trial that may use the treatment regimens being tested in this study. To limit potential bias, any interim efficacy data shared with Investigators while patients are still receiving study therapy will only be presented as graphical summaries (spider and/or waterfall plots of BOR) with cohort names/identifiers masked.

The first interim analysis will be conducted approximately 3 months after the last patient is randomized in the Phase 2 portion. The following endpoints will be summarized for the first interim analysis:

- Study conduct including enrollment, demographics, and disposition
- Adverse events
- Phase 1b efficacy endpoints: ORR, DCR, DOR, OS, PFS
- Phase 2 efficacy endpoints: ORR, DCR

The second interim analysis will be conducted approximately 8 months after the last patient is randomized in the Phase 2 portion. The following endpoints will be summarized for the second interim analysis:

- Study conduct including enrollment, demographics, and disposition
- Adverse events
- Phase 1b efficacy endpoints: ORR, DCR, DOR, OS, PFS

- Phase 2 efficacy endpoints: ORR, DCR, DOR, PFS

The Phase 2 primary endpoint of OS will not be analyzed for Phase 2 patients during either interim analysis. Due to the exploratory nature of this study, no control of type I error will be applied for any of the endpoints at the interim or final analysis.

7 DIFFERENCES COMPARED TO PROTOCOL

- Section 4.4 (Determination of Sample Size): The SAP provides additional justification for the Phase 1b sample size.
- Section 6.1.1(Safety Population): The SAP clarifies that for the safety analyses, patients will be analyzed according to the treatment actually received.
- Section 6.1.2 (DLT-evaluable Population): The SAP clarifies that the DLT-evaluable population is the population for analyses of Phase 1b efficacy and DLTs.
- Section 6.4.7 (Subgroup Analyses): The protocol states that OS will be analyzed in the subset of patients who remain on study for at least 6 weeks. The SAP modifies this subgroup to patients who remain on treatment for at least 3 cycles.
- Section 6.7 (Interim Analyses): The SAP provides justification for and details about the two optional interim analyses of efficacy data.

8 REFERENCES

ICH/FDA Guidance for Industry E9 Statistical Principles for Clinical Trials. U.S. Department of Health and Human Services, Food and Drug Administration, September 1998.

Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691-703.

9 APPENDICES

9.1 Protocol Synopsis

Title of Study:	Open-label, Multicenter, Phase 1b/2 Clinical Study to Evaluate the Safety and Efficacy of CD40 Agonistic Monoclonal Antibody (APX005M) Administered Together with Gemcitabine and nab-Paclitaxel with or without PD-1 Blocking Antibody (Nivolumab) in Patients with Previously Untreated Metastatic Pancreatic Adenocarcinoma
Protocol Number:	PICI0002
Phase of Development:	1b/2
Objectives:	**Phase 1b:** Primary: 1. To determine the feasibility, safety and dose-limiting toxicities (DLT) of each treatment cohort. 2. To determine the recommended Phase 2 dose (RP2D) of APX005M when combined with nab-paclitaxel (NP)/gemcitabine (Gem). 3. To determine the RP2D of APX005M when combined with nivolumab/NP/Gem. Secondary: 1. To determine objective response (OR) and duration of response (DOR) of each treatment cohort. Exploratory: 1. To assess the pharmacokinetics (PK) of APX005M in Cycles 1 to 4. 2. To assess immune pharmacodynamic effects of each treatment cohort, in both blood and tumor tissue. **Phase 2:** Primary: 1. To estimate overall survival (OS) of each treatment arm. 2. To compare 1-year OS rate of each treatment arm to the historical rate for NP/Gem. Secondary: 1. To determine the objective response rate (ORR), disease control rate (DCR), DOR, and progression-free survival (PFS) of each treatment arm. 2. To further characterize the feasibility and safety of each treatment arm. Exploratory: 1. To assess the PK of APX005M in Cycles 1 to 4 (Arms B and C). 2. To assess immune pharmacodynamic effects of each treatment arm, in both blood and tumor tissue. 3. To assess associations between immune biomarkers and clinical outcomes. 4. To evaluate baseline and on-treatment microbiome profiles. 5. To construct multivariable linear models to dissect the pharmacodynamic effects of APX005M and nivolumab on immune biomarkers.

Study Design:	This is a multicenter, open-label, Phase 1b/2 study to evaluate the immunotherapy agents APX005M and nivolumab, in combination with Gem and NP in patients with previously untreated metastatic pancreatic adenocarcinoma. **Phase 1b** In the Phase 1b portion of the study, the following 4 treatment cohorts will be evaluated for feasibility and safety: B1: NP/Gem/APX005M 0.1 mg/kg B2: NP/Gem/APX005M 0.3 mg/kg C1: Nivolumab/NP/Gem/APX005M 0.1 mg/kg C2: Nivolumab/NP/Gem/APX005M 0.3 mg/kg Enrollment in Cohorts B2 and C1 may occur concurrently. Enrollment in Cohort C2 may begin once enrollment in Cohort C1 has been completed. Each cohort in the Phase 1b portion of the study will include approximately 6 DLT-evaluable patients. A cohort corresponding to Arm A of Phase 2 (nivolumab/NP/Gem) will not be tested, since an external study is being conducted to confirm the safety of nivolumab in combination with NP/Gem. DLT is defined as any Grade 3 or higher toxicity that is treatment-related but not related to the natural progression of the tumor and occurs during the DLT observation period. **Phase 2 (Randomized)** Patients will be randomized to one of three arms: Arm A1, Arm B2, or Arm C2 (shown below). <u>Treatment arms:</u> A1: Nivolumab/NP/Gem B2: NP/Gem/APX005M 0.3 mg/kg C2: Nivolumab/NP/Gem/APX005M 0.3 mg/kg A total of approximately 93 patients will be randomized/enrolled in Phase 2 (35 Arm A1, 29 Arm B2, 29 Arm C2). Twelve DLT-evaluable patients from the Phase 1b study, enrolled at the RP2D of APX005M in Arm C (i.e., 6 patients on B2 and 6 patients on C2) will be included in the Phase 2 analysis. Thus, each arm will enroll 35 patients, for a total of approximately 105 patients. In the first step of randomization, 12 patients will be randomized in a 4:1:1 allocation to achieve balance in the total number of patients in each arm (since Arm A1 did not enroll patients in Phase 1b, more patients have to be allocated to Arm A1). Once the 12 patients are randomized, step 2 will randomize the remaining 81 patients in a 1:1:1 allocation.

Selection of Patients:	Main Inclusion Criteria: 1. Patient has histologically or cytologically documented diagnosis of pancreatic adenocarcinoma with metastatic disease. Locally advanced patients are not eligible. 2. Patient must have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. 3. Patients must be age 18 years or older. 4. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 5. A baseline tumor tissue sample is mandatory for enrollment. If archival tumor tissue is not available, then a fresh tumor biopsy must be provided. 6. Patients must have the following laboratory values at Screening, without transfusions or growth factors, within 2 weeks of the first dose of investigational agents: a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L (in absence of growth factor support) b. Platelet count $\geq 150 \times 10^9$/L c. Hemoglobin ≥ 9 g/dL(without transfusion support) d. Serum creatinine ≤ 1.5 mg/dL, and creatinine clearance $\geqslant$ 50 ml/min as measured by Cockcroft and Gault formula e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x institution's ULN for patients with no concurrent liver metastases, OR ≤ 5.0 x institution's ULN for patients with concurrent liver metastases f. Total bilirubin ≤ 1.5 x ULN, except in patients with documented Gilbert's Syndrome who must have a total bilirubin ≤ 3 x ULN 7. Women of childbearing potential (WOCBP) must have a negative pregnancy test (serum or urine) within the 7 days prior to study drug administration, and a negative urine pregnancy test within the 3 days before the first study drug administration, or a negative serum pregnancy test within 24 hours before the first study drug administration. 8. WOCBP and male patients who are sexually active with WOCBP must agree before receiving the first dose of study drugs to use 2 highly effective methods of contraception (including a physical barrier) during the study and for 5 months for women and 7 months for men following the last dose of study drug, as described in the body of the protocol. 9. Patients must have the ability to understand and willingness to sign a written informed consent document. Main Exclusion Criteria: 1. Patient must not have received any prior treatment, including chemotherapy, for metastatic pancreatic adenocarcinoma, with the following exceptions and notes: a. Patients who have received prior adjuvant or neoadjuvant therapy for pancreatic adenocarcinoma are eligible if the last dose of adjuvant therapy was more than 4 months before the date of study entry. In this case, prior Gem and/or NP are allowable. b. Prior resection surgery is allowable. c. Patients initially diagnosed with locally advanced pancreatic cancer who have undergone chemotherapy then resection and were with no evidence of disease are eligible if metastatic relapse of disease has occurred and if the last dose of chemotherapy was more than 4 months before the date of study entry.

