Statistical Analysis Plan

PHASE 1/2, OPEN-LABEL STUDY EVALUATING THE SAFETY OF REPEAT ADMINISTRATION OF AD/PNP-F-ARAAMP (AD/PNP ADMINISTERED INTRATUMORALLY WITH CO-ADMINISTRATION OF FLUDARABINE PHOSPHATE INTRAVENOUSLY) IN SUBJECTS WITH RECURRENT, LOCAL HEAD AND NECK CANCER

Protocol Number: PNP-002

SAP Version and Date:

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STUDY DRUG:
Ad/PNP-F-araAMP

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Contents

ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Class
BOR	Best overall response
BUN	Blood urea nitrogen
CBER	Center for Biologics Evaluation and Research (of the FDA)
CDER	Center for Drug Evaluation and Research (of the FDA)
CI	Confidence Interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
F-araA	Fludarabine
F-araAMP	Fludarabine phosphate
FDA	Food and Drug Administration
INR	International normalized ratio
IV	Intravenous(ly)
kg	Kilogram
LD	Longest diameter
mg	Milligram
mL	Milliliter
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PI	Principal Investigator
PJP	*Pneumocystis jiroveci*
PNP	Purine Nucleoside Phosphorylase
PR	Partial response
PT	Prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SE	Standard Error
SMC	Safety Monitoring Committee
SOC	System Organ Class

STD	Standard Deviation
TEAE	Treatment-emergent adverse event
TTR	Time to response
VP	Viral particle

1 INTRODUCTION

The statistical analysis plan (SAP) details the planned statistical analysis methods required to address the study objectives as described in GeoVax's protocol PNP-002: A Phase 1/2, Open-label Study Evaluating the Safety of Repeat Administration of Ad/PNP-F-araAMP (Ad/PNP Administered Intratumorally with Co-administration of Fludarabine Phosphate Intravenously) in Subjects with Recurrent, Local Head and Neck Cancer.

This SAP should be read in conjunction with the study protocol, case report form (CRF), and any other applicable study documents. This version of the SAP is based on the protocol PNP-002, Version 4.0 06MAY2022, Protocol Clarification Letter v.04 08MAR2023, and CRF 02NOV2022. Changes to these documents may result in subsequent changes to the SAP. The final, sponsor-approved version of the SAP must occur prior to database lock.

A table of contents for tables, figures, and listings, as well as mock shells, will be maintained in a separate document.

1.1 Changes to the Planned Analysis

Additional details may have been provided for analyses and data presentations described in the protocol, but no changes were made to analyses specified in the protocol. Any deviations from the approved statistical analysis plan will be described and justified in the final clinical study report.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary: • To evaluate the safety of repeat administration of a dose level of Ad/PNP-F-araAMP that demonstrated anti-tumor activity in participants with advanced head and neck cancer in the completed Phase 1 study.	• The primary endpoint is safety with repeat cycles of treatment. Safety measures include adverse events (AE) and laboratory parameters.
Secondary: • To evaluate the anti-tumor activity of repeat administration of Ad/PNP-F-araAMP, defined as participants who receive three intratumoral administrations of Ad/PNP and any infusion of F-araAMP.	• Objective response rate (ORR), defined as the percentage of participants with a best overall response (BOR) of a complete response (CR) or a partial response (PR). BOR is the best response achieved during the up to 5 cycles of treatment, separately for injected tumors and overall as determined by RECIST v.1.1. • Durable response rate defined as a BOR of CR or PR, separately for injected tumors and overall as determined by RECIST v.1.1 persisting for at least 4 weeks. • Time to response (TTR) defined as time from first intratumoral injection to date of first response value of CR or PR, separately for injected tumors and overall as determined by RECIST v.1.1. • Overall survival (OS) defined as time from first intratumoral injection to date of death for any cause. • Progression free survival (PFS) defined as time from first intratumoral injection to date of progression or death for any cause, whichever occurs first, separately for injected tumors and overall as determined by RECIST v.1.1. • Duration of response (DOR) defined as time from first documentation of CR or PR until disease progression or death for any cause, whichever occurs first, separately for injected tumors and overall as determined by RECIST v.1.1 .

3 STUDY DESIGN

3.1 General Description

This multi-center, open-label, phase 1/2, single-arm trial will evaluate the safety and anti-tumor activity of Ad/PNP-F-araAMP in participants with recurrent cancer of the head and neck region who have relapsed following curative treatment and without additional potentially curative treatment options. The study is designed to evaluate repeat administration (up to 5 cycles) of a single dose level of Ad/PNP administered intratumorally followed by intravenous (IV) F-araAMP. This study is to be conducted at Stanford University, Emory University, and Thomas Jefferson University.

Ad/PNP will be injected intratumorally twice on Day 1 and once on Day 2 followed by 25 mg/m^2 per infusion F-araAMP daily on Days 3, 4, and 5 infused over approximately 30 minutes. The 25 mg/m^2 F-araAMP dose level is the same as that evaluated in the two highest cohorts in the Phase 1 study. Each enrolled study participant shall receive 0.5 ml/dose of Ad/PNP, to which an amount of diluent will be added based on the volume of tumors selected for treatment. The dilution of study agent is described in protocol section 4.2 and shall not exceed 5 ml regardless of the number of tumors accessible for injection.

Tumor measurements taken on Day 1 of each cycle should be used to calculate dosing for Day 1 and Day 2 of that cycle.

Participants will receive repeat administration of Ad/PNP-F-araAMP every 4 weeks (i.e., each cycle) for 5 cycles or until injected tumor progresses, unacceptable toxicity occurs, no tumor is present for injection, or participant death.

Tumor selection and classification of target vs non-target should be performed according to RECIST 1.1. Target tumors should be selected for treatment at the participant's initial treatment visit. Following the participant's initial treatment, no additional tumors should be identified as target or selected for treatment.

