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 No. PNP-002
Version 04, 06 May 2022

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Document History

Amendment Date	Notes
Version 1 Date: July 2016	During the protocol development phase with the investigator and collaborator- never submitted to the Stanford Institutional Review Board (IRB)
Version 2 Date: 8.7.2017	Initial IRB/SRC Submission
Version 2 Date: 10.6.2017	SRC Edits
Version 2 Date: 11.16.2017	SRC Pre-Comments
Version 02 Date: 05 September 2018	Clarify enrollment numbers; adverse event (AE) reporting criteria and instructions
Version 03 Date: 28 February 2019	Revision includes: - Removal of requirement for emergency equipment beyond usual resources
Version 04 Date: 06 May 2022	Revision includes: - Addition of "Statement of Compliance", "Sponsor's Approval", and "Investigator's Agreement" sections - Coordinating center changed to GeoVax, Inc. and study changed to a multisite study with accompanying edits to the Safety Monitoring Committee Charter and sections in the protocol regarding the Safety Monitoring Committee - Clarification of Inclusion/Exclusion Criteria: patients with histologically or cytologically confirmed diagnosis of recurrent cancer of the head and neck region for whom there is no curative treatment option; for the purposes of trial eligibility, head and neck cancer shall include, in addition to head and neck squamous cell carcinoma (HNSCC), cutaneous squamous cell primary sites and squamous cell carcinoma of unknown primary presenting with neck lymph nodal disease, as well as nasopharyngeal carcinoma, and salivary gland tumors; patients with resolved side effects can receive treatment earlier than 4 weeks after latest chemotherapy dose - Removal of Section 2.6 Correlative Studies Background since there were no correlative studies - Removal of "Description of Study Drug" Section 4.1 since this text was referenced in "Description of Study Drug" Section 5.1. - Edits to study calendar: extension of screening period window; adjustments to pharmacokinetic collection and vitals timepoints, removal of projected study completion timelines; - Moved the first paragraph describing how tumor response will be assessed from Section 12.6 Assessment of Efficacy Measures to Section 10.3.5 Response Review - Clarified responsibilities of Sponsor and Contract Research Organization (CRO) in Section 11.9 Study Monitoring and Auditing - Clarification of endpoints and alignment of terminology with Food and Drug Administration (FDA) guidance and industry standards - Clarification of the Statistical Consideration section and added a description of study power - Minor grammatical and typographical updates throughout to improve clarity and readability - Miscellaneous edits to promote consistency

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by International Conference for Harmonisation (ICH) E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	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
Version Number	04
Version Date	06 May 2022

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

Medical Representative			
Name:	**Title:**	**Signature:**	**Date:**
Kelly McKee, MD, MPH	Chief Medical Officer	DocuSigned by: Kelly McKee Signer Name: Kelly McKee Signing Reason: I approve this document Signing Time: 12-May-2022 | 08:43 EDT 3D5E632A3B7A4FD291F436E15099C3D1	12-May-2022 | 08:43 EDT
Coordinating Investigator			
Name:	**Title:**	**Signature:**	**Date:**
A. Dimitrios Colevas, MD	Professor of Medicine, Stanford University	DocuSigned by: A. Dimitrios Colevas Signer Name: A. Dimitrios Colevas Signing Reason: I have reviewed this document Signing Time: 17-May-2022 | 17:58 PDT FCD48C7BBF7D4F6AA8F28BBB19CBD137	17-May-2022 | 17:59 PDT

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study [insert number] and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each subject's participation and all data required by the protocol

Name	**Title**	**Institution**
[Insert last name, first name]	[Insert title (at institution)]	[Insert address]

Signature	**Date**
	[DD Month YYYY]

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PROTOCOL SYNOPSIS

Title

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

Study Objectives

The primary objective of the study is to evaluate the safety of repeat administration of a dose level of Ad/PNP-F-araAMP that demonstrated anti-tumor activity in patients with advanced head and neck cancer in the completed Phase 1 study.

The secondary objective of the study is to evaluate the anti-tumor activity of repeat administration of Ad/PNP-F-araAMP.

Study Design

The study is an open-label, multisite, Phase 1/2 study evaluating the safety and anti-tumor activity of Ad/PNP-F-araAMP in subjects 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.

Sample Size and Duration of Study

It is anticipated that approximately 10 to 20 subjects will be enrolled into the study in order to have 10 subjects evaluable for efficacy. Each subject will be followed for ~ 60 days following their last dose of study medication. Based on the patient population, it is anticipated that the study will require 36 to 48 months to be completed.

Study Population

Inclusion Criteria

1. Provided Informed Consent
2. Age ≥ 18 years
3. Patients with histologically or cytologically confirmed diagnosis of recurrent cancer of the head and neck region for whom there is no curative treatment option. For the purposes of trial eligibility, cancers of the head and neck shall include, in addition to head and neck squamous cell carcinoma (HNSCC), cutaneous squamous cell primary sites and squamous cell carcinoma of unknown primary presenting with neck lymph nodal disease, as well as nasopharyngeal carcinoma, and salivary gland tumors.
4. All standard or approved treatment options that would provide substantive palliation must have failed, been exhausted, or patient not eligible for them (for example neuropathy, nephropathy, or hearing loss precluding the use of cisplatin).
5. Tumor mass (primary tumor and/or lymphadenopathy) measurable by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and technically suitable for intratumoral injections (otolaryngologist will determine feasibility). Patients with nodal disease (or metastatic disease) that is needle accessible are eligible. Patients with additional tumors (including

PROTOCOL SYNOPSIS (continued)

distant metastatic disease) beyond the intratumoral injection accessible tumor(s) that are not accessible for intratumoral injection are eligible ONLY if the patient has no other treatment option for the metastatic disease and treatment of local disease may provide the patient some benefit or palliation.

6. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
7. In the judgment of the Investigator, the patient has recovered sufficiently from any previous significant therapy side effects or toxicities prior to Ad/PNP administration.
8. Absolute neutrophil count [ANC] ≥ 1,500 cells/µl; hemoglobin ≥ 9 g/dl, platelets ≥ 100,000/µl.
9. Serum creatinine ≤ 1.5 mg/dl, or calculated creatinine clearance ≥ 60 ml/min.
10. Bilirubin ≤ upper limit normal [ULN], alanine aminotransferase [ALT] ≤ 1.5 x ULN and/or aspartate aminotransferase [AST] ≤ 1.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN.
11. Prothrombin time (PT)/international normalized ratio (INR) ≤ 1.5 x ULN.
12. Activated partial thromboplastin (aPTT) time ≤ 1.5 x ULN.
13. Female patients must have a negative urine or serum pregnancy at screening (pregnancy test is not required for patients with bilateral oophorectomy and/or hysterectomy or for those patients who are > 1 year postmenopausal).
14. All patients of reproductive potential must agree to use a medically acceptable form of contraception (e.g., hormonal birth control, double-barrier method) or abstinence.

Exclusion Criteria

1. Prior history or current diagnosis of leukemia.
2. Have received any gene therapy products or oncolytic viral therapy.
3. Receiving allopurinol.
4. Received an investigational drug within 30 days prior to first injection of Ad/PNP.
5. Received radiation treatment < 4 weeks prior to first injection of Ad/PNP and does not have any RECIST 1.1 evaluable lesions that are outside the radiation field. (If the patient has RECIST 1.1 evaluable lesions outside the radiation field then they can be included.)
6. Received chemotherapy (systemic anticancer treatment) < 4 weeks prior to first injection of Ad/PNP and has not recovered from all the related side effects. (If the patient has recovered from all related side effects or has reached a new baseline, then they may begin receiving treatment at **sooner** than 4 weeks).
7. Have significant baseline neuropathy (> Grade 2 based on Common Terminology Criteria for Adverse events [CTCAE] v5.0).
8. Uncontrolled intercurrent disease (e.g., diabetes, hypertension, thyroid disease, active infection).
9. Had within 6 months prior to enrollment: myocardial infarction (MI), cerebral vascular accident (CVA), uncontrolled congestive heart failure (CHF), significant liver disease, unstable angina.
10. Fever (temperature > 38.1°C orally).

PROTOCOL SYNOPSIS (continued)

11. Receiving chronic systemic corticosteroids (> 3 weeks) or any chronic immunosuppressive medications within 14 days prior to first injection of Ad/PNP. Subjects receiving short courses of corticosteroids are considered eligible for the study.
12. Receiving anticoagulants other than those to maintain patency of venous lines.
13. Women who are pregnant or breast feeding
14. Known history of human immunodeficiency virus (HIV) infection. No requirement for testing.

Study Drug and Administration

- 2×10^{11} viral particle (VP) x 3 over 2 days per cycle (total up to: 3×10^{12} Ad/PNP over 5 cycles) intratumorally, followed by:
- 25 mg/m^2 F-araAMP daily x 3 days (total: 75 mg/m^2 per cycle) intravenously, over approximately 30 minutes

Endpoints

The primary endpoint is safety with repeat cycles of treatment. Safety measures include adverse events (AE) and laboratory parameters.

Anti-tumor response will also be assessed for injected tumors and overall as determined by RECIST v.1.1. Efficacy assessments include:

- Objective response rate (ORR), defined as the percentage of patients with a best overall response (BOR) of a complete response (CR) or a partial response (PR). BOR is the best response achieved during the 5 cycles of treatment, for injected tumors and overall as determined by RECIST v.1.1.
- Durable response rate defined as a BOR of CR or PR 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 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 progression or death for any cause, whichever occurs first.
- Progression free survival (PFS) defined as time from first intratumoral injection to date of progression or death for any cause, whichever occurs first.
- Duration of response (DOR) defined as time from first documentation of CR or PR for injected tumors and overall as determined by RECIST v.1.1 until disease progression or death for any cause, whichever occurs first

RECIST as applied here will be version 1.1. Efficacy will be assessed in the population of subjects who receive three intratumoral administrations of Ad/PNP and any infusion of F-araAMP.

PROTOCOL SYNOPSIS (continued)

Statistical Methods

The study is a Phase 1/2 safety study; no formal hypotheses or sample size estimates will be generated. The study will enroll 10 to 20 subjects to achieve 10 subjects evaluable for efficacy; this number of subjects is sufficient to assess preliminary safety and activity to guide design of subsequent clinical studies.

