Statistical Analysis Plan

Protocol Title:	An Open-Label, Phase II, Randomized, Controlled Study of Danvatirsen Plus Pembrolizumab Compared to Pembrolizumab Alone in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)
Brief Title:	Activity and Safety of Danvatirsen and Pembrolizumab in HNSCC
Acronym:	PEMDA-HN
Protocol Number:	FLM-6774-201
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Sponsor:	Flamingo Therapeutics Gaston Geenslaan 3, Building 4 3001 Leuven Belgium
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Statistical Analysis Plan

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Protocol Number: *FLM-6774-201*

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SAP Author: *Andrew D'Amato, M.S.*

REVIEW / APPROVAL SIGNATURES

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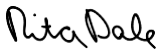
Andrew D'Amato, Senior Statistician, Signature:  Electronically signed by: Andrew DAmato Reason: I am the author of this document Date: 01-Aug-2025 09:07:48 PDT	Rita Dale, Manager Biostatistics Signature:  Electronically signed by: Rita Dale Reason: I am the reviewer of this document Date: 01-Aug-2025 11:49:03 MDT
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug Antibody
AE	Adverse Event
BOP2	Bayesian optimal phase 2
BLQ	Below the Limit of Quantitation
BOR	Best Overall Response
CI	Confidence Interval
CPS	Combined Positive Score
CR	Complete Response
CRR	Complete Response Rate
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DOR	Duration Of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End Of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
HNSCC	Head And Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
ICF	Informed Consent Form
IRT	Interactive Response Technology
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable

Abbreviation	Definition
NE	Not Evaluable
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
QTc	Corrected QT Interval
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings

1 INTRODUCTION

This document details the planned statistical analyses of Flamingo Therapeutics protocol FLM-6774-201, titled "An Open-Label, Phase II, Randomized, Controlled Study of Danvatirsen Plus Pembrolizumab Compared to Pembrolizumab Alone in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)".

The proposed analyses are based on the contents of the protocol amendment 4.0 dated 05 – May 2025.

This is a Phase II, open-label, randomized study. The study consists of a screening period, treatment period, safety follow-up, and survival follow-up. Treatment cycles are based on the schedule of administration of pembrolizumab. Each cycle is considered 21 days in length. The maximum duration of treatment with pembrolizumab is 24 months. There will be no limit on the duration of treatment with Danvatirsen.

This Statistical Analysis Plan (SAP) will only detail analyses for safety and efficacy of the study. Detail of pharmacokinetic and biomarker analyses, unless otherwise noted, are outside the scope of this document and will be handled separately.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives and Endpoints

Study Objects and Endpoints	
Primary Objectives	**Primary Endpoints**
• To determine the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as determined by the Investigator for the combination of danvatirsen and pembrolizumab compared with pembrolizumab alone as first-line treatment of patients with metastatic or unresectable, recurrent HNSCC whose tumors express programmed death-ligand 1 (PD-L1) by Combined Positive Score (CPS) ≥1.	• Confirmed ORR (partial response [PR] + complete response [CR] defined according to RECIST v1.1) (Eisenhauer et al 2009)
Secondary Objectives	**Secondary Endpoints**
• To characterize the safety and tolerability of the combination of danvatirsen and pembrolizumab • To evaluate additional efficacy parameters for the combination of danvatirsen and pembrolizumab compared with pembrolizumab alone • To characterize the pharmacokinetics (PK) of danvatirsen • To determine the immunogenicity of danvatirsen	• Adverse events (AEs), serious adverse events, physical examinations, clinical laboratory values, and tolerability (dose interruptions/reductions) • Duration of response (DOR) by RECIST v1.1 • Disease control rate (DCR) and CR rate by RECIST v1.1 • ORR and DOR by RECIST v1.1 in tumors with CPS ≥ 20 and ≥ 50 • Progression-free survival (PFS) by RECIST v1.1, defined as the time from randomization to the first documentation of progressive disease (PD) or death from any cause, whichever comes first • Overall survival (OS), defined as time from randomization to death from any cause • PK parameters derived from plasma concentrations of danvatirsen at defined timepoints in the combination regimen • Anti-danvatirsen antibody titers at defined timepoints in the combination regimen.