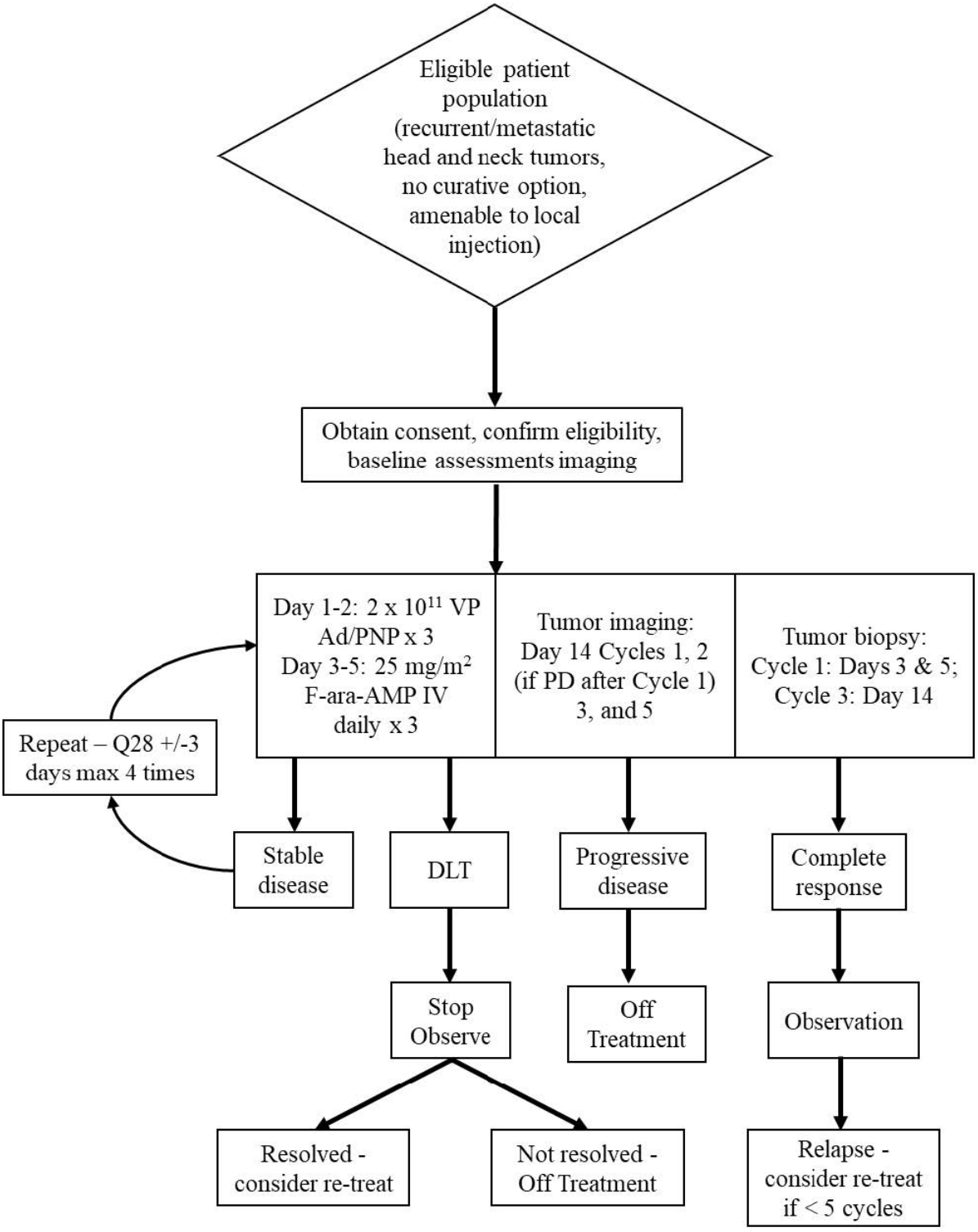
The same tumors should be treated at each administration of study agent. It is possible for target tumors to be identified but not treated. Non-target tumors should not be treated with study agent.

Tumor response in the injected tumor(s) will be assessed by physical examination (tumor measurement using ruler or calipers, if tumor can be assessed by palpation) as well as by radiographic imaging (magnetic resonance imaging [MRI] or computed tomography [CT] scan). The same methods to assess the injected tumor(s) will be used at baseline and subsequent time points.

Participants will be assessed for safety frequently, including Day 14 of each cycle. Participants will be assessed 4 weeks after completion of the last or fifth cycle. During the study, participants will be monitored for AEs including signs of infection, and changes in hematological or chemistry parameters (see Appendix 2, Protocol Study Procedures Table).

Participants who withdraw early from treatment will be asked to complete Day 56 (of the last treatment cycle) study visit evaluations. The study schema is presented in Figure 1.

Figure 1: Study Design



DLT = Dose-limiting toxicity; IV = intravenously; PD = progressive disease, VP = viral particle;

3.2 Randomization and Blinding

PNP-002 is an unblinded, open label study.

3.3 Sample Size

Regarding efficacy, no formal hypotheses or sample size estimates will be generated for this study. It is anticipated that approximately 10 to 20 participants will be enrolled into the to achieve 10 participants evaluable for efficacy. This number of participants is sufficient to assess preliminary safety and activity to guide design of subsequent clinical studies.

A total of 10 to 20 participants in the safety population provides sufficient precision to rule out a treatment-related serious adverse event (SAE) rate of 38.5% or more using a one-sided 80% upper confidence limit as per the following table:

Safety Population N	N of Events	Observed Proportion of Events	One-sided 80% Upper Confidence Limit
10	2	0.2000	0.38094
11	2	0.1818	0.35005
12	2	0.1667	0.32382
13	3	0.2308	0.38397
14	3	0.2143	0.35917
15	3	0.2000	0.33735
16	4	0.2500	0.38452
17	4	0.2353	0.36388
18	4	0.2222	0.34528
19	5	0.2632	0.38418
20	5	0.2500	0.36646

With 10 participants evaluable for efficacy, there is 83% power to reject a null hypothesis ORR of 10% or less when the alternative hypothesis ORR is at least 40% using a one-sided exact binomial test with a target alpha level of 10% (actual alpha is 7%). The null hypothesis is rejected if 3 or more responses are observed (i.e., observed ORR is at least 30%) and is considered sufficient evidence of efficacy to warrant further study of the treatment.

An alternative hypothesis ORR of at least 40% in this study with five cycles of therapy is considered reasonable based on the published phase I results, where 66.7% of participants in the higher dosing cohorts achieved a BOR of CR or PR with a single cycle of treatment.

3.4 Study Committees

3.4.1 Safety Monitoring Committee

The Safety Monitoring Committee (SMC) will review accumulating safety data (i.e., AE reporting, reactions to study treatment, deaths, etc.) and protocol deviations at time intervals specified in the SMC Charter and at any other time when it is determined by the SMC or GeoVax that such a review is warranted. Additional details on the timing, format, and content of data provided to the SMC will be described in the SMC Charter.