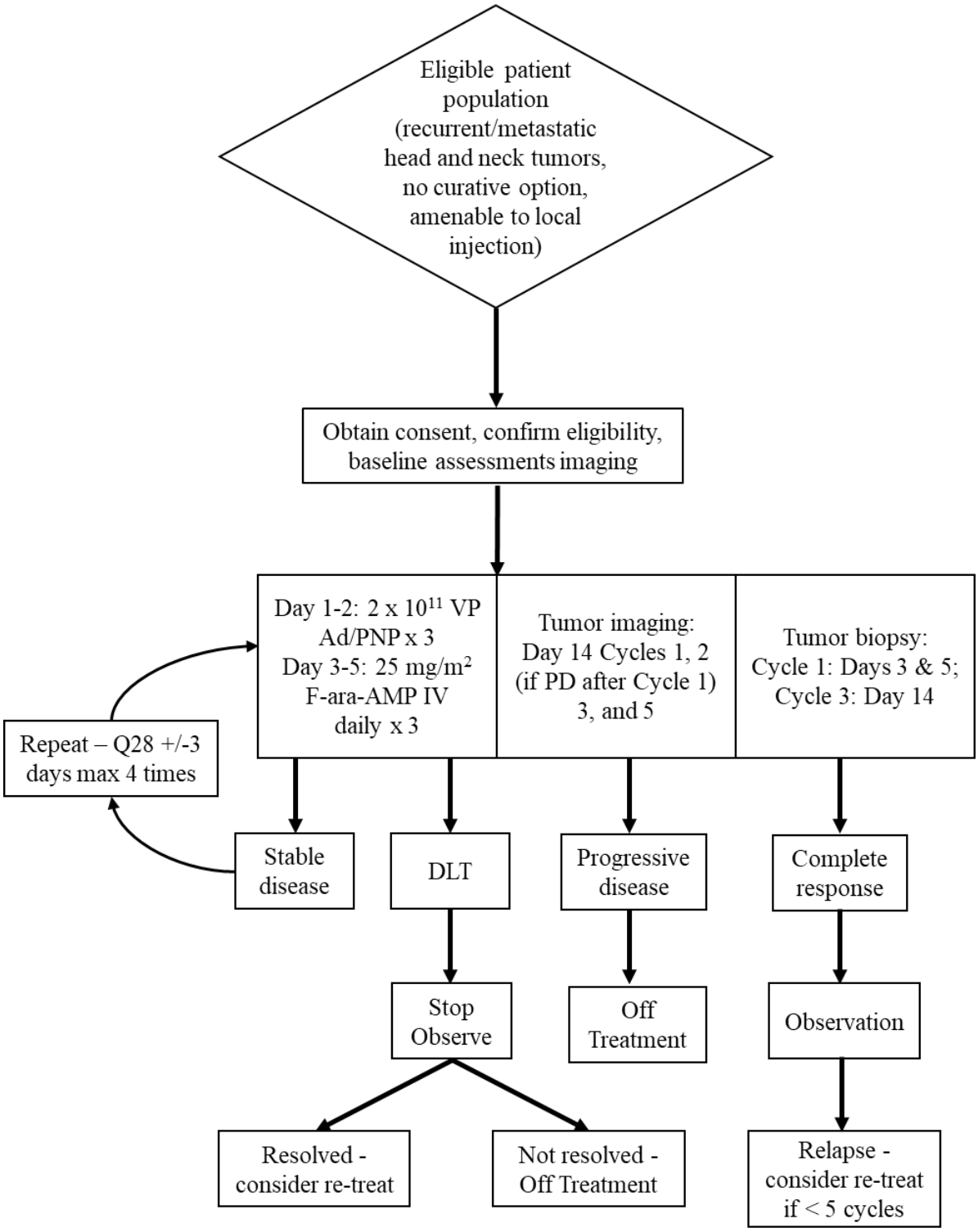
A total of 10 to 20 subjects in the safety population provides sufficient precision to rule out a treatment-related serious adverse event (SAE) rate of 38.5% or more using a one-sided 80% upper confidence limit. With 10 subjects evaluable for efficacy, there is 83% power to reject a null hypothesis ORR 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%).

Descriptive statistics (number and percentage of subjects) will be used to summarize BOR, ORR, and durable response rate. 95% Clopper-Pearson confidence intervals will also be provided. OS, PFS, DOR, and TTR will be analyzed based on Kaplan-Meier methods; Kaplan-Meier curves will be plotted over time. The number and percentage of subjects identified to have had an event and those who were censored will be displayed. The median time to event and its corresponding 95% CI will also be produced. A listing of response for subjects will be provided.

Duration of Study Participation

Each subject will participate for approximately 180 days.

SCHEMA



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

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin
AST	Aspartate aminotransferase
BOR	Best overall response
BUN	Blood urea nitrogen
CBC	Complete blood count
CBER	Center for Biologics Evaluation and Research (of the FDA)
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CLL	Chronic lymphocytic leukemia
Cr	Creatinine
CR	Complete response
CRF	Case report form
CRT	Chemoradiation treatment
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebral vascular accident
CXR	Chest X-ray
dL	Decaliter
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
F-Ade	Fluoroadenine
F-araA	Fludarabine
F-araAMP	Fludarabine phosphate
(F-) ATP	(2-F-) adenosine triphosphate
5-FU	5-fluorouracil
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GCP	Good clinical practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HPLC	High performance liquid chromatography
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous(ly)
kg	Kilogram
LC/MS	Liquid chromatography/mass spectrometry
LD	Longest diameter
mg	Milligram
MI	Myocardial infarction
mL	Milliliter
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NOAEL	No-observable-adverse effect-level

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS (continued)

OBA/NIH	Office of Biotechnology Activities/National Institutes of Health
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
R/M	Recurrent and/or metastatic
RNA	Ribonucleic acid
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SMC	Safety Monitoring Committee
SMX	Sulfamethoxazole
TEAE	Treatment-emergent adverse event
TMP	Trimethoprim
TTR	Time to response
ULN	Upper limit of normal
VP	Viral particle
µl	Microliter

1. OBJECTIVES

1.1 Primary Objective

The primary objective of the study is to evaluate the safety of repeat administration of a dose level of Ad/PNP-F-araAMP that demonstrated anti-tumor activity in patients with advanced head and neck cancer in the completed Phase 1 study.

1.2 Secondary Objectives

The secondary objective is to evaluate the anti-tumor activity of repeat administration of Ad/PNP-F-araAMP.

2. BACKGROUND

2.1 Advanced Head and Neck Cancer

More than half of patients with head and neck squamous cell carcinoma (HNSCC) have locoregionally advanced cancer and approximately 10% have metastatic disease at the time of their initial diagnosis. Patients with resectable disease who receive adjuvant chemoradiation treatment (CRT) following surgery have a 5-year recurrence rate of 20%. Although some patients with recurrent disease can be salvaged with surgery or radiation therapy, the majority are incurable and are treated palliatively with systemic therapy. Patients with recurrent and/or metastatic (R/M) HNSCC receiving first- line chemotherapy for recurrent disease have a median overall survival (OS) of ~7 months. The prognosis for patients with R/M HNSCC when first-line chemotherapy fails for recurrent disease is dismal, with median OS of < 6 months [1].

The most common non-targeted, first-line treatment approach for R/M HNSCC in patients who are not candidates for surgery or radiation treatment is a platinum-containing agent (cisplatin, carboplatin) combined with either 5-fluorouracil (5-FU) or taxane (paclitaxel, docetaxel). Response rates and OS in HNSCC following platinum-based dual agent chemotherapy are low, i.e., response rates are about 20-30% and median OS between 6.5 and 8.0 months, across several studies [2]. Addition of cetuximab improves response marginally; in a Phase 3 study of R/M HNSCC patients receiving platinum-based chemotherapy and 5-FU, the median OS was prolonged from 7.4 months with chemotherapy alone to 10.1 months with addition of cetuximab. Median progression free survival (PFS) was also increased from 3.3 months to 5.6 months [3]. It should be noted that subjects in the study were in good general condition and had good organ function. However, not all patients are able to tolerate the intensive triple-drug chemotherapy regimen and are offered alternative therapies, e.g., dual therapy with platinum + taxane followed by monotherapy with cetuximab [4].

There are limited treatment options for patients with R/M HNSCC whose tumor fails to respond or recurs following first-line salvage treatment. Often, treatment of these patients is limited to therapy with non-cross-resistant agents such as cetuximab, methotrexate, nivolumab, or a taxane with an overall response rate reported to be less than 20%. Treatment options are further limited by poor performance status and patient tolerance. Therefore, patients with recurrent HNSCC for whom platinum-based treatments and cetuximab treatments fail represent a population in need of novel therapeutic approaches.

2.2 Description of Ad/PNP-F-araAMP

The study drug, Ad/PNP-F-araAMP consists of a non-replicating adenoviral vector expressing the *Escherichia. coli* purine nucleoside phosphorylase (PNP) injected intratumorally followed by intravenous (IV) administration of F-araAMP. This combination generates fluoroadenine (F-Ade) within the tumor resulting in focal chemotherapeutic activity.

F-araAMP is an agent that is rapidly cleaved by plasma phosphatases to fludarabine, which is the primary circulating form of the drug and has activity against certain hematological malignancies, but not against solid tumors such as HNSCC. F-araA is an adenosine analog and substrate for *E. coli* PNP, which cleaves the glycosidic bond of F-araA to generate F-Ade. The F-Ade metabolite has shown pronounced activity against human tumor xenografts in mice.

F-Ade is converted to 2-F-adenosine triphosphate (F-ATP), which interferes with enzymatic reactions involving ATP and rapidly results in cell death. F-Ade has been shown to inhibit RNA and protein synthesis, two functions important to cellular metabolism regardless of the proliferative state of the cell (dividing versus quiescent). In contrast to toxins produced by first generation suicide gene therapy strategies such as ganciclovir monophosphate or 5-FU, F-Ade impairs one or more enzymes unrelated to DNA synthesis and kills tumor cells that are not actively proliferating. Many refractory tumors are refractory precisely because they have a very low growth fraction, i.e., a relatively small percentage of tumor cells dividing at any particular point in time. In nonclinical studies, significant *in vivo* anti-tumor activity has been demonstrated by F-Ade generation from F-araAMP in tumors in which 2.5 to 10% of cells express the *E. coli* PNP gene. In addition, anti-tumor effect was seen in patients with advanced solid tumors (melanoma and head and neck cancer) in the higher dose cohorts in a Phase 1 study.

2.3 Tumor Response with Ad/PNP-F-araAMP in Phase 1 Study

The safety and efficacy of Ad/PNP-F-araAMP has been evaluated in a Phase 1 study, PNP-001. Four escalating dose levels were evaluated in 10 subjects with head and neck cancer and 2 subjects with melanoma; clinical activity was observed at the highest dose levels following 3 IT injections of Ad/PNP over 2 days and IV F-araAMP phosphate over 3 days [5]. The overall response rate (complete response [CR] + partial response [PR]) was 66.7% in the 2 highest dose cohorts, Cohorts 3 and 4, versus 33.3% in Cohort 1, and 0% in Cohort 2; these results suggest a dose response effect. The duration of response (DOR) in the injected tumor was limited, with 4 of 5 responding

tumors having disease progression of the injected lesion prior to last follow-up on Day 56, suggesting that repeat administration should be evaluated.