	2. Patients must not have another active invasive malignancy, with the following exceptions and notes: a. History of a non-invasive malignancy, such as cervical cancer in situ, non-melanomatous carcinoma of the skin, in situ melanoma, or ductal carcinoma in situ of the breast, is allowed. b. History of malignancy that is in complete remission after treatment with curative intent is allowed. c. No current or history of a hematologic malignancy is allowed, including patients who have undergone a bone marrow transplant. 3. History of clinically significant sensitivity or allergy to monoclonal antibodies, their excipients or intravenous gamma globulin 4. Previous exposure to CD40, PD-1, PD-L1, CTLA-4 antibodies or any other immunomodulatory agent 5. History of (non-infectious) pneumonitis that required corticosteroids or current pneumonitis, or history of interstitial lung disease 6. Patients must not have a known or suspected history of an autoimmune disorder, including but not limited to inflammatory bowel disease, celiac disease, Wegner syndrome, Hashimoto syndrome, systemic lupus erythematosus, scleroderma, sarcoidosis, or autoimmune hepatitis, within 3 years of the first dose of investigational agent, except for the following: a. Patients with Type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders such as vitiligo, or alopecia not requiring systemic therapy, or conditions not expected to recur in the absence of an external trigger are eligible. b. Patients with a history of Hashimoto syndrome within 3 years of the first dose of investigational agent, which resolved to hypothyroidism alone. 7. Patients must not have an uncontrolled intercurrent illness, including an ongoing or active infection, current pneumonitis, symptomatic congestive heart failure (New York Heart Association class III or IV), unstable angina, uncontrolled hypertension, cardiac arrhythmia, interstitial lung disease, active coagulopathy, or uncontrolled diabetes. 8. Patients must not have a history of myocardial infarction within 6 months or a history of arterial thromboembolic event within 3 months of the first dose of investigational agent. 9. Patients must not have a history of human immunodeficiency virus, hepatitis B (HB), or hepatitis C, except for the following: a. Patients with anti-HB core antibody but with undetectable HB virus deoxyribonucleic acid (DNA) and negative for HB surface antigen b. Patients with resolved or treated hepatitis C virus (HCV) (i.e. HCV antibody positive but undetectable HCV RNA) 10. Patients must not have a history of primary immunodeficiency. 11. Patients must not receive concurrent or prior use of an immunosuppressive agent within 14 days of the first dose of investigational agent, with the following exceptions and notes: a. Systemic steroids at physiologic doses (equivalent to dose of 10 mg oral prednisone) are permitted. Steroids as anti-emetics for chemotherapy are not allowed. b. Intranasal, inhaled, topical, intra-articular, and ocular corticosteroids with minimal systemic absorption are permitted.

	c. Patients with a condition with anticipated use of systemic steroids above the equivalent of 10 mg prednisone are excluded. d. Transient courses of steroids may be approved by the Medical Monitor on a case by case basis, dependent on dose and reason. 12. Patients must not have a history of clinically manifested central nervous system (CNS) metastases. a. Patients with known or suspected leptomeningeal disease or cord compression are not eligible. 13. Patients must not have had major surgery as determined by the PI within 4 weeks before the first dose of study drug. 14. Patients must not have received another investigational agent within the shorter of 4 weeks or 5 half-lives before the first dose of investigational agent. 15. Patients must not have received a live attenuated vaccine within 28 days before the first dose of investigational agent, and patients, if enrolled, should not receive live vaccines during the study or for 180 days after the last dose of investigational agent. 16. Females who are pregnant or lactating or who intend to become pregnant during participation in the study are not eligible to participate. 17. Patients who have any clinically significant psychiatric, social, or medical condition that, in the opinion of the investigator, could increase the patient's risk, interfere with protocol adherence, or affect the patient's ability to give informed consent are ineligible to participate in the study.
Planned Sample Size:	Up to 24 DLT-evaluable patients will be enrolled in the Phase 1b portion of the study. A total of approximately 93 patients will be randomized/enrolled in Phase 2. Thus, the total sample size is expected to be approximately 117 patients.
Investigational Therapy:	**Phase 1b:** APX005M (0.1 or 0.3 mg/kg) in combination with NP (125 mg/m^2) and Gem (1000 mg/m^2), all administrated intravenously (IV) **OR** APX005M (0.1 or 0.3 mg/kg) in combination with nivolumab (240 mg), NP (125 mg/m^2) and Gem (1000 mg/m^2), all administered IV **Phase 2:** Nivolumab (240 mg) in combination with NP (125 mg/m^2) and Gem (1000 mg/m^2), all administered IV **OR** APX005M (0.3 mg/kg) in combination with NP (125 mg/m^2) and Gem (1000 mg/m^2), all administrated IV **OR** APX005M (0.3 mg/kg) in combination with nivolumab (240 mg), NP (125 mg/m^2) and Gem (1000 mg/m^2), all administered IV

Treatment Duration:	Assuming all 4 cohorts are tested, upon completion of enrollment to Phase 1b, 1 additional month of follow-up will occur before declaring the RP2D of APX005M. Then the Phase 2 portion of the study will have 12 additional months of follow-up. Target enrollment completion is within 24 months; however, enrollment will proceed until met or as determined by the study sponsor (Parker Institute for Cancer Immunotherapy [PICI]). Considering several months for data management and statistical analysis, the total duration of the study is likely to be 5 years. Patients will undergo screening and, if eligible, will undergo treatment in the assigned arm of the study until unacceptable toxicity, progression of disease, or withdrawal of consent. All patients will be followed for survival status until death or a maximum of 5 years.
Study Endpoints:	**Phase 1b:** Primary: • The frequency of DLT • The RP2D of APX005M when combined with NP/Gem or nivolumab/NP/Gem • The incidence of treatment-emergent AEs (TEAEs), serious adverse events (SAEs), and adverse events (AEs) causing discontinuation Secondary: • OR is determined by RECIST v1.1 • DOR is defined as the time from first documentation of response (complete response [CR] or partial response [PR]) to first documentation of progressive disease (PD) Exploratory: • PK of APX005M will be determined in Cycles 1 to 4. • Immune pharmacodynamic endpoints may include, but are not limited to, the following: o Changes in the tumor microenvironment (including cellularity, stromal content, cellular infiltration, and tumor apoptosis) may be assessed by tumor multiplex immunohistochemistry or other appropriate technology. Pharmacodynamic and PK parameters, if available, may be used to influence the RP2D. o Gene expression may be determined by tumor RNA sequencing, peripheral blood RNA sequencing, or other appropriate technology. Other sequencing technologies, such as ATAC sequencing, may be performed. o Tumor genomics may be determined when possible by Clinical Laboratory Improvement Amendment-certified mutational panel assessments and/or by whole exome sequencing. o For variant calling and human leukocyte antigen (HLA) determination, normal tissue whole exome sequencing may be performed. In some cases, data regarding germ-line BRCA1/2 mutations or microsatellite instability may be incorporated into analyses. o Cytokine and/or circulating factor analysis may be determined by a multiplex assay or other appropriate technology. o Flow cytometry or other related technologies, such as CyTof analysis of peripheral blood, may be used to assess phenotype, function, and other changes in immune cellular subsets. o Other markers to measure tumor burden, including circulating tumor DNA, tumor cells, and protein markers, may be measured in an exploratory fashion if material is available

	Phase 2: Primary: • OS is defined as the time from initiation of study therapy to date of death due to any cause or date of most recent patient contact. Patients who have not died are censored on their most recent contact date. • 1-year OS rate in each treatment arm. Secondary: • Investigators' assessment of OR is determined by RECIST v1.1 and the ORR is defined as the proportion of patients who achieve a CR or PR. • DCR is defined as the proportion of patients who achieve a CR or PR or SD. • DOR is defined as the time from first documentation of response (CR or PR) to first documentation of PD. • PFS is defined as the time from initiation of study therapy to date of first documented progression of disease, date of death due to any cause or date of most recent patient contact which documented progression-free status (i.e., clinic visit date or scan date). Patients who have not progressed or died are censored on their most recent progression-free date. • The incidence of AEs defined as unacceptable toxicities in Phase 2, TEAEs, SAEs, and AEs causing treatment discontinuation • Clinical laboratory data and vital signs (descriptive statistics) and numbers of patients with values outside limits of the normal range at each time point. Exploratory: ▪ The exploratory endpoints for Phase 2 are the same as those described above for Phase 1b with the addition of evaluation of baseline and on-treatment microbiome profiles with treatment outcomes.
Statistical Methods and Planned Analyses:	This is a multi-center, open-label Phase 1b/2 study of CD40 agonistic monoclonal antibody, APX005M, and/or PD-1 blocking antibody, nivolumab, in combination with NP and Gem and for patients with newly diagnosed metastatic pancreatic cancer. The primary objectives of the Phase 1b study are to determine the feasibility, safety and DLT of each treatment cohort and to determine the RP2D of APX005M in combination with NP/Gem and with nivolumab/NP/Gem. The primary objective of the randomized Phase 2 study is to evaluate OS in three treatment arms: nivolumab/NP/Gem, NP/Gem/APX005M and nivolumab/NP/Gem/APX005M by comparing the 1-year OS rate with the historical value for NP/Gem. **The safety population** consists of all patients who received at least 1 dose of any study drug. This is the population for the primary analyses of safety. **The DLT-evaluable population** consists of patients who received 2 or 3 doses of NP/Gem and 1 dose of APX005M during Cycle 1, thus have completed the DLT observation period (ie, from the time of first administration of study drugs until prior to Cycle 2 Day 1). Patients who do not meet these criteria will be replaced in Phase 1b only, to assist with DLT and RP2D decision-making. **The efficacy population** consists of (1) all patients who were randomized/enrolled in Phase 2 and received at least 1 dose of any study drug and (2) the 12 DLT-evaluable patients (6 on Arm B and 6 on Arm C) who were enrolled in Phase 1b at the RP2D. The efficacy population is the population for the primary analyses of efficacy. **Phase 1b Design:** Four treatment cohorts will be evaluated for feasibility and safety. Cohorts B1 and B2 will escalate the dose of APX005M when combined with NP/Gem, and then Cohorts C1 and C2 will escalate the dose of APX005M