3.5 Timing of Analyses

The final analysis will occur once all participants complete their end of study visit or their last scheduled assessment per the Protocol Study Procedures Table (Appendix 2), or the sponsor terminates the study for any reason.

No interim analysis is planned.

4 ANALYSIS POPULATIONS

Enrolled Population: Defined as all participants who sign an informed consent. The Enrolled Population will be used for summaries of enrollment and participant disposition.

Safety Population (SAF): Defined as all participants who receive any intratumoral administrations of Ad/PNP or any infusion of F-araAMP. The SAF will be the primary population for all safety reporting.

Efficacy Evaluable Population: Defined as all participants who receive at least three intratumoral administrations of Ad/PNP and any infusion of F-araAMP. The efficacy evaluable population will be used as the primary analysis population for all efficacy reporting.

5 GENERAL CONSIDERATIONS

5.1 General Data Handling

All analyses will be conducted based on SAS 9.4 or higher.

Study data will be recorded in eCRFs for all screened and enrolled participants. The electronic data capture (EDC) vendor for this study is Allucent.

The protocol deviation data will be provided in spreadsheet format from the clinical trial management system (CTMS).

Analysis tables will be presented in aggregate (overall) for a specified population.

Data will be presented in by-participant data listings. Unless otherwise stated, all listings will be sorted by site ID, participant number, and assessment date (and time, if available).

Continuous data will be summarized by treatment group based on n, mean, median, standard deviation (STD), first quartile (Q1), third quartile (Q3), minimum value, and maximum value.

Categorical data will be summarized by treatment arm using frequency counts and percentages. Where applicable, 95% confidence intervals (CIs) will be provided. Unless otherwise stated, the denominator of percentages will be the number of participants in the population or the number with non-missing data.

- The number of missing values will be presented as a separate category with no percentage, but only if one or more participants are missing data.
- Counts of zero will be presented without percentages.

Relative to the number of digits after the decimal in the raw data, summary statistics will have the following number of digits after the decimal:

- Minimum and Maximum: same number of significant digits as the raw data
- Mean, Median, Q1, and Q3: one additional significant digit
- Standard Deviation (STD) or Standard Error (SE): two additional significant digits
- Percentages <100% will be reported to one decimal place and percentages of 100% will be reported with no decimal place.
- P-values will be reported to four decimal places. If the value is below 0.0001 it will be noted as < 0.0001; if the value is above 0.9999 it will be noted as > 0.9999.
- Summary statistics will not exceed four digits after the decimal. Some laboratory parameters or other data may require judicious deviation from this rule.

Unless otherwise noted, statistical inference will be based on a 2-sided 5% significance level.

All data up to the time of study completion/withdrawal from the study will be included in the analysis, regardless of duration of treatment.

Numbering for data displays will be based on ICH E3.

5.2 General Definitions

Variable	Definition
Study Day	• Study Day = date of interest - reference date + 1, when the date of interest >= reference date; • otherwise, Study Day = date of interest - reference date. Note: if either day is missing, reference date calculations will not be performed. Should imputation be performed, then Study day may be computed, where appropriate.
Baseline	Defined as the last non-missing value collected prior to receiving the first intratumoral injection (based on date and time of administration as applicable).
Post-baseline	Defined as values collected after receipt of first intratumoral injection (based on date and time of administration as applicable)
Change from Baseline	Defined as: Post-baseline value - Baseline value

Percent Change from Baseline	Defined as: (Post-baseline value - Baseline value)/Baseline value x 100. Note: To calculate percent change from baseline, the baseline value cannot be equal to zero.
Most Extreme Change	The maximum most extreme change will be based on be the maximum post-baseline value; the minimum most extreme change will be based on the smallest post-baseline value. For laboratory data assessed with CTCAE grading, data from scheduled or unscheduled visits will be utilized.
Maximum Reduction from Baseline	The maximum reduction from baseline will be based on the minimum post-baseline value collected and calculated per the change from baseline formula above. For tumor measurements, post-baseline values will be considered until an overall response of PD; measurements collected after start of new cancer therapies will not be included.
Maximum Percent Reduction	Defined as the percent change that is associated with the minimum most extreme change (i.e., the largest decrease from baseline). For tumor measurements, the maximum percent reduction will be the percent change from baseline for the maximum reduction from baseline.
Maximum Percent Increase	Defined as the percent change that is associated with the maximum most extreme change.
Duration on Study (in days)	End of study date - informed consent date +1.
Duration of Time from Initial Diagnosis to Informed Consent (in months)	(Date of Informed Consent - Date of Initial Diagnosis +1) / 30.4375.
Duration of Adverse Event (in days)	• Stop date of event - start date of event + 1, if time is not collected. • (Stop date/time of event - start date/time of event)/24, if time is collected.
Time to Event (in months)	(Date of event - first intratumoral injection +1) / 30.4375. If the event does not occur, participant will be censored as described for the appropriate endpoint in section 6.2.
Reporting in Months	Divide number of days by 30.4375
Reporting in Years	Divide number of days by 365.25
Reporting in Weeks	Divide number of days by 7
Height (in cm)	= height (in inches) * 2.54
Weight (in kg)	= weight (in lbs) * 0.4536
BMI (kg/m^2)	= weight(kg)/[height$(m)^2$]
Age (yr)	Age is collected in the EDC system (or through the IXRS system)

5.3 Data Imputation Rules

Generally, missing data will not be imputed, and will be presented as collected in the study database.

In cases where adverse event or medication dates are missing, the imputation methods described in Appendix 1 will be used to determine flags for treatment-emergent events and concomitant medications.

Conventions for censoring for time-to-event efficacy endpoints are described within the definitions of the endpoints in section 6.2.2.

5.4 Visit Windows

Both efficacy and safety endpoints will be analyzed according to the recorded scheduled visits. Unscheduled visits will not be summarized in tables but will be presented in data listings.

5.5 Pooling of Sites/Centers

Not Applicable.