Ad/PNP + F-araAMP was well tolerated. No subject experienced a dose-limiting toxicity (DLT) and none of the subjects discontinued study treatment. There was no evidence for an increased incidence of treatment-emergent adverse events (TEAEs), treatment-related adverse events (AEs), serious adverse events (SAEs), or Grade 3 or 4 TEAEs across dose cohorts. The most frequently reported TEAEs were those associated with the intratumoral injection site, primarily injection site pain (91.7%). The incidence of these events did not increase with dose, and most were mild or moderate in intensity. However, the single subject who experienced the most significant injection site pain (Grade 3, requiring subsequent pretreatment with local anesthetic) was in Cohort 4. Pain with subsequent Ad/PNP injection in this subject was managed with local lidocaine pre-injection and did not lead to discontinuation of study treatment.

Overall, the activity and safety profile of Ad/PNP seen in the Phase 1 study supports further clinical evaluation of repeat administration of Ad/PNP (intratumorally) and F-araAMP phosphate infusion for patients with recurrent cancer of the head and neck region.

2.4 Purpose of the Study

Based upon the tumor response seen with a single administration of the two highest dose levels of Ad/PNP-F-araAMP in the Phase 1 study, GeoVax plans to investigate the safety and assess anti-tumor activity of repeat cycles of injection of Ad/PNP + F-araAMP in patients with advanced head and neck cancer. The 2×10^{11} viral particle (VP)/injection was selected since there was no difference in tumor activity between the 10^{11} and 10^{12} VP dose levels in Phase 1 testing, and since the total cumulative dose (3.0×10^{12} VP) will be equivalent to the dose of Ad/PNP that was well tolerated in Cohort 4 of the Phase 1 trial (3×10^{12} VP). Subjects in the study will have Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 measurable recurrent cancer of the head and neck region which is amenable to local injection for which there is no curative treatment option. This study population was selected since results from this Phase 1/2 trial are intended to support the safety of repeat dosing in further clinical investigations.

2.5 Study Design

The trial is designed as a single-arm study to evaluate the safety of repeat cycles of Ad/PNP and F-araAMP in patients with recurrent cancer of the head and neck region with tumor(s) accessible for injection.

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. Subjects 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 patient death.

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.

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

The Safety Monitoring Committee (SMC) will review accumulating safety data (i.e., AE reporting, reactions to study drug, deaths, etc.) 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.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Subjects must fulfill the following eligibility criteria.

3.1 Inclusion Criteria

1. Provided Informed Consent
2. Age ≥ 18 years
3. Patients with histologically or cytologically confirmed diagnosis recurrent cancer of the head and neck region for whom there is no curative treatment option. For the purposes of trial eligibility, cancers of the head and neck region shall include, in addition to HNSCC, cutaneous squamous cell primary sites and squamous cell carcinoma of unknown primary presenting with neck lymph nodal disease, as well as nasopharyngeal carcinoma, and salivary gland tumors.
4. All standard or approved treatment options that would provide substantive palliation must have failed, been exhausted, or patient not eligible for them (for example neuropathy, nephropathy, or hearing loss precluding the use of cisplatin)
5. Tumor mass (primary tumor and/or lymphadenopathy) measurable by RECIST 1.1 and technically suitable for intratumoral injections (otolaryngologist will determine feasibility). Patients with nodal disease (or metastatic disease) that is needle accessible are eligible. Patients with additional tumors (including distant metastatic disease) beyond the intratumoral injection accessible tumor(s) that are not accessible for intratumoral injection are eligible ONLY if the patient has no other treatment option for the metastatic disease and treatment of local disease may provide the patient some benefit or palliation.
6. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
7. In the judgment of the investigator, the patient has recovered sufficiently from any previous significant therapy side effects or toxicities prior to Ad/PNP administration.
8. Absolute neutrophil count [ANC] ≥ 1,500 cells/µl; hemoglobin ≥ 9 g/dl, platelets ≥100,000/µl.
9. Serum creatinine ≤ 1.5 mg/dl, or calculated creatinine clearance ≥ 60 ml/min.

10. Bilirubin ≤ upper limit normal [ULN], alanine aminotransferase [ALT] ≤ 1.5 x ULN and/or aspartate aminotransferase [AST] ≤ 1.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN.

11. Prothrombin time (PT)/international normalized ratio (INR) ≤ 1.5 x ULN.

12. Activated partial thromboplastin (aPTT) time ≤ 1.5 x ULN.

13. Female patients must have a negative urine or serum pregnancy at screening (pregnancy test is not required for patients with bilateral oophorectomy and/or hysterectomy or for those patients who are > 1 year postmenopausal).

14. All patients of reproductive potential must agree to use a medically acceptable form of contraception (e.g., hormonal birth control, double-barrier method) or abstinence.

3.2 Exclusion Criteria

1. Prior history or current diagnosis of leukemia.

2. Have received any gene therapy products or oncolytic viral therapy.

3. Receiving allopurinol.

4. Received an investigational drug within 30 days prior to first injection of Ad/PNP.

5. Received radiation treatment < 4 weeks prior to first injection of Ad/PNP and does not have any RECIST 1.1 evaluable lesions that are outside the radiation field. (If the patient has RECIST 1.1 evaluable lesions outside the radiation field then they can be included.)

6. Received chemotherapy (systemic anticancer treatment) < 4 weeks prior to first injection of Ad/PNP and have not recovered from all the related side effects. (If the patient has recovered from all related side effects or has reached a new baseline, then they may begin receiving treatment at **sooner** than 4 weeks).

7. Have significant baseline neuropathy (> Grade 2 based on Common Terminology Criteria for Adverse Events [CTCAE] v5.0)

8. Uncontrolled intercurrent disease (e.g., diabetes, hypertension, thyroid disease, active infection)

9. Had within 6 months prior to enrollment: myocardial infarction (MI), cerebral vascular accident (CVA), uncontrolled congestive heart failure (CHF), significant liver disease, unstable angina.

10. Fever (temperature > 38.1°C orally).

11. Receiving chronic systemic corticosteroids (> 3 weeks) or any chronic immunosuppressive medications within 14 days prior to first injection of Ad/PNP. Subjects receiving short courses of corticosteroids are considered eligible for the study.

12. Receiving anticoagulants other than those to maintain patency of venous lines.

13. Women who are pregnant or breast feeding.

14. History of human immunodeficiency virus (HIV) infection. No requirement for testing.

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the Institutional Review Board (IRB) approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy or certified copy of the consent document must be retained in the medical record and research file. This signed consent form present in the medical record shall be considered documentation that the GCP informed consent process has been completed.

3.4 Subject Withdrawal

While subjects are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Subjects receiving chemotherapy (other than F-araAMP) or radiation therapy will be removed from the study. Participation is voluntary, and declining to participate will involve no penalty, or loss of benefits to which the participant is otherwise entitled. The subject will be encouraged to maintain contact with the investigator and report any serious AEs experienced for the entire study period. Individuals who withdraw early from treatment will be asked to complete Day 56 (of the last treatment cycle) study visit evaluations.

Subjects who withdraw or complete the study are not eligible to re-enter or be treated in the study again. Subjects who drop out following administration of study agent will not be replaced.

Screen failures will include participants who consented and entered into the screening process appropriately, but subsequently did not meet the entry criteria and did not receive study drug. The investigator will maintain a screening log that documents the subject number, subject initials, and reason(s) for screen failure. No data other than reason for screen failure and basic screening data will be collected on Screen Failures. Participants who fail screening will not be followed for safety or activity of study drug, and no other study procedures will be performed. Screen failures will be replaced.

4. TREATMENT PLAN

4.1 Dose and Dose Rationale

The dose selected for evaluation with repeat administration has been chosen based upon tumor response and safety of the vector (Ad/PNP) and prodrug (F-araAMP) seen with single administration of this dose level in the completed Phase 1 study. With each cycle the subject will receive a total dose of 6×10^{11} VP Ad/PNP followed by a total dose of 75 mg/m^2 F-araAMP.

4.2 Administration of Ad/PNP-F-araAMP per Cycle

With each cycle, subjects will receive 3 intratumoral administrations of 2.0×10^{11} VP Ad/PNP over 2 days followed by 3 daily infusions of 25 mg/m^2 F-araAMP in the outpatient clinic or in-hospital at the discretion of the investigator. The physician or a designee trained to do the injections by the Principal Investigator (PI) will administer intratumoral Ad/PNP during each cycle. The outpatient unit is staffed with medical personnel to treat emergency and non-emergency medical events.

Ad/PNP will be given via direct intratumoral injection three times over 2 days. If needed, the investigator may utilize radiologic guidance (e.g., ultrasound) to assist in the injection of Ad/PNP. Two intratumoral administrations will be given on Day 1 and one intratumoral administration on Day 2. The first administration will occur on the morning of Day 1 and the subject monitored closely for 1 hour for acute injection-related events. Approximately 3-6 hours after the first administration, the subject will receive the second intratumoral administration on Day 1. The third intratumoral administration will be given on the morning of Day 2.

Vials of Ad/PNP will be thawed and prepared for injection by the investigational pharmacy according to the Preparation of Investigational Product Instructions. In the Phase 1 study, Ad/PNP was administered intratumorally in a 0.5 ml volume (~2×10^{11} VP/ml or ~2×10^{12} VP/ml); both dose levels showed activity and were well tolerated. In the Phase 1/2 study, 2×10^{11} VP will be administered in volumes up to 5 ml (4×10^{10} VP/ml) so that vector can be dispersed more effectively throughout needle-assessable tumor tissue.

The volume of vector injected into each tumor will be according to tumor volume. All measurable tumors that are accessible for intratumoral injection will be identified and treated for each enrolled subject

Subjects will receive a total of 2 x 10^{11} VP Ad/PNP per injection (3 injections per cycle) distributed across the injected tumors and volume of vector will vary dependent upon estimated tumor volume using the tumor's two dimensions measured by calipers as described in the Operating Procedure - Injection of Investigational Product into the Tumors of Human Subjects. For example, for a subject with 3 tumors of 1.5 ml, 3 ml, and 5 ml size each, 2 x10^{11} VP Ad/PNP will be suspended in 3.5 mL and tumors injected with 0.5 mL, 1.0 mL, and 2.0 mL, respectively. If the tumor mass is very large or the total volume for all discreet tumors exceeds 16 ml, a portion of the tumor mass or certain discrete tumors will be selected by the physician and injected with 5 ml of Ad/PNP. The same tumors will be injected with each administration of 5 ml Ad/PNP.