Study Objects and Endpoints	
Exploratory Objectives	**Exploratory Endpoints**
• To determine the pharmacodynamic activity of danvatirsen in pre- and on-treatment tumor and blood specimens • To determine the relationship between clinical activity and human papillomavirus (HPV) and other biomarkers in pre- and on-treatment specimens	• STAT3 levels and protein levels in pre- and on-treatment samples • Gene expression changes (RNA and/or protein) in pre- and on-treatment samples • Determination of HPV positivity

3 SAMPLE SIZE

Sample size considerations were based on monitoring the primary efficacy endpoint, ORR, using a 2-arm Bayesian optimal phase 2 (BOP2) design.

The primary efficacy evaluation will be the magnitude of ORR in each of the treatment arms and the probability that the combination arm ORR is superior to that of the control (monotherapy) arm, that is Pr(ORRcomb > ORRcon | data).

The design is optimized to maximize the power under H_0: ORRcon = 0.15 and ORRcomb = 0.43, while controlling the type I error rate at 1-sided 0.05.

An interim futility analysis is planned when ORR can be assessed for the first 39 patients, and the final ORR analysis is planned after 81 patients are followed for a minimum of 3 months (2 radiologic scans). A 2:1 combination: control randomization will be used for the 2 arms and will yield 83% power at the 1-sided 5% alpha based on the decision rule to reject the null hypothesis and conclude that the combination arm is superior compared to the control.

4 RANDOMIZATION

Upon confirmation of eligibility, patients will be randomized in a 2:1 ratio to either Danvatirsen + pembrolizumab or Pembrolizumab monotherapy.

Study randomization will be managed centrally through an Interactive Response Technology (IRT) system. Sites will receive the randomized treatment assignment for all patients by logging into the IRT system and entering the required data.

Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1) for patients enrolled under the original protocol or Amendment 1. For patients enrolled under Amendment 2 or later, randomization will be stratified by CPS ($1 \leq$ CPS <20 vs CPS ≥ 20). The change in stratification variables will not impact the intended randomization balance.

A Tumor Proportion Score (TPS) value ≥30 may be used for initial eligibility. The subject will be assigned to the 1≤CPS<20 stratum, if 30≤TPS<50, or the CPS≥20 stratum, if TPS≥50. However, a CPS value must be obtained and reported utilizing a tissue sample obtained prior to the start of study treatment.

Blinding is not applicable for this open-label study.

5 PLANNED ANALYSES

The Statistical Analysis Plan (SAP) and Table, Figure, Listing (TFL) Shells (and any amendments) must be approved prior to database lock. If post database lock, additional statistical analyses or changes to the statistical analysis are required, then those will be documented in a Post Database Lock Statistical Analysis Plan Addendum.

5.1 Analysis Sets

Analysis Set	Description
Full Analysis Set (FAS)	All randomized patients who receive at least 1 dose of study treatment based on the treatment assigned at randomization. The FAS will be the primary analysis set for efficacy analyses.
Safety Analysis Set	The Safety Analysis Set (SAS) is defined as all patients who receive at least 1 dose of study treatment based on the actual treatment received. The Safety Analysis set will be the primary analysis set for safety analyses.
Pharmacokinetic (PK) Analysis Set	The PK Analysis set is defined as all FAS patients with evaluable PK data. Additional details are outlined in the PKAP.
Biomarker Analysis Set	All FAS patients with evaluable biomarker data.

5.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

5.2.1 Race

Where more than one race category has been selected for a patient, these race categories will be combined into a single category labelled “Multiple Race” in the summary tables. The listings will reflect the original selected categories.

5.2.2 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the patient receives the first dose of study drug.

5.2.3 Change from Baseline

Change from Baseline to post-Baseline visit/timepoints will be calculated as follows.

Change from Baseline = Post-Baseline Value – Baseline Value

If the Baseline value is missing, then change from Baseline will be left as missing.

5.2.4 Study Day and Duration

Study day will be calculated as the number of days from the first dose of study treatment as follows.

For events on or after the first dose of study treatment:

Study Day = Date of Event – Date of 1st Dose + 1

For events before the first dose of study treatment:

Study Day = Date of Event – Date of 1st Dose

The duration of an event will be calculated in days as follows.

Duration = (Stop Date- Start Date + 1)/365.25.