6 ANALYSIS METHODS

6.1 Study Participant Data

6.1.1 Participant Enrollment and Disposition

Participant enrollment and disposition data will be summarized for the enrolled population and listed. Enrollment and disposition summaries will include:

- Number of participants in each analysis population

- Number of participants who have discontinued the study
- Primary reason for early withdrawal/discontinuation from study
  - Progressive disease
  - Adverse Event
  - Withdrawal by Subject
  - Lost to follow-up
  - Protocol Specified Withdrawal Criterion Met
  - Protocol Violation
  - Physician Decision
  - Pregnancy
  - Non-Compliance with Study Drug
  - Non-Compliance with Study Schedule
  - Study Terminated by Sponsor
  - Site Terminated by Sponsor
  - Sponsor Request
  - Death
  - Other

- Is early withdrawal/discontinuation from study related to COVID-19?
- Time (months) on study
- Primary reason for early withdrawal/discontinuation from treatment
  - Progressive disease
  - Adverse Event
  - Withdrawal by Subject
  - Lost to follow-up
  - Protocol Specified Withdrawal Criterion Met
  - Protocol Violation
  - Physician Decision
  - Pregnancy
  - Non-Compliance with Study Drug
  - Non-Compliance with Study Schedule
  - Study Terminated by Sponsor
  - Site Terminated by Sponsor
  - Sponsor Request
  - Death
  - Other
- Is early withdrawal/discontinuation from treatment related to COVID-19?

Completion of treatment is defined as participants who have received at least three administrations of Ad/PNP and at least 1 infusion of F-araAMP prior to their withdrawal from the study.

Completion of the study is defined as any participant who completes one or more cycles (visits 1-7).

Participants who are discontinued from the study via the discretion of the investigator, or no longer receiving IP by other criteria specified in the protocol, will be considered to have completed the study if at least 1 cycle (visits 1-7) is completed.

Participants who withdraw from the study will be considered to have completed the study if at least 1 cycle (visits 1-7) is completed.

Participants contributing to each analysis population and final disposition status will be listed.

6.1.2 Protocol Deviations

A listing of protocol deviations will be provided.

6.1.3 Demographic and Baseline Characteristics

Participant demographics will be summarized and listed. These will include age, sex (Male / Female), child-bearing potential (Yes / No), ethnicity (Hispanic / Non-hispanic / Not Reported / Unknown), race (American Indian or Alaska Native / Asian / Black or African American / Native Hawaiian or Pacific Islander / White / Not Reported), baseline height (cm), baseline weight (kg), and baseline BMI (kg/m^2).

Disease history and baseline disease characteristics will be summarized. These will include: Duration of time from initial diagnosis to screening (in months), primary site of cancer, histology type, stage at diagnosis, TNM at study entry, Progression/Recurrence/Metastasis observed after diagnosis, Progression/Recurrence/Metastasis specification and location, extent of disease, baseline tumor measurements, prior chemotherapy (Yes/No), prior immunotherapy (Yes/No), prior radiation (Yes/No), prior surgery (Yes/No), baseline ECOG, Chest Radiograph results, baseline CT scan/MRI results will be summarized, as well as baseline prognostic laboratory values for the following selected laboratory tests:

- Hemoglobin, hematocrit, white blood cell count, lymphocytes (absolute), lymphocytes (percentage), neutrophils (absolute), neutrophils (percentage), platelet count.
- Prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR).

Listings of demographics, disease history, baseline disease characteristics, and Smoking/Alcohol History will be provided.

6.1.4 Medical History

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0 and will be listed by System Organ Class and Preferred Term.

A listing of medical history will be provided.

6.1.5 Prior and Concomitant Medication

The incidence of medication use will be summarized by WHO Drug Dictionary (WHODD) B3 Global March 2023 anatomic therapeutic chemical (ATC) Level 2 classification (i.e. therapeutic main group) and preferred name. A participant will be counted only once at each level of reporting. Prior medications are those which have been identified to have been discontinued prior to the treatment start date (e.g., taken exclusively during the pre-therapy period). Concomitant medications are those which have been identified to have been taken at any point during the on-therapy or post-therapy periods. Prior and concomitant medication use will be summarized separately.

All prior and concomitant medication data will be listed including the verbatim and preferred drug name and ATC Level 2. If anticancer medications have been recorded as taken during study, these will be identified via medical review and flagged in data listings.

6.1.5.1 PJP Prophylaxis Antibiotic Treatment

The incidence of PJP Prophylaxis Antibiotic Treatment use will be summarized. A participant will be counted only once for any use.

All PJP Prophylaxis Antibiotic Treatment data will be listed.

6.1.6 Prior and Concomitant Procedures

Number and percentages of prior and concomitant procedures will be summarized by indication, procedure, location, and laterality. Prior procedures are those which have been identified to have

been discontinued prior to the procedures start date (e.g., taken exclusively during the pre-therapy period). Concomitant procedures are those which have been identified to have been taken at any point during the on-therapy or post-therapy periods. Prior and concomitant procedures will be presented in data listings.

6.1.7 Study Drug Exposure and Compliance

For both Ad/PNP and F-araAMP (separately), completion of a given cycle is defined as follows:

- Completed cycle is defined as all 3 administrations performed.
- Partial cycle is defined as < 3 administrations performed.

Note that, based on the data collection in the eCRF, an administration is either performed or not performed; there is no consideration of partially vs. fully performing an administration. In contrast, a partial Ad/PNP injection or a partial F-araAMP infusion are considered below.

For Ad/PNP, an administration is defined farther below. For F-araAMP, an administration is defined as a full infusion or a partial infusion.

Exposure to Ad/PNP will be summarized using the following measures:

- Total Number of Cycles Completed.
- Total Number of Cycles Received. Defined as the total number of completed or partial cycles.
- Number of administrations performed
- Number of administrations not performed
- Number of administrations delayed
- Number of injections administered (fully or partially)
- Number of injections fully administered
- Number of injections partially administered
- Number of injections not administered
- Treatment Duration (days): Last dose date - First dose date + 1

For the Ad/PNP exposure endpoints listed above, a single Ad/PNP administration is defined without regard to the number of injections or the number of tumors treated, while the number of injections is defined considering the number of tumors treated. For example, a participant might have:

- 3 administrations during any given cycle, comprised of
- 1 tumor treated at each administration, yielding a total of 3 injections.

or,

- 3 administrations during any given cycle, comprised of
- 2 tumors treated at each administration, yielding a total of 6 injections.

F-araAMP exposure will also be summarized using mg/m^2.

- Total Number of Cycles Completed.
- Total Number of Cycles Received. Defined as the total number of completed or partial cycles.