Lesion Volume	**Injection Volume**
> 16 ml	5.0 mL
12 ml to 16 ml	4.0 mL
8 ml to 12 ml	3.0 mL
4 ml to 8 ml	2.0 mL
2 ml to 4 ml	1.0 mL
Less than 2 ml	0.5 ml

Using aseptic technique, the Ad/PNP solution will be injected percutaneously with injection at multiple sites within the tumor to achieve thorough infiltration. A subcutaneous injection of local anesthetic may be used, if desired.

Approximately 24 to 36 hours following the third administration of Ad/PNP into the tumor (Day 3), subjects will receive 25 mg/m^2 F-araAMP daily for 3 days. F-araAMP will be prepared and administered intravenously over approximately 30 minutes per the package insert. Subjects who do not receive all three administrations of Ad/PNP will not receive F-araAMP; all subjects will be assessed for safety at the scheduled study visits. Subjects who do not receive all three full doses of Ad/PNP may be eligible to receive subsequent doses of F-araAMP at the discretion of the investigator.

In this study, each 5-day course of treatment will commence every 28 days +/- 3 days and subjects will receive up to 5 cycles of Ad/PNP-F-araAMP. The 28-day interval complies with the recommended dosing schedule between courses of F-araAMP used to treat hematological malignancies. Treatment will be discontinued prior to 5 cycles in the event of injected tumor progression (and/or the investigator determines the patient may no longer stand to benefit from further

treatment) or if there is no tumor present for injection. In the event that treatment is discontinued, the subject should complete the Day 28 and Day 56 visits of the last treatment cycle.

Subjects will be monitored for clinical safety events and changes in laboratory parameters throughout the study period. Subjects who experience a CR before the next cycle will not receive treatment but will continue to be followed during the study period. Subjects whose tumors achieve a CR but then recur during the study period may resume treatment with Ad/PNP-F-araAMP up to the maximum allowed 5 total cycles.

No formal follow-up visits are planned following the end of the study period (Day 56 of the last treatment cycle). However, the Investigational New Drug (IND) Sponsor may request follow-up information from the investigator on tumor status in subjects who have stable disease (SD), PR, or CR at completion of their study participation.

4.3 Dose Modification

Based on monitoring of efficacy signal from subjects completing treatment, if no anti-tumor activity and no DLTs are observed, GeoVax may increase the dose of vector administered 5-fold from to 2×10^{11} VP/dose to 1×10^{12} VP/dose, which was the high dose of vector used in the Phase 1 clinical trial. DLTs will be determined based on the incidence and intensity of AEs and SAEs assessed as being at least possibly related to Ad/PNP-F-araAMP and occurring up to 28 days after initiation of dosing on Cycle 1 Day 0. Formal approval from the Food and Drug Administration (FDA), IRB, and other regulatory offices as needed will be obtained prior to initiating an increase of vector dose. No serious toxicities were detected with this dose of vector (1×10^{12} VP/dose) in the earlier Phase 1 trial.

The total dose of F-araAMP per cycle is lower than that recommended to treat patients with hematological malignancies. Subjects who experience greater than Grade 2 neurotoxicity should be discontinued from treatment and followed for safety. The investigator may decrease the dose of F-araAMP to 15 mg/m^2 or delay administration based on evidence of high grade (CTCAE v5.0 Grade 3 or higher) hematologic or nonhematologic toxicity not recovered to baseline by day 1 of each subsequent cycle, with the exception of isolated lymphopenia, which will not require a dose reduction. Subjects who require further reduction in F-araAMP in the judgment of the investigator, based upon recurrent high grade AEs not resolved by day 1 of the subsequent cycle should be discontinued from treatment and followed for safety. Growth factor support is not to be used prophylactically in this study.

4.4 Expected Adverse Events

Local injection site reactions have been reported in clinical studies evaluating other non-replicating adenoviral vectors injected intratumorally. The Phase 1 study evaluated two dose levels of Ad/PNP (10^{11} VP/dose in Cohorts 1-3 and approximately 10^{12} VP/dose in Cohort 4) and 3 dose levels of F-araAMP (5, 15, and 25 mg/m^2 in Cohorts 1, 2, and 3, respectively and 25 mg/m^2 in Cohort 4). Among the 12 subjects in the study, the most frequently reported TEAEs were injection site pain (11 subjects, 91.7%) and fatigue (8 subjects, 66.7%). Injection site pain was reported in all but 1 subject receiving 10^{11} VP/dose + 15 mg/m^2 F-araAMP. The event was assessed as treatment-related in 10 subjects (83.3%); most reports were Grade 1 or 2 in severity. All Grade ≥3 events in our Phase I study were assessed as unrelated to study treatment, with the exception of 1 report of injection site pain as noted in this section. One subject receiving 10^{12} VP/dose experienced severe (Grade 3) injection site pain on Day 1 that was assessed as definitely related to Ad/PNP injection. The subject went on to complete the study receiving lidocaine injection prior to injection of Ad/PNP. Other injection site reactions included injection site discharge (4 subjects receiving either 10^{11} or 10^{12} VP/dose, 33.3%); injection site erythema, hemorrhage, and pruritus (2 subjects each receiving 10^{11} VP/dose, 16.7%), and injection site paresthesia (1 subject receiving 10^{12} VP/dose, 8.3%). All of these events were reported in only 1 subject within a cohort and all were assessed as Grade 1 or 2 in severity; most were reported as treatment-related.

F-araAMP is a purine analog used to treat patients with chronic lymphocytic leukemia (CLL). Besides being an anti-tumor agent against lymphoid malignancies, F-araAMP has immunosuppressant activity and is incorporated in preparatory regimens for allogeneic bone marrow transplantation.

When administered in cycles of the standard 25 mg/m^2 five-day course, F-araAMP induces myelosuppression (neutropenia, thrombocytopenia and anemia). Other commonly reported AEs include fever and chills, infection (including opportunistic infections), nausea and vomiting, malaise, fatigue, anorexia, and weakness. Life-threatening autoimmune hemolytic anemia has been reported in patients receiving F-araAMP. Objective weakness, agitation, confusion, visual disturbances, and coma have occurred in CLL patients treated with F-araAMP at the recommended dose. A high incidence of opportunistic infections, including *Pneumocystis jirovecii* pneumonia has been seen in CLL patients, especially those with a substantial history of steroid or alkylator use. Reactivations of latent viral infections such as VZV (herpes zoster), Epstein-Barr virus and JC virus (progressive multifocal leukoencephalopathy) have been reported in patients treated with F-araAMP. Additional information concerning drug related effects reported with F-araAMP are

described more fully in the package insert. It is unknown at this point whether any of these toxicities will be more or less pronounced when F-araAMP is given in conjunction with the Ad/PNP with repeat administration.

The toxicity attributable to intratumorally generated F-Ade with repeat injection is unknown. Based on results from a nonclinical study, systemic exposure to levels of F-Ade higher than expected in this study may cause myelosuppression and/or elevation in liver enzymes. Review of the safety and laboratory data from the Phase 1 clinical study showed that 2 of the 12 subjects experienced Grade ≥ 3 lymphopenia (neither were assessed as definitely related to study treatment) and no subject had elevation in liver enzymes. One of the two subjects with Grade ≥ 3 lymphopenia received 5 mg/m^2 F-araAMP and the other received 25 mg/m^2 F-araAMP daily for 3 days. Neither subject experienced a serious infection.

Two subjects experienced a serious infection. One subject developed a bacteremia related to a central intravenous line and another had a chronic wound over the tumor being injected. There were no reports of opportunistic infections.

4.4.1 Infection Prophylaxis

Although the dose regimen of F-araAMP is shorter than that used to treat hematological malignancy, there remains a potential risk for *Pneumocystis jiroveci* (PJP) infection with repeat cycles. Consequently, all subjects will receive prophylaxis antibiotic treatment, e.g., one double-strength trimethoprim (TMP)/sulfamethoxazole (SMX) (i.e., 160 TMP/800 SMX) three times a week. Prophylaxis will start prior to Day 1 of the first cycle and continue for 8 weeks following the last infusion of F-araAMP. Alternative acceptable prophylactic treatment may be used and should be recorded.

Additional prophylactic antibiotic therapy may be initiated in subjects with clinically relevant reduction in white blood cell counts per the investigator's assessment.

4.5 Stopping Rules

All study agent administration will stop if any of the following events occur during the study:

- Death attributed to study drug;
- Serious systemic anaphylactic tumor injection reaction;

- Serious rare reactions to F-araAMP, such as blindness or coma.

The FDA, Office of Biotechnology Activities/National Institutes of Health (OBA/NIH), IRB and SMC will be notified immediately if one of these AEs occurs and a comprehensive review of the safety data will be conducted prior to resumption of dosing. In addition, findings from the review will be relayed to and discussed between the SMC and Sponsor (GeoVax). Should the SMC and GeoVax agree to stop the study, GeoVax will inform all investigational sites and the appropriate regulatory bodies of the decision to stop the study at all sites.

4.6 Drug Accountability

The investigator will be responsible for dispensing and accounting of Ad/PNP provided by the IND Sponsor. The investigator will also be responsible for documentation of lot numbers, dose and administration of Ad/PNP-F-araAMP given during the study. Under no circumstances will the investigator supply vector to other investigators, allow vector to be used other than directed by this protocol, or destroy or dispose of vector in any other manner without prior authorization from the IND Sponsor.

Any residual vector must be returned to the investigational pharmacy for disposition. The site's Investigational Pharmacy will dispose of all unopened or partially used vials of Ad/PNP at the end of the study. Please see the Pharmacy Manual for full and current details.

4.7 Concomitant Medications

All medications taken at the time of study entry will be recorded. Any changes in concomitant medication, including additions, discontinuations, and dose changes, occurring during study participation will be recorded.

The following concomitant treatments are permitted during the study:

- All supportive measures (including antiemetics, red blood cell transfusions, antibiotics) consistent with optimal patient care will be given throughout the study and should be documented in the case report form (CRF).

- Colony-stimulating factors and erythropoietin may be used during the study if clinically indicated according to the American Society Clinical Oncology guidelines. However,

neither granulocyte colony-stimulating factor (G-CSF) nor granulocyte-macrophage colony-stimulating factor (GM-CSF) will be used prophylactically in this study.

The following concomitant treatments are not permitted during the study:

- Allopurinol
- No systemic anticancer agent other than the study drug
- Palliative radiation therapy (if a subject has need for palliative radiation, they will be removed from the study)
- Subjects that develop symptomatic pleural effusion/pericardial effusion will be taken off study, and treated with standard therapies
- No other investigational therapies or devices will be allowed during study participation.