5.2.5 Conventions for Missing and Incomplete Dates

All dates in the individual subject listings will be presented exactly as recorded on the Electronic Case Report Form (eCRF).

Historical dates, such as the start and stop of concomitant medication and medical history, will not be imputed if missing or incomplete.

Imputation of dates for adverse events with incomplete dates will be performed only for determination of treatment emergence and for he calculation of adverse event duration. Imputed dates will not be presented in data listings. The following algorithm will be used to estimate adverse event start dates for which only partial information is known:

- Completely Missing
  - Earliest of date of first dose of study drug or imputed stop date.
- Missing day and month only
  - If the year is same as the year of first day on drug, then the day and month of the start date of drug will be assigned to the missing fields.
  - If the year is prior to the year of first day on drug, then December 31 will be assigned to the missing fields.
  - If the year is after the year of first day on drug, then January 1 will be assigned to the missing fields.

- Missing month only
    - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only
    - If the month and year are same as the year and month of first day on drug, then the start date of drug will be assigned to the missing day.
    - If the month and year are before the year and month of first day on drug, then the last day of the month will be assigned to the missing day.
    - If the month and year are after the year and month of first day on drug, then the first day of the month will be assigned to the missing day.

If the AE stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed using the stop date.

Adverse events with partially missing stop dates will be imputed a stop date as follows:

- Year is missing - date left missing.
- Month is missing - impute 'December'.
- Day is missing - impute 'last day of that month'.

5.2.6 Conventions for Missing Severity and Causality of Adverse Events

Missing standard toxicity grades will not be imputed. Adverse events with missing toxicity grade will be reported as “No Grade” but will still be included in cumulative summaries for adverse events of any grade.

5.2.7 Inexact Values

In the case where a variable (e.g., Safety or Immunogenicity laboratory parameter value) is recorded as “> x”, “≥ x”, “< x” or “≤ x”, a value of x will be applied for analysis purposes.

5.2.8 Electrocardiogram (ECG) Data

For ECG data recorded on continuous scales, the mean of the triplicates rounded to the integer will be used for summarization.

5.2.9 Vital Signs and Physical Exams

Temperatures reported in Fahrenheit will be reported in Celsius. Height will be reported in centimeters. The following conversations will be used.

Celsius = (Fahrenheit – 32)/1.8

Centimeters = 2.54 x Inches

BMI (kg/m^2) = Weight / (Height)^2

5.2.10 Exposure to Study Drug

A Danvatirsen dose will be considered delayed if it is administered 11 to 14 days after the last dose and skipped if administered 15 to 21 days from the last dose. A second skipped dose will be counted if Danvatirsen is administered 22 to 28 days after the last dose, and so on.

A Pembrolizumab dose will be considered delayed if it is administered 25 to 42 days after the last dose and skipped if administered 43 or more days from the last dose.

Relative Dose Intensity (%) will be calculated separately for Danvatirsen and Pembrolizumab as the actual cumulative dose on study relative to the expected cumulative dose on study, assuming that no doses were missed or reduced. The following formula will be used.

Relative Dose Intensity = Actual Cumulative Dose / Expected Cumulative Dose x 100

Actual cumulative dose (mg) for Danvatirsen is calculated as the cumulative sum of Calculated Dose as collected on the CRF during the study. Actual cumulative dose (mg) for Pembrolizumab is calculated as the cumulative sum of Dose as collected on the CRF during the study.

Expected cumulative dose (mg) for Danvatirsen for subjects that have completed at least 1 week of study drug is defined as follows.

*Expected Cumulative Dose = (6 + 3 x Number of Weeks on Study) * kg*

For subjects that discontinued the study before completing 1 week on study, the expected cumulative dose (mg) is 3 mg/kg at day 1, 6 mg/kg at day 3, and 9 mg/kg at day 5.

Expected cumulative dose (mg) for Pembrolizumab is defined as follows.

Expected Cumulative Dose (mg) = 200 mg x Every 3 Weeks on Study

Treatment Duration for Pembrolizumab will be calculated in months as follows.

Treatment Duration = (Date of Last Dose – Date of First Dose + 1)/30.4375

Treatment Duration for Danvatirsen will be calculated in months as follows.