	when combined with nivolumab/NP/Gem. Enrollment in Cohorts B2 and C1 may occur concurrently. Enrollment in Cohort C2 may begin once enrollment in Cohort C1 has been completed. Approximately 6 DLT-evaluable patients will be enrolled in each cohort. A1 (nivolumab/NP/Gem) will not be tested in Phase 1b, since an external study is being conducted to confirm the safety of nivolumab in combination with NP/Gem. Statistical analyses will include the following: • The number of patients treated in each cohort will be reported, and reasons why any patient is not DLT evaluable will be summarized. • Approximately 6 DLT-evaluable patients will be fully analyzed in each treatment cohort. • Feasibility issues will be described for each treatment cohort. • Toxicities will be graded by NCI-CTCAE, causality attributed, and tabulated by treatment cohort. • RP2D of APX005M when combined with NP/Gem and with nivolumab/NP/Gem will be determined. • RECIST OR will be scored and tabulated along with DOR, by treatment cohort. • PK of APX005M. • Immune pharmacodynamic effects will be measured, including change from baseline, and reported by treatment cohort. **Phase 2 Design:** Once the RP2D of APX005M has been defined, the randomized Phase 2 portion of the study will commence. Patients will be randomized to one of 3 arms, defined by the addition of one or more immunotherapy agents to standard of care NP/Gem. The arms will be either A1 vs B2 vs C2 or A1 vs B1 vs C1. Note that the APX005M dose must be the same in Arms B and C, regardless of whether a higher APX005M dose was determined to be safe in Arm B. For each regimen, efficacy will be evaluated by comparing the 1-year overall survival (OS) rate to the historical value for NP/Gem. Statistical analyses will include the following: • Thirty-five patients will be analyzed on each treatment arm. Twelve DLT-evaluable patients from Phase 1b (Arms B and C) and 93 patients from Phase 2 will comprise the population for the final analysis of efficacy. • OS will be estimated by the Kaplan-Meier method for each treatment arm. • The 1-year OS rate and 1-sided 95% confidence interval (CI) will be calculated for each treatment arm, to determine whether the lower bound of the CI excludes the historical value for NP/Gem. A 1-sided one-sample Z test will also be conducted. The goal is to compare the survival probability at 1-year to the historical value of 0.35. • ORR and DCR and their 95% CIs will be calculated for each treatment arm. • PFS will be estimated by the Kaplan-Meier method for each treatment arm. • DOR will be calculated from dates of first documented response and progression of disease. • Toxicities will be graded by CTCAE v4.03 and tabulated by treatment arm. • PK of APX005M in Cycles 1 to 4 (Arms B and C). • Immune pharmacodynamic effects may be measured, including but not limited to change from baseline, and reported by treatment arm. • Test of associations between immune biomarkers and clinical outcomes

	• Construct multivariable linear models to dissect the pharmacodynamic effects of APX005M and nivolumab on immune biomarkers.

PARKER INSTITUTE
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Statistical Analysis Plan for

Protocol Number: PICI0002

Protocol Title: Open-label, Multicenter, Phase 1b/2 Clinical Study to Evaluate the Safety and Efficacy of CD40 Agonistic Monoclonal Antibody (APX005M) Administered Together with Gemcitabine and nab-Paclitaxel with or without PD-1 Blocking Antibody (Nivolumab) in Patients with Previously Untreated Metastatic Pancreatic Adenocarcinoma

IND Number:	132683
Name of Products:	APX005M (experimental) Nivolumab (experimental) Gemcitabine (standard of care) nab-Paclitaxel (standard of care)
Phase of Development:	1b/2
Indication:	Previously untreated metastatic pancreatic cancer
Sponsor:	Parker Institute for Cancer Immunotherapy 1 Letterman Drive Suite D3500 San Francisco, CA 94129
Date Final:	26 Sep 2019

SPONSOR APPROVAL PAGE

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2 INTRODUCTION

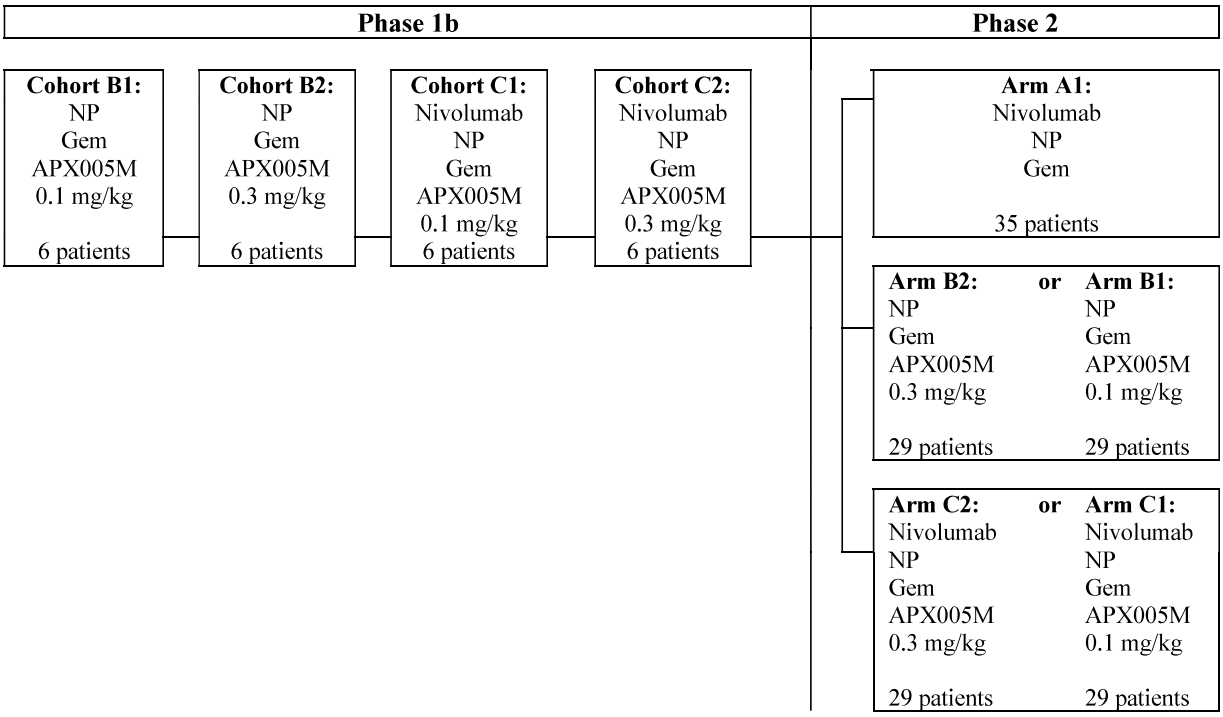
The purpose of this document is to provide details of the planned analyses for Protocol PICI0002. The analyses specified in this document supersede the high-level analysis plan described in the protocol. Statistical analyses will be performed consistent with the principles of the ICH/FDA Guidance for Industry E9 Statistical Principles for Clinical Trials.

3 STUDY DESIGN

PICI0002 is a multi-center, open label, Phase 1b/2 study of the immunotherapy agents APX005M and nivolumab, in combination with Gemcitabine (Gem) and nab-Paclitaxel (NP) in patients with previously untreated metastatic pancreatic adenocarcinoma.

Phase 1b will involve 4 sequential treatment cohorts, and Phase 2 will involve randomization to 3 treatment arms, as shown in Figure 1.

Figure 1 Study Flow Chart



Phase 1b

In the Phase 1b portion of the study, 4 treatment cohorts will be evaluated sequentially for feasibility and safety. Each cohort of the study will have 6 DLT-evaluable patients, defined as patients who experienced a Dose-Limiting Toxicity (DLT) or who completed the DLT observation period, i.e. received at least 2 doses of NP/Gem and 1 dose of APX005M during

Cycle 1. Patients who do not experience a DLT and who do not complete the DLT observation period will be replaced.

In general, a DLT is defined as: (1) any Grade 3 or higher non-hematologic or Grade 4 hematologic toxicity occurring during the DLT observation period that is considered to be at least possibly related to APX005M and/or nivolumab, or (2) an exacerbation of known NP/Gem toxicity that is at least possibly related to APX005M and/or nivolumab. A more comprehensive definition of a DLT can be found in the protocol. The DLT observation period is defined as the time of first administration of investigational agents until Cycle 2 Day 1.

Dose escalation will proceed if 1 or fewer DLT-evaluable patients experience a DLT during this observation period. Dose escalation will cease if 2 or more DLT-evaluable patients in a cohort experience a DLT.

On the basis of discussions among the site PIs, Sponsor, and other stakeholders, concerning feasibility, safety, clinical and immune pharmacodynamic (PD) effects (totality of available data), the recommended Phase 2 dose is defined by the highest APX00M dose with < 2 DLT in 6 DLT-evaluable patients, unless the totality of available data suggests a lower APX005M dose.

Randomized Phase 2

Once the recommended Phase 2 dose (RP2D) of APX005M in combination with nivolumab from Cohort C in the Phase 1b portion of the study is determined, the randomized Phase 2 portion will commence. Patients will be randomized to Arm A1, Arm B2, or Arm C2, or to Arm A1, Arm B1, or Arm C1, if Cohort B2 and/or C2 are deemed unsafe in Phase 1b. Note that the APX005M dose must be the same in Arms B and C, regardless of whether a higher APX005M dose was determined to be safe in Arm B. For each regimen, efficacy will be evaluated by comparing the 1-year overall survival (OS) rate to the historical value for NP/Gem. A total of approximately 93 patients will be randomized in Phase 2 (35 Arm A1, 29 Arm B2, 29 Arm C2).

All patients will be followed up for survival status until death or a maximum of 5 years. Once a patient is in follow-up, follow up can be obtained with a clinic visit or a phone call approximately every 6 months.