4.8 Criteria for Removal from Study

Treatment will be stopped and patients will be removed from study due to unacceptable AEs, withdrawal of consent, or non-compliance.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Description of Study Drug

Study drug for administration to the subjects consists of the vector Ad/PNP for intratumoral administration and F-araAMP for intravenous administration.

F-araAMP (fludarabine phosphate) is licensed as a treatment for hematological malignancies but lacks efficacy to treat solid tumors. In the nonclinical studies, administration of the Ad/PNP vector intratumorally alone had little or minimal activity on tumor size. F-araAMP is being administered as a prodrug where subsequent generation of F-Ade within tumor cells transfected with the vector is expected to have local anti-tumor effect on the solid tumor. Commercial F-araAMP (fludarabine phosphate) available from the site's formulary will be used in this study.

The vector, Ad/PNP, is manufactured by the biologicals manufacturing division of Sigma-Aldrich, SAFC Pharma (Carlsbad, CA).

Ad/PNP will be supplied as a liquid formulation in vials containing 2 x 10^{11} VP/100 µl in 20 mM Tris (pH 8.0), 25 mM NaCl, 2.5% Glycerol and should be stored at less than -60^{o} C. Dilutions of the vector in sterile normal saline USP will be made immediately prior to use. Following dilution, the investigational pharmacy will send the vector to the clinic on ice for administration. Vector should be administered as soon as possible after dilution and must be used within 6 hours of thaw. The vector will be administered percutaneously via injection into the tumor mass. A subcutaneous injection of local anesthetic may be used, if desired.

5.2 Availability

Ad/PNP for this project will be furnished by GeoVax, Inc. (Smyrna, GA). Commercially sourced F-araAMP will be used for this study.

5.3 Agent Ordering

Orders for Ad/PNP will be placed with GeoVax by the study team after approval to proceed has been granted by the IRB and Investigational Pharmacy. Ad/PNP will be transported on dry ice by overnight courier to the site's investigational pharmacy.

5.4 Agent Accountability

Each investigator will be responsible for dispensing and accounting of Ad/PNP provided by the IND Sponsor. The investigator will also be responsible for documentation of lot numbers, dose and administration of Ad/PNP-F-araAMP given during the study. Under no circumstances will the investigator supply vector to other investigators, allow vector to be used other than directed by this protocol, or destroy or dispose of vector in any other manner without prior authorization from the IND Sponsor.

Any residual vector must be returned to the investigational pharmacy for disposition. The site's Investigational Pharmacy will dispose of all unopened or partially used vials of Ad/PNP at the end of the study. Please see the Pharmacy Manual for full and current details.

6. DOSE MODIFICATIONS

See Section 4.3 for dose modifications of Ad/PNP and F-araAMP.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Adverse Event

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.

A 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.

Disease progression is not an AE (non-serious or serious), although signs and symptoms thereof may be reportable as AEs.

7.2 Serious Adverse Event

A SAE (experience) is defined (21CFR312.32) 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 subject 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.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-

threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the above definition. These should be considered serious.

Pregnancy is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered an SAE and must be reported to the Sponsor within 24 hours of the site becoming aware of the event. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

Any pregnancy which occurs during this clinical trial must be treated as a SAE with regard to the reporting timeline. Any pregnancy must be followed until conclusion of the pregnancy (delivery or termination). Administration of study drug will be discontinued in a subject who becomes pregnant. The subject will be asked to complete safety evaluations through Study Day 56 of the subject's last cycle (no follow-up imaging studies for the purposes of this study will be obtained). If a male subject reports a pregnancy of his spouse or significant other within Day 56 of last study treatment, every effort will be made to obtain data regarding the outcome of this pregnancy.

Pregnancies must be reported using the paper Pregnancy Form. All pregnancies must be followed up until delivery or termination of pregnancy and until final outcome, using the paper Pregnancy Follow-Up Form. Reporting of both the initial pregnancy and the outcome must be done via e-mail to GeoVax_PV@cato-sms.com.

7.3 Assessment of Causality

The relatedness of an AE to the study drug is the best estimate of the investigator at the time of the reporting of the causal relationship between the study drug and an AE.

The following study drug relationships will be used for this clinical study:

Unrelated: There is no temporal relationship between the event and the administration of the study drug, and/or the event is clearly due to the subject's medical condition, other therapies, or accident.

Possibly Related: There is some temporal relationship between the event and the administration of the study drug and the event is unlikely to be explained by the participant's medical condition or other therapies.

Probably Related: The temporal relationship between the event and the administration of the study drug is compelling, and the participant's medical condition or other therapies cannot explain the event.

Definitely Related: The temporal relationship between the event and the administration of the study drug is compelling, the participant's medical condition or other therapies cannot explain the event and the event follows a known or suspected response pattern to the medication.

The categories of Definitely, Probably, and Possibly are considered study drug related.

7.4 Severity of the Adverse Event

Adverse events will be graded per National Cancer Institute (NCI) CTCAE v5) (http://evs.nci.nih.gov/ftp1/CTCAE/about.html).

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Life –Threatening (Grade 4)
- Fatal (Grade 5)

7.5 Safety Monitoring and Reporting

7.5.1 Monitoring of Adverse Events

All subjects will be monitored closely for AEs during study participation. Subjects who discontinue prematurely from the study will be encouraged to return for assessment of safety and their physician contacted to obtain follow-up safety information.

The investigator will monitor subjects for the occurrence of AEs throughout their participation in the study and record all observed AEs in the CRF.

Adverse events spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures are to be recorded in the study specific worksheets. Any clinically relevant deterioration in laboratory assessments or other clinical findings, as assessed by the investigator, is considered an adverse event and must be recorded on the appropriate pages of the CRF. Whenever possible, symptoms should be grouped as single syndrome or diagnosis. The investigator should specify the date of onset, maximal intensity, corrective therapy given, outcome, and his/her assessment of causality (i.e., whether the adverse event was related to the study drug) (Section 7.3).

From signing of informed consent through initiation of study treatment, only SAEs considered related to study procedure(s) should be recorded. After initiation of study treatment (Day 1) through Day 56 of the subject's last treatment cycle, all adverse events regardless of seriousness or relationship to study drug should be recorded.

Serious adverse events considered related to prophylactic antibiotic treatment (and not suspected to be related to study treatment) are expected AEs. They should be collected but are not subject to expedited reporting.

Any AE that is not resolved by the end of the study and considered to be potentially related to study drug or was the cause for the subject's withdrawal will be followed as clinically indicated until its resolution, or if non-resolving, until considered stable.

7.5.2 Recording and Reporting Adverse Events and Serious Adverse Events

The investigator must provide the IND Sponsor and monitoring team appropriate information concerning any findings suggesting significant hazards, contraindications, side effects or precautions pertinent to the safety of the study drug. The investigator will instruct subjects prior to administration of study drug to report any physical changes or new symptoms that they notice during the course of the study.

Non-serious AEs and SAEs related only to prophylactic antibiotics will be reported annually to FDA and NIH Office of Science Policy via an Annual Report (by IND Holder GeoVax) and to IRB via Continuing Review (by clinical study team).

The PI must report all SAEs and deaths, whether or not considered related to study treatment, immediately (within 24 hours of knowledge of event) to GeoVax.

For Serious Adverse Events/Pregnancy, please send completed report form to GeoVax_PV@cato-sms.com or fax to 919-361-2536

In the event of a SAE, the investigator must report:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

The PI should report any follow-up information as it becomes available.

Adverse events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB within 10 working days of investigator determination event meets reporting requirements, or within 5 working days for deaths or life-threatening experiences.

Adverse events deemed serious and related to study drug or study procedures (regardless of expectedness) will be reported to any applicable oversite board at the site within 5 working days of knowledge of event.

Adverse events deemed serious, unexpected (i.e., not described in the protocol, Investigator's Brochure or informed consent documents) and related to study drug must be reported to GeoVax using the SAE Report Form within 24 hours of knowledge of event at contact information listed above. The Sponsor is responsible for reporting any event meeting IND Safety Reporting criteria to FDA. SAEs considered related to antibiotic treatment are considered expected.

7.5.3 Safety Monitoring Committee

The SMC will meet and review safety data (i.e., adverse events reporting, reactions to study drug, 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. The SMC will be comprised of, at a minimum, a Sponsor representative, medical monitor (SMC facilitator), and

investigative site designees from each participating site. Only the investigative site designees will be voting members of the SMC. SMC voting members will be experienced professionals in evaluating safety and efficacy data derived from oncology clinical trials. The medical monitor and Sponsor representative will be part of the SMC but will not be voting members. Observers without voting rights are also allowed to join the SMC meetings. All SMC recommendations will be documented and communicated to GeoVax and the investigators at each study site. Following their review, the SMC will recommend whether or not dosing may continue or the need for modifications to the protocol and/or safety monitoring.

In addition, an ad hoc SMC meeting can be planned on initiative from the Medical Monitor/Sponsor based on the regular surveillance of the safety data and/or upon request from an investigator. The SMC may recommend stopping the study at any time that an unacceptable type and/or frequency of AEs is observed.

8. CORRELATIVE/SPECIAL STUDIES

Special studies to assess safety and efficacy of Ad/PNP with F-araAMP are planned and will be conducted by collaborators at Emory University (with IRB approval at that institution) or outsourced to commercial organizations specializing in testing of this sort. These studies are described in Section 9.1 (Procedures Table) as well as Sections 9.2 and 9.3, and include: 1) blood samples for adenovirus, 2) urine for adenovirus, 3) blood samples for antibody against adenovirus, 4) F-Ade plasma level, and 5) tumor biopsy for studies of PNP activity, histochemistry, tumor growth fraction, and adenoviral distribution. Samples will be shipped to Emory or commercial site with the same strict attention to patient confidentiality described throughout the protocol. Please also see Section 10.

Methods regarding tumor biopsy and analysis, as well as serum F-Ade to be arranged by investigators at Emory or designated subcontractor are described below:

1) **Measurement of *E. coli* PNP activity.** Approximately 50 mg of tumor tissue will be obtained using a 3 mm dermal punch from the injected tumor site on day 3 just prior to treatment with F-araAMP. This timing coincides with robust transgene expression observed in our preclinical studies and will allow us to ascertain *E. coli* PNP activity at the beginning of F-araAMP treatment. Tissue samples will be immediately frozen and stored at -80°C. Crude extracts will be prepared and incubated with 50 mM potassium phosphate, 100 µM 6-methylpurine-2'-deoxyriboxide (MeP-dR, a standardized *E. coli* PNP substrate), and

100 mM HEPES buffer (pH 7.4) at a concentration of tumor lysate that results in a linear reaction over the incubation period. The formation of 6- methylpurine will be monitored using reverse phase high performance liquid chromatography (HPLC). Care will be taken to thoroughly homogenize samples in order to release PNP enzyme.