Treatment Duration = (Date of Last Dose – Date of First Dose + 1)/30.4375

5.2.11 Unscheduled Visits

Scheduled visits, unscheduled visits, and repeat assessments will be considered for any analysis of the patient's worst or maximum post-Baseline grade. For all other safety analyses, when summarizing post-Baseline visits, only data collected at scheduled visits will be tabulated. Unscheduled visits and repeat assessments will be excluded. All collected data (scheduled, unscheduled, or repeat) will be presented in the listings.

5.3 Randomization Strata

Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) for patients enrolled under the original protocol or Amendment 1. For patients enrolled under Amendment 2 or later, randomization will be stratified by CPS ($1 \leq$ CPS <20 vs CPS ≥ 20). The change in stratification variables will not impact the intended overall randomization balance.

A TPS value ≥30 may be used for initial eligibility. The subject will be assigned to the 1≤CPS<20 stratum, if 30≤TPS<50, or the CPS≥20 stratum, if TPS≥50. However, a CPS value must be obtained and reported utilizing a tissue sample obtained prior to the start of study treatment.

5.4 Reporting Conventions

All CDISC submission datasets, data listings, summaries, figures, and statistical analyses will be generated using SAS version 9.4 or higher.

Summaries will be presented by treatment arm and a cumulative overall column. Treatment arm labels will be displayed as follows.

Danvatirsen + Pembrolizumab (N=XX)	Pembrolizumab (N=XX)	Overall (N=XX)

Danvatirsen + Pembrolizumab = Danvatirsen 2 mg/kg or 3 mg/kg + Pembrolizumab 200 mg IV
Pembrolizumab = Pembrolizumab 200 mg IV

Table summaries will present patient by either planned or actual treatment assignment, as specified in the Statistical Analysis Plan. In the rare case that a subject is mis-randomized or administered the incorrect treatment, actual treatment assignment is defined as the treatment the patient received for the majority of the study.

Unless otherwise stated, listings will be sorted in the following order: Treatment arm, Subject ID, Start Date, End Date, and Parameter.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum. Summaries of change from Baseline values will only include patients with a values at both baseline and the post-baseline time-point.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of patients in the column header unless otherwise specified in the footnote. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Means, medians, and percentiles will be displayed to one more decimal place than the source data**,** dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data.

Confidence Interval (CI) will be displayed in two decimal places. *p*-values will be quoted to 4 decimal places consistent with SAS PVALUE*w.d* format set to PVALUE6.4. *P*-values < 0.0001 will be presented as p<0.0001.

5.5 Patient Disposition

The number and percentage of the following will be summarized for all screened subjects.

- Patients that were enrolled
- Screen failures and the reasons for screen failure
- Patients who were randomized
- Patients who were randomized but not treated with Danvatirsen and or Pembrolizumab and reason(s) not treated
- Patients who discontinued Pembrolizumab and reason for discontinuation
- Patients who discontinued Danvatirsen and reason for discontinuation

A separate summary will be provided for the number of subjects in each analysis set.

5.6 Protocol Deviations

Major protocol deviations will be summarized for the Safety Analysis Set by actual treatment. The summary will include number and percentage of subjects with each deviation as well as the number of individual protocol deviations as events. Details for identification and classification of protocol deviations are outlined in the Protocol Deviation Handling Plan (PDHP).

All major and minor protocol deviations will be listed.

5.7 Demographics and Baseline Characteristics

Standard continuous or categorical variable summaries will be presented for the Safety Analysis Set based on actual treatment..

Demographics

- Age at Informed Consent (years),
- Age Category (<65, >= 65, >= 65 to <75, >=75)
- Sex at Birth
- Fertility Status for Women
- Ethnicity
- Race

Other Baseline characteristics

- Height (cm),
- Weight (kg),
- Tobacco History
- ECOG Performance Status (0, 1)

5.8 Cancer History, Surgical History, and Prior Cancer Therapy

All cancer history and prior cancer therapy summaries will be reported by actual treatment for the Safety Analysis Set. All cancer history, surgical history, and prior cancer therapy data will be listed. Systemic anti-cancer therapy data will be listed.