- Total Cumulative Dose Received. Defined as total mg/m^2 received from first dose date up to and including last dose date.
- Number of infusions administered (fully or partially)
- Number of infusions which were temporarily interrupted or had flow rate modified.
- Number of infusions fully administered
- Number of infusions partially administered
- Number of infusions not administered
- Number of infusions delayed
- Dose Intensity (mg/m^2/Cycle). Defined as [total cumulative dose (mg/m^2)] / [number of Cycles Received].
- Treatment Duration (days): Last dose date - First dose date + 1

No assessment of study drug compliance will be performed for this study.

6.2 Efficacy

Efficacy analyses will be conducted on the Efficacy Evaluable Population (refer to section 4).

In addition to the tabular summaries detailed below, efficacy data will be provided in by-participant data listings.

6.2.1 Primary Efficacy Endpoint(s) and Analyses

There is no primary efficacy endpoint, and therefore no primary efficacy analysis, as the primary endpoint for this study is safety. However, an efficacy endpoint of primary focus is defined in section 6.2.2.

6.2.2 Secondary Efficacy Endpoints and Analyses

Secondary efficacy endpoints involving response, including progression, will be assessed 2 distinct ways:

- For injected tumors (per the criteria specified in protocol section 9.3.4), and
- Overall as determined per RECIST v1.1 (http://www.ctep.info.nih.gov).

Efficacy responses assessments for injected tumors should be performed using the (RECIST-like) assessment according the to the criteria established in section 9.3.4 (Tumor Response) of the protocol (CR, PR, PD, SD). Per the protocol, this response for injected tumors is the primary focus for response, with the efficacy endpoint of primary focus being ORR for injected tumors.

Overall efficacy response assessments should be performed per RECIST 1.1 for target and non-target tumors without consideration for which tumors were treated with the study agent. Per the protocol, this overall response per RECIST 1.1 is not the primary focus for response. Total tumor burden is also being evaluated because there is a possibility of immune-mediated anti-tumor benefit.

RECIST and protocol established response evaluation criteria should be performed/evaluated in combination with CT scan/MRI at the timepoints specified in the protocol (Visit 7 of the first,

second (if PD after first cycle), third, and last cycle. Participants with CR, PR, or SD in the injected tumor at Day 14 of the fifth or last cycle will have imaging on Day 56).

To emphasize:

- Injected tumors will not be assessed per RECIST v1.1 but solely per the criteria (from protocol section 9.3.4) which are specified below.
- Many of the endpoints differ for injected tumors vs. overall as determined per RECIST v.1.1 due to differences in their underlying component definitions of CR, PR, and PD.
- All efficacy endpoints are secondary.

Injected Tumor Response Criteria Details

The following criteria will be used to define response in injected tumors:

- Complete Response (CR): Disappearance of the injected tumor(s).
- Partial Response (PR): At least a 30% decrease in the longest diameter (LD) of the injected tumor(s), taking as reference the smallest LD.
- Progression (PD): At least a 20% increase in the LD of the injected lesion(s), taking as reference the smallest LD recorded on study (this includes the baseline LD if that is the smallest on study). Note: appearance of one or more new lesions will be considered progression in assessing overall tumor response.
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to quality for PD taking as reference the smallest LD while on study.

Regarding injected tumors, only tumors identified as target per RECIST 1.1 at the initial study visit should be treated with the study agent (AdPNP). It is possible, based on the size(s) and location(s) of the target tumor(s), that not all target tumors will be treated with the study agent. At each administration, investigators should treat only the same tumor(s) based on those target tumors treated at the initial treatment visit. No other target tumors should be treated with the study agent at any subsequent visit. Non-target tumors should not be treated with the study agent. Response for injected lesions is assessed by the investigator and recorded in the eCRF.

Regarding non-injected tumors, the protocol does not define response assessment criteria for these tumors. Therefore, efficacy response for non-injected tumors will be taken into consideration only as an input to the RECIST 1.1 response assessment. No formal criteria-based response assessment will be performed or analyzed for non-target tumors alone. Any observable effect on non-injected tumors may be recorded by investigators in the study database.

Response Per RECIST v1.1 Criteria Details

Response status per RECIST v1.1 will also be assessed by the investigator using all lesions (target, non-target, and new [if present]) as part of each evaluation. Post-baseline evaluation CT or MRI imaging (per RECIST) is to be done in all participants at Screening and at Visit 7 of the first, second (if PD after first cycle), third, and last cycle. Participants with CR, PR, or SD in the injected tumor at Day 14 of the fifth or last cycle will have imaging on Day 56. There will be no PFS follow up beyond the treatment period. RECIST v1.1 results will be assessed by the investigator

and entered into applicable eCRF pages, including separate assessment of response for overall, target lesions, and non-target lesions.

Secondary Efficacy Analyses

All efficacy analyses are secondary, because all efficacy endpoints are secondary.

Efficacy analyses will be conducted on the Efficacy Evaluable Population (refer to section 4).

Regarding analyses, efficacy response results for injected tumors and overall (per RECIST v1.1) will be reported separately. Generally, though, unless otherwise specified, both ways of assessment will be analyzed in the same manner.

6.2.2.1 Best Overall Response, Objective Response Rate and Durable Response Rate

Best Overall Response

Separately for injected tumors and overall (per RECIST v1.1), a participant's best overall response (BOR) is determined by the highest qualitative value assessed during the study for the following hierarchy of objective response results: CR > PR > SD > PD > NE. In order for a valid value of SD to be assigned, there must be evidence of stable disease for at least 6 weeks. If the minimum time for SD has not been met on the first assessment, the assignment of BOR will depend on subsequent response assessments. Participants which do not have follow up data after a first assessment of SD prior to the minimum time requirement will be considered as not evaluable (NE). BOR will be based on assessments collected after the first intratumoral injection until disease progression; assessments collected after the start of new anticancer treatment will not be considered. Confirmation of response will not be required for BOR. Participants who do not have any post-baseline results for response will be considered as not evaluable (NE).

Separately for injected tumors and overall (per RECIST v1.1), BOR will be summarized using the efficacy evaluable population.

Waterfall plots of BOR results for each criterion will be presented graphically using maximum percent reduction. Swimmer plots identifying participant response patterns over time will also be separately provided.