2) **Metabolism of F-araAMP.** An important measurement to evaluate effectiveness of vector delivery is to quantify active metabolites in tumor tissue following F-araAMP treatment, with the goal to determine levels of F-Ade produced from F-araAMP by E. coli PNP. F-Ade in tumor tissues is activated by purine metabolic enzymes to F-Ade - containing nucleotides (primarily F-ATP) and incorporated into RNA, which is responsible for cell killing action of F-Ade. For this measurement, tumor tissue will be obtained using a dermal punch from the tumor site one hour after the final F-araAMP treatment on Day 5. We have shown in mouse tumor xenografts that F-Ade metabolites are retained in tumor parenchyma for prolonged periods (t½ greater than 24 hours) and obtaining tumor samples one hour after the final injection of F-araAMP should allow for an assessment of F-Ade tumor levels attributable to cumulative administration of prodrug. Because cellular nucleotides rapidly degrade during extraction of tumor tissue, we plan to measure total F-Ade levels by treating the extract with RNase and phosphatases (in the presence of immucillin, a potent E. coli PNP inhibitor) to degrade all F-Ade nucleotides to 2-fluoro-adenosine (F-Ado). We will utilize an liquid chromatography/mass spectrometry (LC/MS) method to measure both F-Ade and F-Ado. Since tumor cells may also contain F-araA nucleotides, we will configure a parallel LC/MS method to measure F-araA. Please note that investigators in this project have access to LC/MS protocols specifically for analysis of nucleoside and related compounds, and over 20 years' experience with measurements of this type.

3) **Plasma levels of F-Ade.** It will be important to determine the extent to which F-Ade escapes into the general circulation, and we will monitor systemic release of the compound. Plasma samples will be obtained after F-araAMP injection on Days 3 and 5, and analyzed for F-Ade, F-Ado, and F-araA using LC/MS procedures familiar to our laboratories. In our Phase 1 study, no F-Ade was measurable in plasma with an LC/MS assay of sufficient sensitivity to detect F-Ade at levels approximately 100-fold below the no-observable-adverse effect-level (NOAEL) in rats given the compound daily for 7 days.

4) **Tumor growth fraction and effects on the stem cell compartment, and evidence for PNP protein expression**. Tumor punch biopsies obtained above will also be studied by histochemistry for markers of active cell cycling (e.g., Ki67) or the tumor stem cell

compartment (e.g., SOX2, Nanog, Oct-4, CD44+/CD24+). Comparisons will be made to original (pretreatment) tumor sections. We will also use the biopsy samples to evaluate levels of PNP expression and adenoviral localization by immunohistochemistry with antibodies to the transgene uniquely available in our laboratory. A portion of each biopsy (e.g., 10%) will be placed in RNA-later for analysis of the same antigens by RT- PCR.

9. STUDY CALENDAR

9.1 Study Procedures Table

Enrolled subjects will follow the schedule of evaluations provided below.

		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^{+}, CO2, 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 jiroveci* (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

9.2 Study Procedures

Subjects screened and enrolled will follow schedule of evaluations provided at the beginning of this protocol. The following evaluations will be performed:

9.2.1 Visit 1 (Day -30 to 0, Screening and Baseline Laboratory Values)

The following evaluations and tests will be performed: Preliminary Screening:

- Obtain written informed consent
- Medical history including current medication
- Assessment of performance status
- Physical examination
- Record vital signs

Complete screening if entry criteria are met on preliminary screening:

- Electrocardiogram (ECG)
- Chest X-ray if no chest CT. Chest radiograph within two weeks prior to screening may be used
- Blood samples for: Hematology, CD4/CD8 T-cell subsets, Chemistry, PT/aPTT
- Serum pregnancy test in women of childbearing potential
- Urine analysis
- Assessment of tumor with CT scan or MRI

For injected tumors palpable on physical examination, measurement with calipers or rulers, if possible, with photo documentation.

During each 28-Day Cycle of Ad/PNP-F-araAMP:

The following tests and evaluations scheduled on Visits 2 through 7 are to be done during each treatment cycle. Up to five treatment cycles are planned in the study. At each clinic visit, any change in concomitant medication or adverse events will be recorded.

Note that Day 28 of a cycle is Day 1 of the next repeat cycle. Tests and evaluations to be done on Day 1 of each cycle (i.e., Visit 2) should be conducted prior to study drug administration unless otherwise noted.

9.2.2 Visits 2 and 3 (Days 1 and 2 of Intratumoral Administration of Ad/PNP)

Subjects may receive intratumoral administrations in the clinic or hospital (in-patient) at the discretion of the investigator.

The following tests and evaluations will be performed:

- Physical exam (Day 1 only) or examination of injected tumor site(s) (Day 2 only).
- Record vital signs.
- Record performance status on Day 1 of cycle.
- For injected tumors palpable on physical examination, measurement with calipers or rulers, if possible, with photo documentation (Day 1).
- Obtain blood sample for hematology and chemistry prior to first administration of Ad/PNP on Day 1 of cycle.
- Obtain blood sample for antibody to adenovirus prior to the first administration of Ad/PNP on Day 1 of the first and third cycle.
- Obtain blood samples for measurement of adenovirus level prior to first administration of Ad/PNP on Day 1 and 2 hours after the third administration of Ad/PNP on Day 2 of the first and third cycle.

- Obtain urine sample for testing adenovirus prior to first administration of Ad/PNP on Day 1 and 2 (+/-1 hour) hours after the third administration of Ad/PNP on Day 2 of the first and third cycle.

- Give two administrations of Ad/PNP intratumorally 3-6 hours apart on Day 1 and one administration early (morning) on Day 2. Following each intratumoral administration the subject will be observed closely for tumor injection reactions or other acute safety events. Vital signs will be recorded at 30 +/- 15 min, and 60 +/- 15 minutes following each administration. Non-hospitalized subjects will be discharged from the clinic after 1 hour of observation as long as the investigator considers them clinically stable.

- Initiate PJP prophylaxis (Day 1).

- Record any AEs.

- Record any change in medications.

9.2.3 Visit 4 (Day 3, First infusion of F-araAMP)

Subjects may receive F-araAMP daily in the clinic or as in-patients at the discretion of the investigator.

- Examination of injected tumor site(s).

- Record vital signs.

- Obtain blood specimen prior to infusion of F-araAMP for:
  - CD4/CD8 T-cell counts (first cycle only)

- Obtain tumor biopsy, first cycle only.

- Administer F-araAMP intravenously over approximately 30 minutes.

- Blood specimen for F-Ade plasma level prior to and 15 - 30 minutes following infusion of F- araAMP in the first and third cycle.

- Record any AEs.

- Record any change in medications.

9.2.4 Visits 5 and 6 (Days 4 and 5)

- Examination of injected tumor site(s).
- Record vital signs.
- For injected tumors palpable on physical examination, measurement with calipers or rulers, if possible (Day 5).
- Administer F-araAMP intravenously over approximately 30 minutes.
- Draw blood for F-Ade plasma level prior to and 15-30 minutes following infusion of F-araAMP on Day 5 in the first and third cycle.
- Obtain tumor biopsy, Day 5 of first cycle only.
- Record any AEs.
- Record any change in medications.

9.2.5 Visit 7 (Days 14 ± 2)

- Record vital signs
- Examination of injected tumor site(s)
- For injected tumors palpable on physical examination, measurement with calipers or rulers, if possible
- Obtain blood specimen for hematology and chemistry parameters
- Assessment of tumor with CT scan or MRI on first, second (if PD after first cycle), third and last cycle.
- Obtain tumor biopsy, third cycle only.
- Record any AEs.
- Record any change in medications.

Following Visit 7 of the Last Cycle

9.2.6 Visit 8 (Day 28 ± 3 of the Last Cycle)

- Examination of injected tumor site(s)
- Record vital signs
- Record any new or resolution of adverse events
- Record any change in medications
- For injected tumors palpable on physical examination, measurement with calipers or rulers, if possible
- Blood specimen for:
  - Hematology
  - Chemistry
  - Antibody to adenovirus (last cycle)

9.2.7 Visit 9 or Termination Visit (Day 56 ± 3 of the Last Cycle)

- Examination of injected tumor site(s)
- Record vital signs
- Record any new or resolution of adverse events
- Record any change in medications
- For injected tumors palpable on physical examination, measurement with calipers or rulers, if possible
- ECG
- Obtain blood specimen for:
  - Hematology
  - Chemistry

  - CD4/CD8 T-cell counts

- Urine analysis

- MRI or CT scan for subjects who had CR, PR, or SD following last cycle

9.3 Description of Evaluations

9.3.1 Laboratory Evaluations

Hematology values include complete blood count (CBC) with differential and platelet count. CD4 and CD8 T-cell subsets will be obtained at baseline and at specified time points following infusion of F-araAMP.

Chemistry values include Na^+, K^+, CO_2, Cl, glucose, magnesium (Mg^{++}), calcium (Ca^{++}), blood urea nitrogen (BUN), creatinine (Cr), phosphorus, albumin, alkaline phosphatase, ALT, AST, total bilirubin, total protein.

Blood samples for F-Ade plasma measurement will be drawn prior to and 15-30 minutes after infusion of F-araAMP (See Study Procedures Table) F-Ade plasma levels will be measured by HPLC mass spectrometry. Blood and urine samples will be collected prior to the first administration and 2 hours after the third administration of Ad/PNP (See Study Procedures Table) samples will be stored and assayed for adenovirus following study completion.

Blood samples for antibody to adenovirus will also be collected prior to the first administration of Ad/PNP on the first and third cycle, and Day 28 of the last cycle.

9.3.2 Physical Examination

Vital signs include blood pressure, respiration, heart rate, and temperature. A full physical examination will be done at screening and at the second study visit. At other time points in the study a physical that includes symptom directed examination (in addition to examination of tumor(s)) will be conducted as determined by the study clinician. The subject's height and weight will be recorded at baseline.

Injected tumors will be examined at each study visit. For injected tumors palpable on examination, the tumor will be measured with ruler or calipers (if possible) and assessed for any changes as

specified in the study as shown in the Study Procedures Table. The injection site(s) will be examined for local reactions to the injection.

9.3.3 Medical History

A complete medical history includes age, race, and/or ethnicity, past or current treatments including surgical, radiation treatment, and chemotherapy. Current or past illnesses, current medications, and use of tobacco and alcohol will be recorded at baseline.