It is common for randomized Phase 2 studies that test the addition of an experimental agent to a standard of care regimen to include the standard of care arm. However, the setting for this study is unique. NP/Gem, the standard of care regimen, was reported recently in a very similar patient population, and the 1-year OS rate was estimated with extremely high precision (i.e., 1-year OS rate was 35% with 95% CI 30%-39%) based on 431 treated patients (Von Hoff et al.). With hundreds of pancreatic patients treated with NP/Gem since that report, experts in this

field agree that the 1-year OS rate estimate appears to be very robust. Thus, this study will not include a standard of care arm.

The 12 DLT-evaluable patients who were enrolled in Phase 1b at the recommended Phase 2 doses (6 on Arm B and 6 on Arm C) will be included in the efficacy evaluation and 93 additional patients will be randomized in Phase 2, for a total sample size of 105 patients (35 per treatment arm).

3.1 Protocol Synopsis

The Protocol Synopsis is provided in Section 8.1.

3.2 Study Objectives

This study will be conducted in two phases, each with its own objectives.

3.2.1 Phase 1b

Primary Objectives:

1. To determine the feasibility, safety, and DLTs of each treatment cohort.
2. To determine the recommended Phase 2 dose of APX005M when combined with NP/Gem.
3. To determine the recommended Phase 2 dose of APX005M when combined with nivolumab/NP/Gem.

Secondary Objectives:

1. To determine objective response rate (ORR) and duration of responses (DOR) of each treatment cohort.

Exploratory Objectives:

1. To assess the pharmacokinetics (PK) of APX005M in Cycles 1 to 4.
2. To assess immune pharmacodynamic effects of each treatment cohort, in both blood and tumor tissue.

3.2.2 Phase 2

Primary Objectives:

1. To estimate the OS of each treatment arm.
2. To compare 1-year OS rate of each treatment arm to the historical rate for NP/Gem.

Secondary Objectives:

1. To determine the ORR, disease control rate (DCR), DOR, and progression-free survival (PFS) of each treatment arm.
2. To further characterize the feasibility and safety of each treatment arm.

Exploratory Objectives:

1. To assess the PK of APX005M in Cycles 1 to 4 (Arms B and C).
2. To assess immune pharmacodynamic effects of each treatment arm, in both blood and tumor tissue.
3. To assess associations between immune biomarkers and clinical outcomes.
4. To evaluate baseline and on-treatment microbiome profiles.
5. To construct multivariable linear models to dissect the pharmacodynamic effects of APX005M and nivolumab on immune biomarkers.

3.3 Study Endpoints

The study endpoints are listed in the Protocol Synopsis (Section 8.1).

3.4 Determination of Sample Size

3.4.1 Phase 1b

Assuming 4 treatment cohorts will be evaluated sequentially for feasibility, safety, and dose-limiting toxicities, 24 DLT-evaluable patients will be enrolled (6 per cohort). Patients who do not experience a DLT and who do not complete the DLT observation period will be replaced.

The Phase 1b sample size was determined by practical considerations and was not based on statistical power calculations. Six patients dosed in each group was deemed sufficient to characterize the feasibility, safety, and DLTs of each cohort. Based on this sample size, Table 1 provides the probability of failing to accept a cohort as safe, defined as ≥ 2 DLTs in 6 treated patients, assuming different DLT rates.

Table 1 Probability of Failing to Accept a Dose Level at Different Event Rates

DLT Event Rate	1%	10%	20%	25%	33%	50%
Probability [a]	0.001	0.11	0.34	0.47	0.64	0.89

DLT = dose-limiting toxicity

[a] Assumes $P(X \geq 2)$ where X is a binomial random variable with sample size n = 6 and p = DLT event rate.

3.4.2 **Phase 2**

The 12 DLT-evaluable patients who were enrolled in Phase 1b at the recommended Phase 2 doses (6 on Arm B and 6 on Arm C) will be included in the efficacy evaluation and approximately 93 additional patients will be randomized in Phase 2, for a total sample size of 105 patients (35 per treatment arm). This is a screening study, such that for each treatment arm, the 1-year OS rate will be estimated and compared with a historical value of 35% for NP/Gem (Von Hoff et al.). The study is not powered to detect a meaningful difference in OS among the 3 arms, since these are novel experimental arms and OS is unknown.

The null hypothesis is a 1-year OS rate of 35% and the alternative hypothesis is a 1-year OS rate of 58%. The 1-year OS rate is estimated by the Kaplan-Meier method. A sample size of 35 patients on each arm provides 88% power to test this hypothesis, using a 1-sided one-sample Z test with 5% type I error rate, assuming a minimum of 1 year of follow-up for each patient. Moreover, the sample size of 35 patients on each arm, provides 81% power to statistically test the null hypothesis versus a slightly more conservative alternative hypothesis that the 1-year OS rate is 55%, given the same design assumptions.

These calculations assume that 105 patients (35 patients x 3 arms) will be enrolled. There is no assumption about the duration of patient enrollment, only that there will be a minimum of 1 year of follow-up for each patient.

3.5 Analysis Timing

The database lock for analysis of the Phase 2 primary endpoint of 1-year overall survival (OS) rate will occur approximately one year after the last patient is randomized. No changes to the SAP will be allowed at the time of or subsequent to database lock.

Analysis of the Phase 1b endpoints may be performed prior to the time of primary analysis. These results may be presented and/or published prior to the primary analysis.

The study will formally end once all patients have been followed for survival status until death or a maximum of 5 years, withdrawal of consent, or loss to follow-up. A survival analysis of long-term follow-up may be performed after the primary analysis has been completed.

4 STUDY CONDUCT

4.1 Randomization Details

In Phase 1b, patients will be enrolled sequentially into 4 cohorts (B1, B2, C1, and C2) as summarized in Table 2. The Phase 1b portion of the study is non-randomized. Enrollment in Cohorts B2 and C1 may occur concurrently.

Table 2 Phase 1b Treatment Assignment

Arm	Regimen	Number of DLT-Evaluable Patients
B1	NP/Gem/APX005M 0.1 mg/kg	6
B2	NP/Gem/APX005M 0.3 mg/kg	6
C1	Nivolumab/NP/Gem/APX005M 0.1 mg/kg	6
C2	Nivolumab/NP/Gem/APX005M 0.3 mg/kg	6

DLT = dose-limiting toxicity; Gem = gemcitabine; NP = nab-paclitaxel

Once the RP2D of APX005M in combination with nivolumab from Cohort C in the Phase 1b portion of the study is determined, the randomized Phase 2 portion will commence. Patients will be randomized to Arm A1, Arm B2, or Arm C2, or to Arm A1, Arm B1, or Arm C1, if Cohort B2 and/or C2 are deemed unsafe in Phase 1b. Note that the APX005M dose must be the same in Arms B and C, regardless of whether a higher APX005M dose was determined to be safe in Arm B.

A total of 105 patients will be evaluated in the Phase 2 portion of the study, including 12 DLT-evaluable patients from Phase 1b (i.e., 6 patients on B1 and 6 patients on C1 or 6 patients on B2 and 6 patients on C2). The remaining 93 patients will be randomized and treated only in Phase 2. In step 1 of randomization, 12 of the 93 new patients will be randomized to the 3 arms in a 4:1:1 ratio in Arms A1, B2, and C2 (or A1, B1, and C1), to achieve balance in the total number of patients enrolled on the arms (since Arm A1 does not accrue in Phase 1b, more patients need to be enrolled in Arm A1). In step 2 of randomization, 81 patients will be randomized to Arms A1, B2, and C2 (or A1, B1, and C1) in a 1:1:1 allocation. The randomization design is outlined in Table 3.

Table 3 Phase 2 Design

Arm	Regimen	Phase 1b	Phase 2		Total
			Step 1	Step 2	
		Number of patients	Number of patients	Number of patients	Number of patients
A1	Nivolumab/NP/Gem	0	8	27	35
B2 [a]	NP/Gem/APX005M 0.3 mg/kg	6	2	27	35
C2 [a]	Nivolumab/NP/Gem/APX005M 0.3 mg/kg	6	2	27	35

[a] Or B1 and C1, if either B2 or C2 is not tolerable.
Gem = gemcitabine; NP = nab-paclitaxel

Randomization will be managed by the Parker Institute for Cancer Immunotherapy (PICI), using an interactive voice response system (IVRS). The randomization is not stratified by baseline patient or tumor characteristics.

4.2 Blinding

This is an open-label study with no blinding.

4.3 Data Monitoring

The study will be closely monitored, and data will be reviewed on an ongoing basis. In order to ensure the safety and well-being of participating patients, as well as the validity of data during the study, a Data Review Team (DRT) will review the safety and further emerging data on a regular basis. The DRT consists of members from the Sponsor, the overall Principal Investigator (PI), the lead statistician, and all active PIs. The DRT will adjudicate DLTs relevant for the treatment and will decide by consensus on dose escalation, dose de-escalation, prolongation of the DLT observation period, suspension of enrollment based on safety, PK, or possibly pharmacodynamic data, and will recommend the dose level for the Phase 2 portion.

4.3.1 Early Termination Rules for Unacceptable Toxicity in Phase 2

A Bayesian rule will be employed to monitor toxicity during Phase 2. A minimally informative beta (0.5, 2.5) prior has been assumed, which is information that is equivalent to ½ the weight of 1 DLT in 6 patients treated, the definition of a safe dose in Phase 1b. For each treatment arm, if the number of patients with an unacceptable toxicity (defined the Section 6.1 of the study protocol) is greater than or equal to the number in Table 4, then termination of that particular treatment arm will be considered, as it is likely that the toxicity rate is >30%, as noted by the Bayesian posterior probabilities. This rule is intentionally conservative early in the enrollment phase.