Objective Response Rate

Separately for injected tumors and overall (per RECIST v1.1), the objective response rate (ORR) is defined as the number of participants who exhibit a BOR response of CR or PR during the up to 5 cycles of treatment divided by the number of participants in the efficacy evaluable population.

Separately for injected tumors and overall (per RECIST v1.1), the ORR will be presented; corresponding two-sided 95% Clopper-Pearson exact confidence intervals (CIs) and the underlying number of participants will also be provided. The efficacy analysis of primary focus will be the analysis of ORR for injected tumors.

Durable Response Rate

Separately for injected tumors and overall (per RECIST v1.1), the durable response rate will be determined via persistence of CR or PR for at least 28 days, with the corresponding response duration calculation, in days, as (the earliest date of PD or death for any cause - the date of first documentation of CR or PR + 1). Participants who do not have at least 28 days of data following BOR of CR or PR will be considered to not have had durable response. Participants who discontinue prior to being evaluated for post-baseline tumor assessments will be considered as non-responders.

Separately for injected tumors and overall (per RECIST v1.1), the durable response rate will be presented; corresponding two-sided 95% Clopper-Pearson exact CIs will also be provided.

6.2.2.2 Progression Free Survival

Separately for injected tumors and overall (per RECIST v1.1), PFS is defined as time from first intratumoral injection to date of progression or death for any cause, whichever occurs first, and is calculated, in months, as:

(Date of first PD or death or censoring - date of first intratumoral injection + 1) / 30.4375.

PFS derivation will not include tumor assessments collected after the end of study treatment as these are not planned for collection beyond the final cycle. Tumor assessments taken after switch to another anti-cancer therapy will be excluded from consideration.

The first date of PD would be the earliest date of any post-baseline response finding of progressive disease or death unless a participant is censored at an earlier date. If an assessment occurs over several days, the date of assessment as collected on the Response Assessments eCRF page will be used. If there are no adequate assessments for a participant, they will be censored on their first intratumoral injection date unless they died prior to having their first assessment (in which case the death would be treated as an event). If a participant receives subsequent anticancer therapy prior to documentation of progressive disease, PFS will be censored at the latest adequate assessment prior to additional therapy initiation. Otherwise, if a participant does not have documented progression within this PFS observation period (i.e., until any PFS event or censoring), the participant will be censored at the latest adequate assessment.

Separately for injected tumors and overall (per RECIST v1.1), PFS will be analyzed based on Kaplan-Meier methods; Kaplan-Meier curves will be plotted over time. The number and percentage of participants identified to have had a PFS event and those who were censored will be displayed. The median time to PFS and its corresponding 95% CI will also be produced.

6.2.2.3 Time to Response

Separately for injected tumors and overall (per RECIST v1.1), TTR is defined as time from first intratumoral injection to date of first response value of CR or PR during the PFS observation period (i.e., until any PFS event or censoring), and is calculated, in months, as:

(Date of first response or censoring - date of first intratumoral injection + 1) / 30.4375.

TTR will be analyzed in the same manner as PFS, including the same censoring conventions with exception that date of death is used for censoring, not as an event).

6.2.2.4 Overall Survival

Separately for injected tumors and overall (per RECIST v1.1), overall survival (OS) is defined as time from first intratumoral injection to date of death for any cause, and is calculated, in months, as:

(Date of death or censoring - date of first intratumoral injection + 1) / 30.4375.

Participants still alive as of the data cut-off date will be censored on the last known alive date from mortality status follow up. For participants that are lost to follow up, the last visit in the database or last contact date where the participant is documented to be alive will be used to estimate last known date alive.

OS will be analyzed based on the Kaplan-Meier methods described for PFS.

6.2.2.5 Duration of Response

Separately for injected tumors and overall (per RECIST v1.1), for participants who have been identified as a responder (achieved an overall response of CR or PR during the PFS observation period, i.e., until any PFS event or censoring), duration of response (DOR) is defined as time from first documentation of CR or PR until disease progression or death for any cause, whichever occurs first, and is calculated, in months, as:

(Date of PD or death - date of first response + 1) / 30.4375.

Censoring algorithms analogous to those for PFS will be used for DOR. If sample size permits, DOR will be analyzed based on the Kaplan-Meier methods described for PFS.

6.2.3 Exploratory Efficacy Endpoints and Analyses

Not Applicable.

6.2.4 Multiplicity

No multiplicity adjustments will be performed for multiple analyses or multiple endpoints.

6.3 Interim Analysis

No interim analysis will be performed.

6.4 Subgroup Analyses

No subgroup analyses are planned.

6.5 Correlative/Special Studies

Correlative/special studies, as described in protocol section 8., are outside of the scope of this SAP.

6.6 Safety

The primary endpoint of the study is safety which will be assessed on clinical examination and measurement of laboratory parameters.

All participants who receive a dose of Ad/PNP-F-araAMP will be included in the safety analysis population. Each participant will be followed for safety for ~ 60 days following their final study dose. All safety assessments including adverse events, clinical laboratory evaluations, and vital signs will be summarized with descriptive statistics, where appropriate, and listed in the data listings using Medical Dictionary for Regulatory Activities (MedDRA) terms.

Protocol section 12.2 states consideration of the repeat administration of Ad/PNP-F-araAMP as safe if the one-sided 80% upper confidence limit of the percentage of participants in the safety population experience treatment-related Serious Adverse Events as defined in Protocol section 7.2. For example, if 2 of 10 participants experience a treatment related SAE, then the one-sided 80% upper confidence limit is 38.1% and the repeat administration of Ad/PNP-F-araAMP would be considered safe. However, evaluations of the investigational product's (potential) safety profile will not be considered strictly using only assessment of that criterion, but rather will involve broader considerations in addition to assessment of that criterion.

All safety analysis reporting will be based on the Safety Population.

6.6.1 Adverse Events

An adverse event (AE) is any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen. For this study, only abnormal laboratory findings with clinical significance as determined by the PI are considered AEs. AEs will be recorded from the date of informed consent through the study follow-up period (~ 60 days after last dose of study drug). AEs will be assessed for severity, using the NCI-CTCAE version 5.0, relationship to study treatment, relationship to non-study treatment, and seriousness. Relationship assessments of possibly related or greater are defined to be related. Any missing relationship assessments will be assumed to be related, and any missing severity assessments will be assumed to be Severe/Grade 3. Disease progression is not an AE (non-serious or serious), although signs and symptoms thereof may be reportable as AEs.