9.3.4 Tumor Response

For this study, response will focus on the injected tumor(s) and be based on criteria according to those in RECIST v1.1.[6] In addition, overall tumor response will be assessed according to RECIST 1.1 criteria.

The following criteria will be used to define response in injected tumor(s):

- 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.

Target tumors accessible for needle injection on physical examination will be injected. Size of the injected tumor masses will be measured with ruler or calipers, as possible, and it is preferable if the same practitioner measures using the same technique at each visit.

9.3.5 Radiographic Imaging

Lesions will also be assessed qualitatively using MRI or CT scan with the site's available MRI and CT techniques. The same imaging technique will be used for all evaluations. The target lesions and injected tumors for intratumoral administration will be assessed radiographically at baseline and within 2 weeks of Ad/PNP-F-araAMP on the first, third, and last cycle (and during the second cycle for those showing PD). In subjects who have CR, PR or SD on imaging 2 weeks after the last drug administration, follow-up imaging will be obtained again approximately 6 weeks later. Non-neck tumor sites may be followed by conventional CT/MRI.

9.4 Tumor Biopsies

A sample of tumor tissue will be obtained on three occasions from one of the injected tumors: Days 3 and 5 of the first cycle and on Day 14 of the third cycle. Biopsies will be evaluated by a number of tests intended to investigate the mechanism of tumor cell clearance including PNP expression, F-araAMP cleavage, and immunohistochemistry.

In the event that more than one tumor was injected with Ad/PNP and the biopsied tumor has CR, then a tissue sample may be obtained from an alternate injected tumor.

10. MEASUREMENTS

10.1 Primary Outcome Measure

Title:

The primary objective of the study is to evaluate the safety of repeat administration of a dose level of Ad/PNP-F-araAMP that demonstrated anti-tumor activity in patients with advanced head and neck cancer in the Phase 1 study.

Timeframe:

Primary outcome will be evaluated on a longitudinal basis and at study completion. The study is expected to require 36-48 months.

Safety Issue:

Studies conducted here are intended to evaluate safety.

10.2 Secondary Outcome Measure

Title:

The secondary objective of the study is to evaluate the anti-tumor activity of repeat administration of Ad/PNP-F-araAMP.

Timeframe:

Secondary outcome will be evaluated on a longitudinal basis and at study completion.

Safety Issue:

N/A, please see above

10.3 Primary and Secondary Outcome Measures-Discussion:

Primary Outcome Measurements for this study are directed towards safety and will be evaluated by: medical history, physical examination, vital signs, inspection of tumor site, performance status,

EKG, chest X-ray (CXR), blood chemistry, hematology, CD4/CD8 T-cell counts, urinalysis, PT/PTT, blood sample for adenovirus, urine for adenovirus, F-Ade plasma level, blood sample for antibody against adenovirus, and monitoring adverse events. Additional detail regarding these endpoints is furnished in Section 9.1, 9.2, and 9.3.

Secondary Outcome Measurements are directed towards efficacy and will include: Objective response rate (ORR), defined as the percentage of patients with a best overall response (BOR) of a complete response (CR) or a partial response (PR). BOR is the best response achieved during the 5 cycles of treatment, for injected tumors and overall, as determined by RECIST v.1.1. Other measurements will include:

- Durable response rate defined as a BOR of CR or PR 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 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 progression or death for any cause, whichever occurs first.
- Progression free survival (PFS) defined as time from first intratumoral injection to date of progression or death for any cause, whichever occurs first.
- Duration of response (DOR) defined as time from first documentation of CR or PR for injected tumors and overall, as determined by RECIST v.1.1 until disease progression or death for any cause, whichever occurs first.

10.3.1 Relevant Subset

N/A

10.3.2 Measurement Definition

Please see below.

10.3.3 Measurement Methods

Primary outcome measurement methods will include clinical evaluation (physical examination, medical history, performance status, vital signs, evaluation of tumor site for evidence of tissue injury) by investigators conducting the study (or their designees). Laboratory and additional parameters (EKG, CXR, blood chemistry, hematology, CD4/CD8 T-cell counts, urine analysis, PT/PTT, etc.) will be measured according to standard hospital/clinic procedures, and as detailed in Section 7 of this document.

Secondary outcome measurement methods are defined in Sections 9.3.4 and 9.3.5 and will be performed according to RECIST 1.1.

Special Studies include

Blood samples for adenovirus, urine for adenovirus, F-Ade plasma level, blood sample for antibody against adenovirus, tumor biopsy for studies of PNP activity, histochemistry, growth fraction, and adenoviral distribution. Specific studies are described in Section 8.

10.3.4 Measurement Time Points

Please see Section 9.1, Tabular Summary, for information regarding time points at which each outcome measure will be assessed.

10.3.5 Response Review

The study is designed primarily to evaluate safety with repeat treatment cycles, although the anti-tumor effect of Ad/PNP-F-araAMP will be assessed. For this study, response will focus primarily on the injected tumor(s) as the target lesion(s). Any observed effect on non-injected tumors and overall tumor response will also be assessed and recorded. Efficacy response results for injected tumors, non-injected tumors, and overall will be reported separately. Although we will evaluate response of the total tumor burden, only the injected mass will be used to primarily define efficacy. Because there is a possibility of immune-mediated anti-tumor benefit, we will also evaluate total tumor burden.

Response (CR, PR, SD, PD) is based on RECIST v1.1 (http://www.ctep.info.nih.gov v1.1). [6]

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the IRB. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation.

The investigator will ensure that all necessary approvals are obtained from the hospital or other institution at which he or she will conduct the clinical study. A copy of the original IRB approval for the protocol and the Informed Consent form must be forwarded to the Sponsor or their representative before subject enrollment can begin. The investigator will retain copies of any and all correspondence with the IRB, and the Institution will make them available for review by the Sponsor's representative or the FDA upon request. The investigator must inform the IRB of all protocol amendments and of serious or unexpected adverse events occurring during the study which are likely to affect the safety of the subjects or conduct of the study. The investigator must transmit in writing IRB approval to the Sponsor or representative.

The investigator or designee will notify the IRB when the study is placed on "hold", completed, or closed to further subject enrollment.

11.2 Safety Monitoring Plan

Trial safety will be monitored and reviewed by the SMC as described in the SMC Charter. The Sponsor, GeoVax, will coordinate among all study sites to monitor safety (i.e., AE reporting, reactions to study drug, deaths, etc.). GeoVax will be responsible for reporting these AEs, unanticipated problems, and other relevant data to the FDA and to all study sites.

The SMC will regularly review AE reporting associated with the research to ensure the protection of human subjects. Results of the SMC audit will be communicated to the Sponsor, GeoVax, the IRB, and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed. If the SMC and GeoVax agree to stop the study, GeoVax will inform the regulatory authorities and all the investigational sites of the decision to stop the study.

11.3 Informed Consent and HIPAA Authorization

The investigator will be responsible for obtaining from every subject prior to his/her participation in the study a written Informed Consent signed and dated in accordance with U.S. federal regulations (21CFR 50 and 21CFR 312.60) and Health Insurance Portability and Accountability Act (HIPAA) authorization to use and disclose protected health information (PHI). Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The IRB must approve the Informed Consent. The written Informed Consent and HIPAA Authorization will be obtained after the investigator has provided to the subjects a full explanation, both verbally and in writing, of the purpose, risks and discomforts involved. The original signed and dated copy of the Informed Consent and HIPAA Authorization must be maintained in the institution's records. The names of subjects enrolled during the study will be considered confidential.

11.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties, other than those cited below, is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers for all reports. Subject names will not be supplied in the IND Sponsor data. Study findings stored on a computer will be maintained in accordance with local data protection laws.

In compliance with regulatory guidelines regarding the monitoring of clinical studies and in fulfillment of the investigator's obligations to the IND Sponsor, it is required that data generated as a result of the study be available for inspection, on request, by personnel from the IND Sponsor and regulatory agencies. These will include all study-relevant documentation, including medical histories to verify eligibility, laboratory test results to verify transcription accuracy, treatment and diagnostic reports, admission/discharge summaries for hospital admissions occurring while the subject is on study, and autopsy reports (if available) for deaths occurring during or in temporal proximity to the study.

As part of the required content of the informed consent, participants must be informed that their records will be reviewed by the monitoring team, IND Sponsor, and regulatory agencies. Should access to medical record require a separate waiver or authorization, it is the investigator's

responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

11.5 Adherence to Reporting Requirements

Within a reasonable time following completion of the study, a final study report will be written, reviewed by the IND Sponsor or designee, and submitted to FDA.

11.6 Records

The FDA requires that an investigator retains records for a period of two years following the date a New Drug Application or Product License Application is approved for the drug for the indication for which it is being investigated; or, if no application or license is to be filed or, if the application or license is not approved for such indication, until two (2) years after the investigation is discontinued (21CFR 312.62).

The investigator should ensure that the following records are maintained:

- Signed informed consent documents for all subjects
- Patient identification code list and enrollment log
- Record of all communications between the investigator and the IRB
- Record of all communication between the investigator, monitoring team, and the Sponsor
- List of subinvestigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study and their signatures
- Copies of CRFs and of documentation of corrections for all subjects
- Pharmacy files containing copies of the record of use for the study drug, instructions for completion of these records, and the Investigator's Brochure
- All other source documents (subject medical records, laboratory records, etc.)

- Investigator files containing copies of the documents required for the initiation of the study (executed form FDA 1572, signed Investigator's Agreement, Curricula Vitae for the investigator, copy of the IRB approval of the protocol and Informed Consent forms). Note: Scanned documents are acceptable as source materials.

11.7 Protocol Approval and Amendments

Before the start of the study, the investigator will submit the clinical study protocol, informed consent document, and any other appropriate documents to the IRB with a cover letter listing the documents submitted, the dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. The IND Sponsor will submit the protocol and appropriate documents to the FDA and OBA/NIH in accordance with legal requirements.

The investigator will notify the IRB of all protocol amendments and administrative changes, in accordance with the site's requirements. The Sponsor or designee will notify the FDA and OBA/NIH of all protocol amendments and administrative changes in accordance with legal requirements. Amendments must be evaluated to determine whether the informed consent document should be revised.

The investigator must keep a record of all communication with the IRB and, if applicable, between the coordinating investigator and the IRB. This also applies to any communication between the investigator (or coordinating investigator, if applicable) and the IND Sponsor or its designee.

11.8 Closure of the Study

The study must be closed at the site upon completion. Furthermore, the IND Sponsor or the investigator has the right to close a study site at any time. As far as possible, premature closure should occur after mutual consultation. The IRB should be notified when the study is completed or terminated. The IND Sponsor will notify FDA and OBA/NIH when the study is completed or terminated including the reason for premature termination.