Cancer History

- Tumor Details at Baseline
    - Number of Total Lesions
    - Number of Target Lesions
    - Number of Non-Target Lesions
    - Location of Metastatic Disease
- Initial Diagnosis
    - Primary Tumor Location
    - Tumor Stage
    - Histology
    - Complete Surgical Resection Performed
    - TNM Stage

- Current Diagnosis
  - Tumor Stage
  - TNM Stage
- HPV Status
- Combined Positive Score
- Combined Positive Score (0, >= 20, 20 - 49, >=50)
- Tumor Proportion Score
- Tumor Proportion Score (>=30, >=50)

Surgical History

- Extent of Resection
- Time from Surgery (years).

Prior Cancer Therapy

- Patients with any Prior Cancer Therapy
- Patients with any Prior Radiation Therapy
  - Number of Prior Radiation Therapies
  - Time Since Last Radiation Therapy (months)
- Patients with any Systemic Anticancer Therapy
  - Number of Prior Systemic Therapies (1 or 2+)
  - Time Since Last Systemic Anticancer Therapy (months)
  - Type of Therapy (Immunotherapy, Chemotherapy, Other)
  - Setting
  - Reason for Discontinuation
  - Best Overall Response

5.9 Medical History

Medical History will be presented for the Safety Analysis Set by actual treatment. Medical history will be presented by Medical Dictionary of Regulated Activities (MedDRA) primary system organ class and preferred term.

Separate tabulations of previous and ongoing conditions at Screening will be presented by actual treatment arm and overall, for the Safety Analysis Set. Previous medical history is defined as any medical history with an end date before Screening. Concomitant medical history is defined as any medical history that is reported as ongoing or has an end date on or after the date of Screening. All medical history will be listed.

5.10 Prior and Concomitant Medications

Medications will be presented for the Safety Analysis Set by actual treatment. All prior and concomitant medications taken from 30 days prior to enrollment in the study until 30 days after the patient's last dose of the study treatment will be captured in the CRF. Medication terms will be coded as per the WHO Drug dictionary (version B3 Global Mar-2023) and presented by preferred term and ATC level 2 term.

Separate tabulations will be produced for prior and concomitant medications presented by the actual treatment group and overall, for the Safety Analysis Set. Prior Medication is defined as any medication with an end date prior to the first dose of any study drug. Concomitant Medication is defined as any medication that is reported as ongoing or has a end date on or after the date of first dose of any study drug.

5.11 Exposure and Compliance to Study Drug

Danvatirsen is an investigational medicinal product (IMP). Pembrolizumab is the standard of care. Collectively, these 2 drugs are referred to as the "study drug".

The following exposure to study drug parameters will be summarized for the Safety Analysis Set for both Danvatirsen and Pembrolizumab

- Treatment Cycles Completed
- Treatment Duration (Months)
- Treatment Duration of Any Study Drug (Months)
- Number of Doses
- Number of Cycles Infusion Interrupted
- Number of Doses Delayed
- Number of Doses Skipped
- Dose Reductions (Danvatirsen only)

All study drug exposure data will be listed.

5.12 Efficacy Analyses

All efficacy analyses will be presented by planned treatment for the FAS.

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. All comparisons between treatments will be reported with 90% and 95% confidence intervals for the difference.

The following efficacy parameters will be derived as per RECIST v1.1 for the FAS.

- Overall Response Rate
- Disease Control Rate
- Complete Response Rate
- Duration of Response
- Progression-Free Survival
- Overall Survival

A summary of RECIST v1.1 tumor assessments, methods, and criteria are presented in Appendix 5 of the protocol. All efficacy parameters are derived from overall response as per RECIST v1.1. Overall response at each tumor assessment is determined using measurements of both target and non-target lesions. The overall response categories are as follows.

All target lesion, non-target lesion, and new lesion data will be listed separately.

Overall Response Categories by RECIST v.1.1	
CR	Complete Response
PR	Partial Response
SD	Stable Disease
PD	Progressive Disease
NE	Not Evaluable

A response of CR or PR must be confirmed by a repeat assessment at least 4 weeks after the initial CR or PR. A tumor assessment at least 35 days after the first dose is required for an overall response of SD, otherwise the BOR is considered not evaluable (NE).

Overall response rate (ORR), complete response rate (CR), and disease control rate (DCR) are each calculated using the subject's best overall response (BOR) on study. This is determined based on the following hierarchy for overall response category:

$$CR > PR > SD > PD > NE$$

Tumor assessments after the first PD will not be considered for BOR.