A treatment-emergent adverse event (TEAE) is defined as an AE with onset occurring at any time point after the first intratumoral administration of Ad/PNP. A TEAE also may be a continuing AE reported prior to the date of the first dose of study drug, which worsens in severity after the first administration of Ad/PNP.

A serious adverse event (SAE) is defined as any adverse experience that suggests a significant hazard, contraindication, side effect, or untoward medical occurrence that:

- Results in death,

- Is life-threatening (Note: the term "life-threatening" refers to an event in which the participant was at risk of death at the time of the event rather than to an event which hypothetically might have caused death if it were more severe.),
- Requires (or prolongs) hospitalization,
- Causes persistent or significant disability/incapacity,
- Results in congenital anomalies or birth defects, or
- Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome.

An overview of TEAEs will be produced, including counts and percentages of participants with any incidences of: TEAEs, TEAEs related to study treatment, TEAEs related to non-study treatment, TEAEs related to study treatment or non-study treatment, TEAEs of grade 3 or greater, related TEAEs of grade 3 or greater, TEAEs that are dose limiting toxicities (DLTs), serious adverse events (SAEs), TEAEs leading to study treatment discontinuation, and fatal SAEs.

Adverse events will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA) version 21.0 for reporting by system organ class (SOC) and preferred term in descending order of overall incidence.

Summaries of adverse events by SOC and preferred term will include the following types:

- TEAEs;
- TEAEs related to study treatment;
- TEAEs related to non-study treatment;
- TEAEs related to study treatment or non-study treatment;
- TEAEs by maximum CTCAE Grade;
- TEAEs with CTCAE Grade 3 or greater;
- TEAEs with CTCAE Grade 3 or greater related to study treatment;
- DLTs;
- SAEs; and
- TEAEs leading to study treatment discontinuation.

When calculating the incidence of AEs, each AE will be counted only once for a given participant within a MedDRA category (e.g., overall, system organ class, or preferred term). When AEs are summarized within levels of another AE assessment (e.g., relatedness or severity), AEs will be counted once per participant at the worst level of the assessment (e.g., strongest relationship to study treatment or greatest severity).

A comprehensive listing of all AEs will be provided in a by-participant data listing. In addition, the following by-participant data listings will be provided:

- SAEs;
- TEAEs related to study treatment or non-study treatment;
- TEAEs leading to study treatment discontinuation; and
- Fatal AEs.

6.6.2 Clinical Laboratory Evaluations

Clinical laboratory tests (including hematology, serum chemistry, coagulation, CD4/CD8 T-Cell Subsets, and urinalysis) will be performed at local laboratory facilities at each site, at visits per the Protocol Study Procedures Table (Appendix 2). Hematology and serum chemistry test values will be converted as required to values based on the International System of Units (SI). All summaries and listings will use SI units.

The following laboratory tests will be reported in data summaries:

Hematology: hematocrit, hemoglobin, platelet count, RBC, and WBC, MCH, MCHC, MCV, neutrophils (absolute), eosinophils (absolute), basophils (absolute), lymphocytes (absolute), and monocytes (absolute). Percentage differentials of neutrophils, eosinophils, basophils, lymphocytes, and monocytes.

Serum chemistry: sodium, potassium, carbon dioxide, chloride, glucose, magnesium, calcium, blood urea nitrogen (BUN), creatinine (Cr), phosphorus, albumin, alkaline phosphatase, ALT, AST, total bilirubin, total protein.

Coagulation: PT, INR, aPTT.

CD4/CD8 T-Cell Subsets: CD4/CD8 T-cell.

Urinalysis: pH, specific gravity, Leukocyte esterase (Leukocytes), Nitrite, Urolbilinogen, Protein, Phosphorus, Occult blood (Hemoglobin & erythrocytes), Ketones, Bilirubin, Glucose.

Pregnancy: serum/urine pregnancy test.

Results of laboratory tests from hematology and chemistry evaluations that are outside of the reference range will be flagged and displayed in the summary tables. Descriptive statistics (e.g., number of participants, mean, STD, median, Q1, Q3, minimum, and maximum) for hematology and serum chemistry measurements will be calculated for each time point. The same descriptive statistics will be generated for these changes from baseline for each measurement. For the selected laboratory tests identified in section 6.1.3, a spaghetti plot will visually track measurements over time for each participant. Baseline is defined as the last measurable value prior to dosing on Day 1. All clinical laboratory data will be provided in data listings, with values outside of the reference range flagged. No grading of laboratory tests results will be performed.

6.6.3 Vital Signs

Vital signs include: pulse rate (bpm), respiratory rate (bpm), temperature (ºC), systolic and diastolic blood pressure (mmHg). Observed values and changes from baseline for these vital signs will be summarized at each visit and time point.

Vital signs will be provided in a by-participant data listing.

6.6.4 ECOG Performance Status

ECOG data will be summarized by score categories 0-4 at scheduled visits with frequency count and percent. Percentages will be based on the number of non-missing observations. In addition, a shift table of baseline to the last visit will be provided. ECOG data will be provided in a by-participant data listing.

6.6.5 Electrocardiogram (ECG)

Electrocardiogram (ECG) parameters include: HR, PR, QT, QTcF. Observed values and changes from baseline for ECG parameters will be summarized at each visit and time point.

ECG data will be provided in a by-participant data listing.

6.6.6 Physical Examinations

Physical examination results will be presented in a by-participant data listing.