Table 4 Bayesian Termination Rules

Rules for Unacceptable Toxicity Rate >30%					
Patients treated on an arm	10	15	20	25	30
Patients with unacceptable toxicity	4	6	9	11	13
Posterior Probability [toxicity rate >30%]	0.61	0.69	0.87	0.88	0.90
Action	Consider termination of arm, re-evaluate study design.				

5 STATISTICAL METHODS

Summary statistics will be presented by treatment arm. For continuous variables, data will be summarized with the number of patients (N), mean, standard deviation, median, minimum, and maximum by treatment arm. For categorical variables, data will be tabulated with the number and proportion of patients for each category by treatment arm.

5.1 Analysis Populations

5.1.1 Safety Population

The safety population consists of all patients who received at least 1 dose of any study drug. This is the population for the analyses of safety. A subset of the safety population is the DLT-evaluable population.

For the safety analyses, patients will be analyzed according to the treatment regimen actually received. Using a conservative approach:

- Phase 1b patients who receive at least one dose of nivolumab but do not receive APX005M will be analyzed under Arm C1. Phase 2 patients who receive at least one dose of nivolumab but do not receive APX005M will be analyzed under Arm A1.
- Phase 1b patients who receive at least one dose of APX005M but do not receive nivolumab will be analyzed under Arm B1 or B2, depending on the highest dose level of APX005M received. Phase 2 patients who receive at least one dose of APX005M but do not receive nivolumab will be analyzed under Arm B2 (the dose level selected for Phase 2 enrollment).
- Phase 1b patients who receive at least one dose of both APX005M and nivolumab will be analyzed under Arm C1 or C2, depending on the highest dose level of APX005M received. Phase 2 patients who receive at least one dose of both APX005M and nivolumab will be analyzed under Arm C2 (the dose level selected for Phase 2 enrollment).
- Patients who receive at least one dose of NP/Gem but do not receive APX005M or nivolumab will be analyzed under the treatment arm assigned at enrollment (Phase 1b) or randomization (Phase 2).

5.1.2 DLT-evaluable Population

The DLT-evaluable population consists of patients who (1) were enrolled in Phase 1b, (2) received at least 2 doses of NP/Gem and 1 dose of APX005M during Cycle 1, and (3) completed the DLT observation period (i.e. from the time of first administration of study

intervention until Cycle 2 Day 1). Alternatively, patients who did not complete the DLT observation period due to a DLT event will also be considered DLT evaluable.

The DLT-evaluable population is the population for analyses of Phase 1b efficacy and DLTs. Patients will be grouped according to the treatment arm assigned at enrollment, regardless of the treatment actually received.

5.1.3 Efficacy Population

The efficacy population consists of (1) all patients who were randomized in Phase 2 and received at least 1 dose of any study drug and (2) the 12 DLT-evaluable patients (6 on Arm B and 6 on Arm C) who were enrolled in Phase 1b at the recommended Phase 2 dose. The efficacy population is the population for the primary analyses of efficacy in Phase 2. Patients will be grouped according to the treatment arm assigned at enrollment/randomization, regardless of the treatment actually received.

5.2 Analysis of Study Conduct

The number of patients enrolled in Phase 1b and randomized in Phase 2 will be tabulated by treatment arm. Patient disposition (e.g. the number of patients enrolled/randomized, receiving at least one dose of study drug) and time on study will be tabulated by treatment arm and may be represented graphically (e.g. swim lane plot). Reasons for premature discontinuation from study treatment and reasons for premature discontinuation from the study, including the 5-year follow-up period, will be summarized.

Feasibility, defined by the number of Phase 1b patients who complete the DLT observation period and receive the intended therapy without delays or dose modification, will be described for each treatment arm.

5.3 Analysis of Treatment Group Comparability

Demographic and baseline characteristics, including but not limited to age, sex, race, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status at baseline, cancer location (pancreas body, head, or tail) and cancer stage at initial diagnosis and enrollment will be summarized by treatment arm using descriptive statistics for all enrolled/randomized patients.

The baseline value of any variable will be defined as the last available value recorded prior to the first administration of study drug.

Previous and concomitant cancer therapy will also be summarized, including radiotherapy and surgery, as well as subsequent anti-cancer therapy. Previous and concurrent diseases and medications will be listed.

5.4 Efficacy Analysis

Phase 2 efficacy analyses will be conducted on the efficacy population (see Section 5.1.3), with patients grouped according to the treatment assigned at randomization. Phase 1b efficacy analyses will be conducted on the DLT-evaluable population.

Efficacy summaries will include data from patients who discontinued study drug early but continued with study assessments and may include data collected at unscheduled visits, early termination visits, or follow-up visits.

5.4.1 Comparisons of Interest

The 1-year OS rate and 1-sided 95% confidence interval will be calculated for each treatment arm, to determine whether the lower bound of the confidence interval (CI) excludes the assumed historical value for NP/Gem of 35%.

This study is not powered for statistical comparisons between arms.

5.4.2 Type I Error Management

Due to the exploratory nature of this study, no control of type I error will be applied for any of the endpoints.

5.4.3 Covariate Adjustment

Unless otherwise noted, analyses of primary and secondary efficacy endpoints will not be adjusted for additional covariates.

5.4.4 Primary Efficacy Endpoint

There is no primary efficacy endpoint for Phase 1b. The Phase 2 primary efficacy endpoint is the 1-year OS rate in each treatment arm. OS is defined as the time from initiation of study therapy to date of death due to any cause. Patients who are not reported as having died at the time of analysis will be censored at their most recent contact date they were known to be alive. Patients who do not have post-baseline survival information will be censored at the date of randomization. See Section 5.6.2 for handling of missing or partial death dates.

OS will be estimated by the Kaplan-Meier method for each treatment arm. For each treatment arm, the following parameters and analyses will be provided: Kaplan-Meier product-limit estimates of the OS distribution functions, the total number of patients, the total censored, the total deaths, the OS time (median and its 95% CI; 25th and 75th percentiles), and the survival rates at monthly intervals (i.e. 3, 6, 9, 12, etc. months).

The 1-year OS rate and 1-sided 95% confidence interval will be calculated for each treatment arm, to determine whether the lower bound of the confidence interval (CI) excludes the assumed historical value for NP/Gem of 35%.

A 1-sided one-sample Z test will also be conducted. The goal is to compare the survival probability at time *t* to the historical value. The null hypothesis is H_0: $S(t) \leq s^*$ at time *t*. The alternative hypothesis is H_1: $S(t) > s^*$, a one-sided test.

The Z test is:

$$\frac{\hat{S}(t) - s^*}{\widehat{SE}(\hat{S}(t))}$$

where $\hat{S}(t)$ and $\widehat{SE}$ are sample estimates. For this study, t = 1 year, $\hat{S}(t)$ = estimated 1-year OS probability from the Kaplan-Meier analysis, $\widehat{SE}(\hat{S}(t))$ = standard error of $\hat{S}(t)$ and null hypothesis $s^* = 0.35$.

A survival follow-up analysis may be performed based on more mature data.

5.4.5 **Secondary Efficacy Endpoints**

Secondary efficacy endpoints for Phase 1b include ORR and DOR. The Phase 1b efficacy endpoints will be analyzed for the DLT-evaluable population.

Secondary efficacy endpoints for Phase 2 include ORR, DCR, DOR, and PFS. The Phase 2 efficacy endpoints will be analyzed for the efficacy population.

5.4.5.1 Objective Response Rate

ORR, on the basis of investigator assessment, is defined as the proportion of patients who attain a complete response (CR) or partial response (PR). Per RECIST v1.1, confirmation of objective response is not required for this secondary endpoint. Patients without a post-baseline tumor assessment will be considered non-responders, as well as patients with a best overall response of stable disease (SD), progressive disease (PD) or not evaluable (NE).

A 95% confidence interval for the rate will be estimated for each treatment arm using the Clopper-Pearson method.

Spider plots and waterfall plots will be generated to visualize changes in the sum of target lesions.

5.4.5.2 Duration of Response

For patients who have experienced an objective response (CR or PR) during the study as assessed by the investigator, DOR is defined as the time from the first tumor assessment that documents response (CR or PR, whichever is recorded first) to first documentation of radiographic PD per RECIST v 1.1. Patients who have not progressed at the time of analysis will be censored at the last tumor assessment date prior to the start of subsequent systemic anti-

cancer therapy. The Kaplan-Meier method will be used to estimate the median DOR for each treatment arm with 95% confidence limits.

5.4.5.3 Disease Control Rate

DCR is defined as the proportion of patients who achieve a best response of CR, PR, or SD. For a patient to have a best overall response of SD, he/she must have at least one post-tumor assessment of SD at least 7 weeks after treatment initiation (8 week minus 7 day window; study day 49). Patients without a post-baseline tumor assessment will be considered non-responders, as well as patients with a best overall response of PD or NE. A 95% confidence interval for the rate will be estimated for each treatment arm using the Clopper-Pearson method.

DCR will also be estimated at 6 and 12 months. For these landmark analyses, DCR is defined as the proportion of patients who have a response of CR, PR, or SD at the first tumor assessment on or after the landmark time. Accounting for the Q8W (i.e. every 8 weeks) schedule and 7-day window for disease assessment, 6-month DCR will consider the first evaluable scan after study day 161 (24 weeks – 7 days) and 12-month DCR will consider the first evaluable scan after study day 329 (48 weeks – 7 days). Patients without an evaluable disease assessment after the landmark time will be considered non-responders.