At the end of the study, all study drug must be returned, disposed of, or retained as directed by the Sponsor.

11.9 Study Monitoring and Auditing

The Sponsor/Contract Research Organization (CRO) will monitor study conduct in accordance with industry standards, best practice, and all applicable regulations and may summarize various aspects of the study for SMC review.

11.10 Documentation of Study Findings

Each investigational site will collect and compile clinical data for patients enrolled at their site(s) using the electronic data capture platform. All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the CRF. Paper charts in the form of printouts of the electronic medical record will be kept at the investigational site for each subject enrolled and stored in a locked office with limited access for only research staff. Details of CRF completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the CRF, the names, positions, signatures, and initials of these persons must be supplied to the Sponsor.

The investigator or designated representative should complete the CRF pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure.

12. STATISTICAL CONSIDERATIONS

12.1 Sample Size

This study is an open-label, multisite, Phase 1/2 study evaluating the safety of repeat administration of a single dose level Ad/PNP-F-araAMP in subjects with head and neck cancer and who have failed or exhausted all standard or approved therapies. No formal sample size estimation will be conducted. Approximately 10 to 20 subjects will be enrolled into the study in order to have 10 subjects evaluable for efficacy; this number of subjects is sufficient to assess preliminary safety and activity to guide design of subsequent clinical studies. This study is to be conducted at Stanford University, Emory University, and Thomas Jefferson University.

A total of 10 to 20 subjects in the safety population provides sufficient precision to rule out a treatment-related 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 subjects 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 subjects in the higher dosing cohorts achieved a BOR of CR or PR with a single cycle of treatment.

12.2 Assessment of Safety Measures

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

All subjects who receive a dose of Ad/PNP-F-araAMP will be included in the safety analysis population. Each subject 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. We consider the repeat administration of Ad/PNP-F-araAMP safe if the one-sided 80% upper confidence limit of the percentage of subjects in the safety population experience treatment-related Serious Adverse Events as defined in Section 7.2. For example, if 2 of 10 subjects 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 is considered safe.

12.3 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term using MedDRA v25.0.

Summary tables for treatment emergent adverse events will include number of occurrences of events by SOC, and numbers and percentages of subjects experiencing adverse events by SOC and preferred term. If a subject has more than one AE which codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within an SOC category, the subject will be counted only once in that SOC category. Summary tables to be generated include: summary of AEs, relationship of AEs to study drug, severity of AEs, AEs leading to study drug discontinuation and serious AEs. Data listings will be provided for AEs, AEs leading to study drug discontinuation, and serious AEs.

12.4 Clinical Laboratory Results

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 subjects, mean, standard deviation, minimum, maximum, median and interquartile) 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. A

spaghetti plot will visually track selected measurements over time for each patient. Baseline is defined as the last measurable value prior to dosing on Day 1. All clinical laboratory data will be provided in the data listing.

12.5 Vital Signs and Physical Examination

Descriptive statistics (e.g., number of subjects, mean standard deviation, minimum, maximum, and median) of vital sign measurements for systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature will be calculated for each measurement. Baseline is defined as the last measurable value prior to dosing on Day 1. All vital signs will be provided in the data listing. Physical examination of individual subjects will be presented in the data listings. No summary tables will be provided.

12.6 Assessment of Efficacy Measures

Response (CR, PR, SD, PD) is based on the Response Evaluation Criteria in Solid Tumors (RECISThttp://www.ctep.info.nih.gov v1.1) [6] and defined in Sections 9.3.4 and 10.

Efficacy assessments include:

- ORR is defined as the percentage of patients with a BOR of CR or PR. BOR is the best response achieved during the 5 cycles of treatment, as per Section 9.3.4 for injected tumors and overall as determined by RECIST v.1.1.
- Durable response rate is defined as a BOR of CR or PR as per Section 9.3.4 for injected tumors and overall as determined by RECIST v. 1.1 persisting for at least 4 weeks.
- TTR is defined as time from first intratumoral injection to date of first response value of CR or PR for injected tumors as per Section 9.3.4 and overall as determined by RECIST v.1.1.
- OS is defined as time from first intratumoral injection to date of progression or death for any cause, whichever occurs first.
- PFS is defined as time from first intratumoral injection to date of progression or death for any cause, whichever occurs first.

- DOR is defined as time from first documentation of CR or PR for injected tumors as per Section 9.3.4 and overall, as determined by RECIST v.1.1.until disease progression or death for any cause, whichever occurs first.

Efficacy will be assessed in the population of subjects who receive three intratumoral administrations of Ad/PNP and any infusion of F-araAMP.

Descriptive statistics (number and percentage of subjects) will be used to summarize BOR, ORR, and durable response rate. 95% Clopper-Pearson confidence intervals will also be provided. OS, PFS, DOR, and TTR will be analyzed based on Kaplan-Meier methods; Kaplan-Meier curves will be plotted over time. The number and percentage of subjects identified to have had an event and those who were censored will be displayed. The median time to event and its corresponding 95% CI will also be produced. A listing of response for subjects will be provided.

13. REFERENCES

1. Machiels JPH, *et al.,* Rationale and design of LUX-Head & Neck 1: A randomised, Phase III trial of afatinib versus methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who progressed after platinum-based therapy. *BMC Cancer* 2014. 14:473.

2. Fury MG and Pfister DG. Current recommendations for systemic therapy of recurrent and/or metastatic head and neck squamous cell cancer. *JNCCN,* 2011. 9: 681-690.

3. Vermorken JB, *et al*., Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med,* 2008. 359:1116-27.

4. Peron J, *et al.,* An effective and well-tolerated strategy in recurrent and/or metastatic head and neck cancer is successive lines of active chemotherapeutic agents. *BMC Cancer*, 2014. 15:504.

5. Rosenthal EL, *et al.,* Phase I dose-escalating trial of Escherichia coli purine nucleoside phosphorylase and F-araAMP gene therapy for advanced solid tumors. *Ann Oncol*, 2015. 26:1481-7.

6. Eisenhauer EA, *et al*., New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *European J Cancer*, 2009. 45: 228-247.

APPENDICES

Appendix A: Participant Eligibility Checklist

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulatory Binder.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other electronic medical record progress note.

Protocol Title:	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 F-araAMP Phosphate Intravenously) in Subjects with Recurrent, Local Head and Neck Cancer

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved IRB Approved Contract signed

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Provided Informed Consent	☐	☐	
2. Age ≥ 18 years.	☐	☐	
3. Patients with histologically or cytologically confirmed diagnosis of recurrent cancer of the head and neck region for whom there is no curative treatment option. For the purposes of trial eligibility, cancers of the head and neck region shall include, in addition to head and neck squamous cell carcinoma (HNSCC), cutaneous squamous cell primary sites and squamous cell carcinoma of unknown primary presenting with neck lymph nodal disease, as well as nasopharyngeal carcinoma and salivary gland tumors.	☐	☐	
4. All standard or approved treatment options that would provide substantive palliation must have failed, been exhausted, or patient not eligible for them (for example neuropathy, nephropathy, or hearing loss precluding the use of cisplatin).	☐	☐	
5. Tumor mass (primary tumor and/or lymphadenopathy) measurable by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and technically suitable for intratumoral injections (otolaryngologist will determine feasibility). Patients with nodal disease (or metastatic disease) that is needle accessible are eligible. Patients with additional tumors (including distant metastatic disease) beyond the intratumoral injection accessible tumor(s) that are not accessible for intratumoral injection are eligible ONLY if the patient has no other treatment option for the metastatic disease and treatment of local disease may provide the patient some benefit or palliation.	☐	☐	
6. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.	☐	☐	
7. In the judgment of the Investigator, the patient has recovered sufficiently from any previous significant therapy side effects or toxicities prior to Ad/PNP administration.	☐	☐	

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
8. Absolute neutrophil count [ANC] ≥ 1,500 cells/µl; hemoglobin ≥ 9 g/dl, platelets ≥ 100,000/µl.	☐	☐	
9. Serum creatinine ≤ 1.5 mg/dl, or calculated creatinine clearance ≥ 60 ml/min.	☐	☐	
10. Bilirubin ≤ upper limit normal [ULN], alanine aminotransferase [ALT] ≤ 1.5 x ULN and/or aspartate aminotransferase [AST] ≤ 1.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN.	☐	☐	
11. Prothrombin time (PT)/international normalized ratio (INR) ≤ 1.5 x ULN.	☐	☐	
12. Activated partial thromboplastin (aPTT) time ≤ 1.5 x ULN.	☐	☐	
13. Female patients must have a negative urine or serum pregnancy at screening (pregnancy test is not required for patients with bilateral oophorectomy and/or hysterectomy or for those patients who are > 1 year postmenopausal)	☐	☐	
14. All patients of reproductive potential must agree to use a medically acceptable form of contraception (e.g., hormonal birth control, double-barrier method) or abstinence.	☐	☐	

Exclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Prior history or current diagnosis of leukemia.	☐	☐	
2. Have received any gene therapy products or oncolytic viral therapy.	☐	☐	
3. Receiving allopurinol.	☐	☐	
4. Received an investigational drug within 30 days prior to first injection of Ad/PNP.	☐	☐	
5. Received radiation treatment < 4 weeks prior to first injection of Ad/PNP and does not have any RECIST 1.1 evaluable lesions that are outside the radiation field. (If the patient has RECIST 1.1 evaluable lesions outside the radiation field then they can be included).	☐	☐	
6. Received chemotherapy (systemic anticancer treatment) < 4 weeks prior to first injection of Ad/PNP and have not recovered from all the related side effects. (If the patient has recovered from all related side effects or has reached a new baseline, then they may begin receiving treatment at **sooner** than 4 weeks).	☐	☐	
7. Have significant baseline neuropathy (> Grade 2 based on Common Terminology Criteria for Adverse Events [CTCAE] v5.0).	☐	☐	
8. Uncontrolled intercurrent disease (e.g., diabetes, hypertension, thyroid disease, active infection).	☐	☐	
9. Had within 6 months prior to enrollment: myocardial infarction (MI), cerebral vascular accident (CVA), uncontrolled congestive heart failure (CHF), significant liver disease, unstable angina.	☐	☐	
10. Fever (temperature > 38.1° C orally).	☐	☐	
11. Receiving chronic systemic corticosteroids (> 3 weeks) or any chronic immunosuppressive medications within 14 days prior to first injection of Ad/PNP. Subjects receiving short courses of corticosteroids are considered eligible for the study.	☐	☐	
12. Receiving anticoagulants other than those to maintain patency of venous lines,	☐	☐	
13. Women who are pregnant or breast feeding,	☐	☐	
14. History of HIV infection. No requirement for testing.	☐	☐	

* All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

V. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	