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8 APPENDICES

8.1 APPENDIX 1: Partial Date Conventions

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study treatment start date, then not TEAE If start date >= study treatment start date and < (end of treatment + 60 days), then TEAE If start date > (end of treatment + 60 days), then not TEAE *if time is collected, consider time in determining if event is a TEAE
Partial, but known components show that it cannot be on or after study treatment start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study treatment start date	Known	If stop date < study treatment start date, then not TEAE If stop date >= study treatment start date, then TEAE *if time is collected, consider time in determining if event is a TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study treatment start date, then not TEAE If stop date >= study treatment start date, then TEAE
	Missing or ongoing is checked	Assumed TEAE
Missing	Known	If stop date < study treatment start date, then not TEAE If stop date >= study treatment start date, then TEAE *if time is collected, consider time in determining if event is a TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study treatment start date, then not TEAE If stop date >= study treatment start date, then TEAE
	Missing or ongoing is checked	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study treatment start date, assign as prior If stop date >= study treatment start date and start date <= end of treatment + 60 days, assign as concomitant If stop date >= study treatment start date and start date > 60 days after the end of treatment, assign as subsequent
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study treatment start date, assign as prior If stop date >= study treatment start date and start date <= end of treatment + 60 days, assign as concomitant If stop date >= study treatment start date and start date > 60 days after the end of treatment, assign as subsequent
	Missing	If "Ongoing" is flagged, assign as concomitant If "Ongoing" is not flagged and stop date is missing, assign as concomitant If start date <= end of treatment + 60 days, assign as concomitant If start date > 60 days after the end of treatment, assign as subsequent
Partial	Known	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study treatment start date, assign as prior If stop date >= study treatment start date and start date <= end of treatment + 60 days, assign as concomitant If stop date >= study treatment start date and start date > 60 days after the end of treatment, assign as subsequent
	Partial	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study treatment start date, assign as prior If stop date >= study treatment start date and start date <= end of treatment + 60 days, assign as concomitant If stop date >= study treatment start date and start date > 60 days after the end of treatment, assign as subsequent
	Missing	If "Ongoing" is flagged, assign as concomitant Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing, assign as concomitant If start date <= end of treatment + 60 days, assign as concomitant If start date > 60 days after the end of treatment, assign as subsequent
Missing	Known	If stop date < study treatment start date, assign as prior If stop date >= study treatment start date, assign as concomitant Cannot be assigned as subsequent

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study treatment start date, assign as prior If stop date >= study treatment start date, assign as concomitant Cannot be assigned as subsequent
	Missing	If "Ongoing" is flagged, assign as concomitant If "Ongoing" is not flagged, assign as concomitant

Partial dates for additional anticancer therapies, as recorded in the concomitant medication eCRF forms, will not typically be imputed, but may be needed to support efficacy outcome derivation (i.e., PFS and similar). This is applicable to anticancer therapy and radiotherapy but may also apply to surgical procedures. In this case, should it be needed after every attempt to gather information from the investigative site(s), the following will be applied for imputation of new anticancer therapies taken after treatment start date:

- If the new anticancer therapy start date is completely missing, no imputation will be conducted.
- For other missing data scenarios for new anticancer therapy, concomitant medication data will be reviewed, and conventions will be developed only if needed.

8.2 APPENDIX 2: Protocol Study Procedures Table

		Cycles 1-5 (28-day cycles)[12]						Cycle 5 or last cycle	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Day	**Screen -30 to 0**	**1**	**2**	**3**	**4**	**5**	**14± 2**	**28 ±3**	**56 ±3**
Informed Consent	X								
Medical History	X								
Physical examination[1]	X	X							
Vital Signs[16]	X	X	X	X	X	X	X	X	X
Inspect injected tumor site(s)			X	X	X	X	X	X	X
Performance Status	X	X							
ECG	X								X
CXR (If no chest CT)	X								
Chemistries[2]	X	X[8]					X	X	X
Hematology[3]	X	X[8]					X	X	X
CD4/CD8 T-cell subsets	X			X[11]					X[11]
Urine analysis	X								X
Serum pregnancy	X								
PT/aPTT	X								
CT scan/MRI[4]	X						X		(X)
Physical measurement of tumor size[5]	X	X				X	X	X	X
Blood samples for Adenovirus[6]		X	X						
Urine for adenovirus[6]		X	X						
F-Ade plasma level				X[9]		X[9]			
Blood sample for antibody to adenovirus		X[10]						X[10]	
Intratumoral administration Ad/PNP[7]		X	X						
PJP Prophylaxis[13]		X	→	→	→	→	→	→	X
Tumor Biopsy[14]				X		X	X		
Infusion of F-araAMP				X	X	X			
Adverse Events		X	X	X	X	X	X	X	X
Medications[15]	X	X	X	X	X	X	X	X	X

1. A thorough physical examination will be done at screen and second study visit; system-oriented examination will be conducted as needed on other visits. Weight and height should be recorded at baseline. Injected tumor will be examined at each visit.
2. Chemistries include: Na^+, K^+, CO_2, Cl, glucose, Mg^{++}, Ca^{++}, blood urea nitrogen (BUN), creatinine (Cr), phosphorus, albumin, alkaline phosphatase, ALT, AST, total bilirubin, total protein.
3. Hematology values include CBC with differential and platelet count.
4. CT or MRI Imaging is to be done in all subjects at Screen and at Visit 7 of the first, second (if PD after first cycle), third, and last cycle. Subjects with CR, PR, or SD in the injected tumor at Day 14 of the fifth or last cycle will have imaging on Day 56.
5. For injected tumors palpable on physical examination, tumor size is to be assessed by physical measurement (ruler or calipers), if possible.
6. Samples will be collected prior to the first administration of Ad/PNP on Day 1 and 2 (+/-1 hour) hours after the third administration on Day 2 of the first and third cycle.
7. Ad/PNP will be administered intratumorally three times: two administrations 3-6 hours apart on Day 1 and 1 administration early (morning) on Day 2. Subjects will be monitored continuously for 1 hour after each administration.
8. Blood sample to be drawn and routine chemistry and hematology results reviewed by the Clinical Investigator prior to administration of study drug.
9. Draw two blood samples for F-Ade: one prior to F-araAMP infusion and one 15-30 minutes after infusion of F-araAMP on Days 3 and 5 of the first and third cycle.
10. Blood sample for antibody to be drawn prior to first administration of Ad/PNP on the first and third cycle, and Day 28 of the last cycle.
11. Blood sample to be drawn prior to first infusion of F-araAMP on the first cycle and Day 56 of the last cycle.
12. Evaluations on Visit 2 through 7 are to be done for each 28-day cycle.
13. Prophylaxis for *Pneumocystis jirovеci* (PJP) extends pre-dose dose on Day 1 of cycle 1 through Day 56 following the last cycle. This will be one double-strength trimethoprim (TMP)/sulfamethoxazole (SMX) (i.e., 160 TMP/800 SMX) three times a week.
14. Biopsy of injected tumor will be done on Days 3 and 5 of the first cycle and on Day 14 of the third cycle.
15. Medications will be recorded at screening and any change in medications will be recorded at study visits.
16. Vital signs will be recorded at 30 +/- 15 min, and 60 +/- 15 minutes following each administration