5.4.5.4 Progression-free Survival

PFS is defined as the time from initiation of study therapy to date of first documented radiographic progression of disease or date of death due to any cause, whichever occurs first. PFS will be determined on the basis of investigator assessment of progression using RECIST v1.1. Patients who have not progressed or died at the time of analysis will be censored at the last tumor assessment date prior to the start of subsequent systemic anti-cancer therapy. Patients with no post-baseline tumor assessment will be censored at the date of study therapy initiation. The Kaplan-Meier method will be used to estimate the median PFS for each treatment arm with 95% confidence limits.

PFS will also be estimated at various landmark times (e.g. 6 and 12 months).

5.4.6 **Exploratory Efficacy Endpoints**

Exploratory endpoints defined in the protocol and listed in Section 8.1 are outside the scope of this SAP. Biomarker analyses will be detailed in a Translational Analysis Plan.

5.4.7 **Subgroup Analyses**

For each treatment arm, OS will be analyzed in the subset of patients in the efficacy population who remain on treatment for at least 3 cycles (i.e. receive at least one dose of any study drug in Cycle 4) vs. those who remain on treatment for 3 cycles or less. This subset is in contrast to

the efficacy population analyzed in the primary analysis. The 1-year OS rate and 1-sided 95% confidence interval will be calculated.

5.4.8 Sensitivity Analyses

The following sensitivity analyses will be performed:

- Efficacy analyses will be performed on the Phase 2 Efficacy Population, defined as all patients who were randomized in Phase 2 and received at least 1 dose of any study drug. This population similar to the Efficacy Population but excludes the 12 DLT-evaluable patients who were enrolled in Phase 1b at the recommended Phase 2 dose.
- If the number of patients dosed in Phase 1b does not match the DLT-evaluable population, ORR and DOR will be calculated for all patients who received at least one dose of study drug in Phase 1b (i.e. the safety population).
- If any Phase 2 patients were randomized but not dosed, Phase 2 primary and secondary efficacy endpoints may be analyzed using an intention-to-treat (ITT) approach. For these analyses, all randomized patients will be included, grouped according to the treatment assigned at randomization.
- The impact of response confirmation on ORR will be assessed by requiring confirmation of CR or PR at least 4 weeks after initial documentation.
- The effect of death on DOR will be assessed by defining DOR as the time from the first tumor assessment that documents response (CR or PR, whichever is recorded first) to first documentation of radiographic progressive disease or death, whichever occurs first. Patients who have not progressed or died at the time of analysis will be censored at the last tumor assessment date prior to the start of subsequent systemic anti-cancer therapy.

5.5 Safety Analysis

Safety will be assessed through the summary of adverse events (AEs), serious adverse events (SAEs), DLTs, laboratory test results (hematology and serum chemistry), vital signs, and physical examinations. This may include data collected at unscheduled visits, early termination visits, or follow-up visits.

The baseline value of any variable will be defined as the last available value recorded prior to the first administration of study medication. If multiple values are available at the same visit, the mean of the values will be used for analysis at that timepoint.

Safety outcomes will be summarized based on the safety population (see Section 5.1.1). Safety summaries will be presented by the treatment regimen actually received.

5.5.1 Exposure to Study Medication

The number of patients exposed to each study drug and the extent of exposure (as number of doses, cumulative dose received, and relative dose received) will be summarized using descriptive statistics. Relative dose received is defined as the total amount of each drug actually received divided by the amount of drug the patient would have been expected to receive had he/she received all planned doses without any dose modifications until the date of treatment discontinuation.

5.5.2 **Adverse Events**

All reported AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A treatment-emergent adverse event (TEAEs) is defined as any new adverse event or any worsening of an existing condition with an onset date on or after the first dose of study drug. AEs with relationship to study drug of "Possibly", "Probably", "Definitely" or unknown (missing) will be considered treatment related.

For each patient and each AE, the worst severity/grade recorded will be attributed and used in the severity summaries. If severity is missing, the event will be considered grade 3.

Listings for all AEs, SAEs, and TEAEs will be presented by patient. Listings will include information regarding onset day/date, end day/date, duration, relationship to study drug, severity, action taken with study drug, whether concomitant medication was administered and outcome.

Summaries of TEAEs (overall, by system organ class and preferred term and by severity) by treatment arm will be provided for each of the following categories:

- AEs
- AEs by most extreme severity
- Treatment-related AEs
- SAEs
- Treatment-related SAEs
- AEs leading to discontinuation of study treatment
- DLTs
- AEs from patients enrolled in Phase II that meet the protocol-defined unacceptable toxicity criteria

The proportion of events that are resolved at the time of analysis will be presented. In addition, patient deaths and the primary cause of death will be listed, as well as any cases of pregnancy.

5.5.3 **Laboratory Data**

Descriptive summaries of clinical laboratory values at each timepoint, including changes from baseline, will be generated for hematology and chemistry parameters by treatment arm. The proportion of patients with values outside the normal upper and lower limit at each visit will be displayed.

In addition, select laboratory parameters (including, but not limited to, AST, ALT, alkaline phosphatase and total bilirubin) will be summarized by grade using the CTCAE grading scale.

Missing laboratory values will not be imputed. Analysis will only occur on observed values.

5.5.4 Vital Signs

Vital signs will be summarized by treatment arm using descriptive statistics including mean values and mean change from baseline.

Missing vital signs will not be imputed. Analysis will only occur on observed values.

5.6 Missing Data

5.6.1 Missing and Partial Missing Adverse Event Dates

If the AE start date is not a complete date, the following rules will be applied to determine whether the event is treatment-emergent.

- If the start date is completely missing: The AE will be assumed to be treatment-emergent unless the AE stop date is earlier than the date of first dose of study drug.
- If the day part of the AE start date is missing: If the month and year of the start date are later than or equal to the month and year of the date of first dose of study drug, then the AE will be assumed to be treatment-emergent. If the month and year of the stop date are earlier than the month and year of the date of first dose of study drug, then the event will be assumed to be non-treatment-emergent.
- If the day and month of the start date are missing: If the year of the start date is later than or equal to year of the date of first dose of study drug, then the AE will be assumed to be treatment-emergent. If the year of the stop date is earlier than the year of the date of first dose of study drug, then the event will be assumed to non-treatment-emergent.

5.6.2 Missing and Partial Missing Death Dates

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive plus 1 day, and the maximum will be considered as the death date.

- If the month or the year is missing, the death date will be imputed as the last known date alive plus 1 day.
- If the date is completely missing but the reason for death is present, the death date will be imputed as the last known date alive plus 1 day.

5.7 Interim Analyses

Given the hypothesis generating nature of this study, the Sponsor may conduct two interim analyses of safety and efficacy during the Phase 1b and Phase 2 portions of the study. Should an interim analysis occur, it will be performed and interpreted by members of the Sponsor study team. If warranted, interim safety and efficacy results may be shared with study Investigators. This SAP will be amended prior to any interim analyses to provide justification and document the scope and statistical details. The clinical study report will also document that such an interim analysis occurred.

The first interim analysis will be conducted approximately 3 months after the last patient is randomized in the Phase 2 portion. This interim is strictly meant to support decision making for future studies. No adaptations (e.g. sample size re-estimation, early stopping for futility or efficacy, dropping/adding arms, modifying dose levels) will be made to the study based on the interim results. The analysis will be performed and interpreted by members of the Sponsor study team and management. Full results will be shared with management of the pharmaceutical partners of this study (Apexigen and Bristol-Myers Squibb), as their input is critical for decision making and design of future studies using this treatment regimen. Safety and limited efficacy results will be shared with study Investigators because they are key contributors to the design of an in-development clinical trial that may use the treatment regimens being tested in this study. To limit potential bias, any interim efficacy data shared with Investigators while patients are still receiving study therapy will only be presented as graphical summaries (spider and/or waterfall plots of BOR) with cohort names/identifiers masked.

The following endpoints will be summarized for the first interim analysis:

- Study conduct including enrollment, demographics, and disposition
- Adverse events
- Phase 1b efficacy endpoints: ORR, DCR, DOR, OS, PFS
- Phase 2 efficacy endpoints: ORR, DCR

The Phase 2 primary endpoint of OS will not be analyzed for Phase 2 patients during this interim analysis. Due to the exploratory nature of this study, no control of type I error will be applied for any of the endpoints at the interim or final analysis.

6 DIFFERENCES COMPARED TO PROTOCOL

- Section 3.4 (Determination of Sample Size): The SAP provides additional justification for the Phase 1b sample size.
- Section 5.1.1(Safety Population): The SAP clarifies that for the safety analyses, patients will be analyzed according to the treatment actually received.
- Section 5.1.2 (DLT-evaluable Population): The SAP clarifies that the DLT-evaluable population is the population for analyses of Phase 1b efficacy and DLTs.
- Section 5.4.7 (Subgroup Analyses): The protocol states that OS will be analyzed in the subset of patients who remain on study for at least 6 weeks. The SAP modifies this subgroup to patients who remain on treatment for at least 3 cycles.
- Section 5.7 (Interim Analyses): The SAP provides justification for and details about the first optional interim analysis of efficacy data.

7 REFERENCES

ICH/FDA Guidance for Industry E9 Statistical Principles for Clinical Trials. U.S. Department of Health and Human Services, Food and Drug Administration, September 1998.

Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691-703.

8 APPENDICES

8.1 Protocol Synopsis

Title of Study:	Open-label, Multicenter, Phase 1b/2 Clinical Study to Evaluate the Safety and Efficacy of CD40 Agonistic Monoclonal Antibody (APX005M) Administered Together with Gemcitabine and nab-Paclitaxel with or without PD-1 Blocking Antibody (Nivolumab) in Patients with Previously Untreated Metastatic Pancreatic Adenocarcinoma
Protocol Number:	PICI0002
Phase of Development:	1b/2
Objectives:	**Phase 1b:** Primary: 1. To determine the feasibility, safety and dose-limiting toxicities (DLT) of each treatment cohort. 2. To determine the recommended Phase 2 dose (RP2D) of APX005M when combined with nab-paclitaxel (NP)/gemcitabine (Gem). 3. To determine the RP2D of APX005M when combined with nivolumab/NP/Gem. Secondary: 1. To determine objective response (OR) and duration of response (DOR) of each treatment cohort. Exploratory: 1. To assess the pharmacokinetics (PK) of APX005M in Cycles 1 to 4. 2. To assess immune pharmacodynamic effects of each treatment cohort, in both blood and tumor tissue. **Phase 2:** Primary: 1. To estimate overall survival (OS) of each treatment arm. 2. To compare 1-year OS rate of each treatment arm to the historical rate for NP/Gem. Secondary: 1. To determine the objective response rate (ORR), disease control rate (DCR), DOR, and progression-free survival (PFS) of each treatment arm. 2. To further characterize the feasibility and safety of each treatment arm. Exploratory: 1. To assess the PK of APX005M in Cycles 1 to 4 (Arms B and C). 2. To assess immune pharmacodynamic effects of each treatment arm, in both blood and tumor tissue. 3. To assess associations between immune biomarkers and clinical outcomes. 4. To evaluate baseline and on-treatment microbiome profiles. 5. To construct multivariable linear models to dissect the pharmacodynamic effects of APX005M and nivolumab on immune biomarkers.

Study Design:	This is a multicenter, open-label, Phase 1b/2 study to evaluate the immunotherapy agents APX005M and nivolumab, in combination with Gem and NP in patients with previously untreated metastatic pancreatic adenocarcinoma. **Phase 1b** In the Phase 1b portion of the study, the following 4 treatment cohorts will be evaluated for feasibility and safety: B1: NP/Gem/APX005M 0.1 mg/kg B2: NP/Gem/APX005M 0.3 mg/kg C1: Nivolumab/NP/Gem/APX005M 0.1 mg/kg C2: Nivolumab/NP/Gem/APX005M 0.3 mg/kg Enrollment in Cohorts B2 and C1 may occur concurrently. Enrollment in Cohort C2 may begin once enrollment in Cohort C1 has been completed. Each cohort in the Phase 1b portion of the study will include approximately 6 DLT-evaluable patients. A cohort corresponding to Arm A of Phase 2 (nivolumab/NP/Gem) will not be tested, since an external study is being conducted to confirm the safety of nivolumab in combination with NP/Gem. DLT is defined as any Grade 3 or higher toxicity that is treatment-related but not related to the natural progression of the tumor and occurs during the DLT observation period. **Phase 2 (Randomized)** Patients will be randomized to one of three arms: Arm A1, Arm B2, or Arm C2 (shown below). <u>Treatment arms:</u> A1: Nivolumab/NP/Gem B2: NP/Gem/APX005M 0.3 mg/kg C2: Nivolumab/NP/Gem/APX005M 0.3 mg/kg A total of 93 patients will be randomized in Phase 2 (35 Arm A1, 29 Arm B2, 29 Arm C2). Twelve DLT-evaluable patients from the Phase 1b study, enrolled at the RP2D of APX005M in Arm C (i.e., 6 patients on B2 and 6 patients on C2) will be included in the Phase 2 analysis. Thus, each arm will enroll 35 patients, for a total of 105 patients. In the first step of randomization, 12 patients will be randomized in a 4:1:1 allocation to achieve balance in the total number of patients in each arm (since Arm A1 did not enroll patients in Phase 1b, more patients have to be allocated to Arm A1). Once the 12 patients are randomized, step 2 will randomize the remaining 81 patients in a 1:1:1 allocation.

Selection of Patients:	Main Inclusion Criteria: 1. Patient has histologically or cytologically documented diagnosis of pancreatic adenocarcinoma with metastatic disease. Locally advanced patients are not eligible. 2. Patient must have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. 3. Patients must be age 18 years or older. 4. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 5. A baseline tumor tissue sample is mandatory for enrollment. If archival tumor tissue is not available, then a fresh tumor biopsy must be provided. 6. Patients must have the following laboratory values at Screening, without transfusions or growth factors, within 2 weeks of the first dose of investigational agents: a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L (in absence of growth factor support) b. Platelet count $\geq 150 \times 10^9$/L c. Hemoglobin ≥ 9 g/dL(without transfusion support) d. Serum creatinine ≤ 1.5 mg/dL, and creatinine clearance $\geqslant$ 50 ml/min as measured by Cockcroft and Gault formula e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x institution's ULN for patients with no concurrent liver metastases, OR ≤ 5.0 x institution's ULN for patients with concurrent liver metastases f. Total bilirubin ≤ 1.5 x ULN, except in patients with documented Gilbert's Syndrome who must have a total bilirubin ≤ 3 x ULN 7. Women of childbearing potential (WOCBP) must have a negative pregnancy test (serum or urine) within the 7 days prior to study drug administration, and a negative urine pregnancy test within the 3 days before the first study drug administration, or a negative serum pregnancy test within 24 hours before the first study drug administration. 8. WOCBP and male patients who are sexually active with WOCBP must agree before receiving the first dose of study drugs to use 2 highly effective methods of contraception (including a physical barrier) during the study and for 5 months for women and 7 months for men following the last dose of study drug, as described in the body of the protocol. 9. Patients must have the ability to understand and willingness to sign a written informed consent document. Main Exclusion Criteria: 1. Patient must not have received any prior treatment, including chemotherapy, for metastatic pancreatic adenocarcinoma, with the following exceptions and notes: a. Patients who have received prior adjuvant or neoadjuvant therapy for pancreatic adenocarcinoma are eligible if the last dose of adjuvant therapy was more than 4 months before the date of study entry. In this case, prior Gem and/or NP are allowable. b. Prior resection surgery is allowable. c. Patients initially diagnosed with locally advanced pancreatic cancer who have undergone chemotherapy then resection and were with no evidence of disease are eligible if metastatic relapse of disease has occurred and if the last dose of chemotherapy was more than 4 months before the date of study entry.

	2. Patients must not have another active invasive malignancy, with the following exceptions and notes: a. History of a non-invasive malignancy, such as cervical cancer in situ, non-melanomatous carcinoma of the skin, in situ melanoma, or ductal carcinoma in situ of the breast, is allowed. b. History of malignancy that is in complete remission after treatment with curative intent is allowed. c. No current or history of a hematologic malignancy is allowed, including patients who have undergone a bone marrow transplant. 3. History of clinically significant sensitivity or allergy to monoclonal antibodies, their excipients or intravenous gamma globulin 4. Previous exposure to CD40, PD-1, PD-L1, CTLA-4 antibodies or any other immunomodulatory agent 5. History of (non-infectious) pneumonitis that required corticosteroids or current pneumonitis, or history of interstitial lung disease 6. Patients must not have a known or suspected history of an autoimmune disorder, including but not limited to inflammatory bowel disease, celiac disease, Wegner syndrome, Hashimoto syndrome, systemic lupus erythematosus, scleroderma, sarcoidosis, or autoimmune hepatitis, within 3 years of the first dose of investigational agent, except for the following: a. Patients with Type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders such as vitiligo, or alopecia not requiring systemic therapy, or conditions not expected to recur in the absence of an external trigger are eligible. b. Patients with a history of Hashimoto syndrome within 3 years of the first dose of investigational agent, which resolved to hypothyroidism alone. 7. Patients must not have an uncontrolled intercurrent illness, including an ongoing or active infection, current pneumonitis, symptomatic congestive heart failure (New York Heart Association class III or IV), unstable angina, uncontrolled hypertension, cardiac arrhythmia, interstitial lung disease, active coagulopathy, or uncontrolled diabetes. 8. Patients must not have a history of myocardial infarction within 6 months or a history of arterial thromboembolic event within 3 months of the first dose of investigational agent. 9. Patients must not have a history of human immunodeficiency virus, hepatitis B (HB), or hepatitis C, except for the following: a. Patients with anti-HB core antibody but with undetectable HB virus deoxyribonucleic acid (DNA) and negative for HB surface antigen b. Patients with resolved or treated hepatitis C virus (HCV) (i.e. HCV antibody positive but undetectable HCV RNA) 10. Patients must not have a history of primary immunodeficiency. 11. Patients must not receive concurrent or prior use of an immunosuppressive agent within 14 days of the first dose of investigational agent, with the following exceptions and notes: a. Systemic steroids at physiologic doses (equivalent to dose of 10 mg oral prednisone) are permitted. Steroids as anti-emetics for chemotherapy are not allowed. b. Intranasal, inhaled, topical, intra-articular, and ocular corticosteroids with minimal systemic absorption are permitted.

	c. Patients with a condition with anticipated use of systemic steroids above the equivalent of 10 mg prednisone are excluded. d. Transient courses of steroids may be approved by the Medical Monitor on a case by case basis, dependent on dose and reason. 12. Patients must not have a history of clinically manifested central nervous system (CNS) metastases. a. Patients with known or suspected leptomeningeal disease or cord compression are not eligible. 13. Patients must not have had major surgery as determined by the PI within 4 weeks before the first dose of study drug. 14. Patients must not have received another investigational agent within the shorter of 4 weeks or 5 half-lives before the first dose of investigational agent. 15. Patients must not have received a live attenuated vaccine within 28 days before the first dose of investigational agent, and patients, if enrolled, should not receive live vaccines during the study or for 180 days after the last dose of investigational agent. 16. Females who are pregnant or lactating or who intend to become pregnant during participation in the study are not eligible to participate. 17. Patients who have any clinically significant psychiatric, social, or medical condition that, in the opinion of the investigator, could increase the patient's risk, interfere with protocol adherence, or affect the patient's ability to give informed consent are ineligible to participate in the study.
Planned Sample Size:	Up to 24 DLT-evaluable patients will be enrolled in the Phase 1b portion of the study. A total of 93 patients will be randomized in Phase 2. Thus, the total sample size is expected to be approximately 117 patients.
Investigational Therapy:	**Phase 1b:** APX005M (0.1 or 0.3 mg/kg) in combination with NP (125 mg/m^2) and Gem (1000 mg/m^2), all administrated intravenously (IV) **OR** APX005M (0.1 or 0.3 mg/kg) in combination with nivolumab (240 mg), NP (125 mg/m^2) and Gem (1000 mg/m^2), all administered IV **Phase 2:** Nivolumab (240 mg) in combination with NP (125 mg/m^2) and Gem (1000 mg/m^2), all administered IV **OR** APX005M (0.3 mg/kg) in combination with NP (125 mg/m^2) and Gem (1000 mg/m^2), all administrated IV **OR** APX005M (0.3 mg/kg) in combination with nivolumab (240 mg), NP (125 mg/m^2) and Gem (1000 mg/m^2), all administered IV

Treatment Duration:	Assuming all 4 cohorts are tested, upon completion of enrollment to Phase 1b, 1 additional month of follow-up will occur before declaring the RP2D of APX005M. Then the Phase 2 portion of the study will have 12 additional months of follow-up. Target enrollment completion is within 24 months; however, enrollment will proceed until met or as determined by the study sponsor (Parker Institute for Cancer Immunotherapy [PICI]). Considering several months for data management and statistical analysis, the total duration of the study is likely to be 3 years. Patients will undergo screening and, if eligible, will undergo treatment in the assigned arm of the study until unacceptable toxicity, progression of disease, or withdrawal of consent. All patients will be followed for survival status until death or a maximum of 5 years.
Study Endpoints:	**Phase 1b:** Primary: • The frequency of DLT • The RP2D of APX005M when combined with NP/Gem or nivolumab/NP/Gem • The incidence of treatment-emergent AEs (TEAEs), serious adverse events (SAEs), and adverse events (AEs) causing discontinuation Secondary: • OR is determined by RECIST v1.1 • DOR is defined as the time from first documentation of response (complete response [CR] or partial response [PR]) to first documentation of progressive disease (PD) Exploratory: • PK of APX005M will be determined in Cycles 1 to 4. • Immune pharmacodynamic endpoints may include, but are not limited to, the following: o Changes in the tumor microenvironment (including cellularity, stromal content, cellular infiltration, and tumor apoptosis) may be assessed by tumor multiplex immunohistochemistry or other appropriate technology. Pharmacodynamic and PK parameters, if available, may be used to influence the RP2D. o Gene expression may be determined by tumor RNA sequencing, peripheral blood RNA sequencing, or other appropriate technology. Other sequencing technologies, such as ATAC sequencing, may be performed. o Tumor genomics may be determined when possible by Clinical Laboratory Improvement Amendment-certified mutational panel assessments and/or by whole exome sequencing. o For variant calling and human leukocyte antigen (HLA) determination, normal tissue whole exome sequencing may be performed. In some cases, data regarding germ-line BRCA1/2 mutations or microsatellite instability may be incorporated into analyses. o Cytokine and/or circulating factor analysis may be determined by a multiplex assay or other appropriate technology. o Flow cytometry or other related technologies, such as CyTof analysis of peripheral blood, may be used to assess phenotype, function, and other changes in immune cellular subsets. o Other markers to measure tumor burden, including circulating tumor DNA, tumor cells, and protein markers, may be measured in an exploratory fashion if material is available

	Phase 2: Primary: • OS is defined as the time from initiation of study therapy to date of death due to any cause or date of most recent patient contact. Patients who have not died are censored on their most recent contact date. • 1-year OS rate in each treatment arm. Secondary: • Investigators' assessment of OR is determined by RECIST v1.1 and the ORR is defined as the proportion of patients who achieve a CR or PR. • DCR is defined as the proportion of patients who achieve a CR or PR or SD. • DOR is defined as the time from first documentation of response (CR or PR) to first documentation of PD. • PFS is defined as the time from initiation of study therapy to date of first documented progression of disease, date of death due to any cause or date of most recent patient contact which documented progression-free status (i.e., clinic visit date or scan date). Patients who have not progressed or died are censored on their most recent progression-free date. • The incidence of AEs defined as unacceptable toxicities in Phase 2, TEAEs, SAEs, and AEs causing treatment discontinuation • Clinical laboratory data and vital signs (descriptive statistics) and numbers of patients with values outside limits of the normal range at each time point. Exploratory: ▪ The exploratory endpoints for Phase 2 are the same as those described above for Phase 1b with the addition of evaluation of baseline and on-treatment microbiome profiles with treatment outcomes.
Statistical Methods and Planned Analyses:	This is a multi-center, open-label Phase 1b/2 study of CD40 agonistic monoclonal antibody, APX005M, and/or PD-1 blocking antibody, nivolumab, in combination with NP and Gem and for patients with newly diagnosed metastatic pancreatic cancer. The primary objectives of the Phase 1b study are to determine the feasibility, safety and DLT of each treatment cohort and to determine the RP2D of APX005M in combination with NP/Gem and with nivolumab/NP/Gem. The primary objective of the randomized Phase 2 study is to evaluate OS in three treatment arms: nivolumab/NP/Gem, NP/Gem/APX005M and nivolumab/NP/Gem/APX005M by comparing the 1-year OS rate with the historical value for NP/Gem. **The safety population** consists of all patients who received at least 1 dose of any study drug. This is the population for the primary analyses of safety. **The DLT-evaluable population** consists of patients who received 2 or 3 doses of NP/Gem and 1 dose of APX005M during Cycle 1, thus have completed the DLT observation period (ie, from the time of first administration of study drugs until prior to Cycle 2 Day 1) Patients who do not meet these criteria will be replaced in Phase 1b only, to assist with DLT and RP2D decision-making. **The efficacy population** consists of (1) all patients who were randomized in Phase 2 and received at least 1 dose of any study drug and (2) the 12 DLT-evaluable patients (6 on Arm B and 6 on Arm C) who were enrolled in Phase 1b at the RP2D. The efficacy population is the population for the primary analyses of efficacy. **Phase 1b Design:** Four treatment cohorts will be evaluated for feasibility and safety. Cohorts B1 and B2 will escalate the dose of APX005M when combined with NP/Gem, and then Cohorts C1 and C2 will escalate the dose of APX005M

	when combined with nivolumab/NP/Gem. Enrollment in Cohorts B2 and C1 may occur concurrently. Enrollment in Cohort C2 may begin once enrollment in Cohort C1 has been completed. Approximately 6 DLT-evaluable patients will be enrolled in each cohort. A1 (nivolumab/NP/Gem) will not be tested in Phase 1b, since an external study is being conducted to confirm the safety of nivolumab in combination with NP/Gem. Statistical analyses will include the following: • The number of patients treated in each cohort will be reported, and reasons why any patient is not DLT evaluable will be summarized. • Approximately 6 DLT-evaluable patients will be fully analyzed in each treatment cohort. • Feasibility issues will be described for each treatment cohort. • Toxicities will be graded by NCI-CTCAE, causality attributed, and tabulated by treatment cohort. • RP2Ds of APX005M when combined with NP/Gem and with nivolumab/NP/Gem will be determined. • RECIST OR will be scored and tabulated along with DOR, by treatment cohort. • PK of APX005M. • Immune pharmacodynamic effects will be measured, including change from baseline, and reported by treatment cohort. **Phase 2 Design:** Once the RP2D of APX005M has been defined, the randomized Phase 2 portion of the study will commence. Patients will be randomized to one of 3 arms, defined by the addition of one or more immunotherapy agents to standard of care NP/Gem. The arms will be either A1 vs B2 vs C2 or A1 vs B1 vs C1. Note that the APX005M dose must be the same in Arms B and C, regardless of whether a higher APX005M dose was determined to be safe in Arm B. For each regimen, efficacy will be evaluated by comparing the 1-year overall survival (OS) rate to the historical value for NP/Gem. Statistical analyses will include the following: • Thirty-five patients will be analyzed on each treatment arm. Twelve DLT-evaluable patients from Phase 1 (Arms B and C) and 93 patients from Phase 2 will comprise the population for the final analysis of efficacy. • OS will be estimated by the Kaplan-Meier method for each treatment arm. • The 1-year OS rate and 1-sided 95% confidence interval (CI) will be calculated for each treatment arm, to determine whether the lower bound of the CI excludes the historical value for NP/Gem. A 1-sided one-sample Z test will also be conducted. The goal is to compare the survival probability at 1-year to the historical value of 0.35. • ORR and DCR and their 95% CIs will be calculated for each treatment arm. • PFS will be estimated by the Kaplan-Meier method for each treatment arm. • DOR will be calculated from dates of first documented response and progression of disease. • Toxicities will be graded by CTCAE v4.03 and tabulated by treatment arm. • PK of APX005M in Cycles 1 to 4 (Arms B and C). • Immune pharmacodynamic effects may be measured, including but not limited to change from baseline, and reported by treatment arm. • Test of associations between immune biomarkers and clinical outcomes

	• Construct multivariable linear models to dissect the pharmacodynamic effects of APX005M and nivolumab on immune biomarkers.