When a patient has at least one overall response of CR or PR, BOR will be assigned using the following rules. This algorithm is not applied for analyses based on unconfirmed response. (See Section 5.12.5)

Overall Response	**Overall Response of Subsequent Assessment**	**Best Overall Response** (Confirmed)
CR	CR >= 4 weeks later	CR
CR	PR, SD, or PD	SD if duration criteria* PD otherwise
CR	No Evaluable Assessment	SD if duration criteria* NE otherwise
PR	CR >= 4 weeks later	PR
PR	PR >= 4 weeks later	PR
PR	SD	SD
PR	PD	SD if duration criteria* PD otherwise
PR	No Evaluable Assessment	SD if duration criteria* NE otherwise

* Assessment occurred a minimum of 35 days since Baseline

5.12.1 Primary Endpoint

The primary efficacy endpoint is the confirmed Objective Response Rate (ORR) defined according to RECIST v1.1. ORR is defined as the proportion of patients with a confirmed objective response of CR or PR.

Hypothesis testing will be performed to compare the ORR between both treatment groups. The null hypothesis is that the ORR of the combination treatment arm is superior to that of the control treatment arm:

$$Null\ hypothesis:\ H_0:\ ORR_{comb} <= ORR_{con}$$

$$Alternative\ hypothesis:\ H_1:\ ORR_{comb} > ORR_{con}$$

5.12.2 Primary Efficacy Analysis

The primary efficacy analysis for ORR will be conducted once all patients are treated and followed for a minimum of 3 months (2 radiologic scans).

The number and percentage of patients with each BOR category will be summarized.

The ORR will be defined as the proportion of patients with a confirmed objective response as assessed by the Investigator in the FAS. “Patients who receive at least one dose of either study

treatment but have no valid post-baseline tumor assessment or not available confirmed BOR will be considered non-responders."

The ORR estimate along with the corresponding 2-sided 90% and 95% confidence interval using Clopper-Pearson exact binomial test will be presented for each treatment arm.

Comparison of the ORR between treatment arms will be analyzed using Fisher's Exact test and by reporting the risk difference and corresponding 90% and 95% confidence intervals. Both a 1-tailed and 2-tailed p-value for Fisher's Exact test will be provided. The risk difference for ORR is calculated as the difference in ORR between both treatment arms. Confidence intervals for the risk difference will be calculated using the Wald Method.

The following SAS code will be used, where adrs_freq is a frequency table of planned treatment by responder status. (Sorted so that first row is responders for the combination arm).

ORR Estimate and Corresponding Exact Binomial Confidence Intervals:

```
ods output binomial=<outdata>;
proc freq data=adrs_freq;
      tables avalc / binomial(level="RESPONDER") alpha=0.05;
      by trt01pn;
      weight count;
run;
```

Lower Limit is nvalue1 where name1="XL_BIN".
Upper Limit is nvalue1 where name1="XU_BIN".
Use alpha=0.10 for 90% CI.

Risk Difference and Corresponding Confidence Intervals:

```
ods output riskdiffcol2=<outdata>;
proc freq data=adrs_freq order=data;
      tables trt01pn*avalc / riskdiff alpha=0.05;
      weight count;
run;
```

Use risk, lowercl, and uppercl where row="Difference".
Use alpha=0.10 for 90% CI.

Fisher's Exact Test:

```
ods output fishersexact=<outdata>;
proc freq data=adrs_freq order=data;
  tables trt01pn*avalc / fisher;
  weight count;
run;
```

For 1-tailed test, nvalue1 where name1="XPR_FISH".
For 2-tailed test, nvalue1 where name1="XP2_FISH".

5.12.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints also include the following rates.

- Disease Control Rate
- Complete Response Rate
- Overall Response Rate in tumors a Combined Positive Score ≥ 20 and ≥ 50

The secondary efficacy endpoints include the following time-to-event parameters by RECIST v1.1.

- Duration of Response
- Duration of Response in Tumors with a Combined Positive Score ≥ 20 and ≥ 50
- Progression-Free Survival
- Overall Survival

Analysis for all rates will be the same as performed for the primary endpoint. Time-to-event parameters will be compared descriptively, using quartiles and corresponding confidence intervals. Comparison between treatment arms for progression-free survival and overall survival will be summarized using a stratified log-rank test.

5.12.4 Secondary Efficacy Analysis

The interim analysis for PFS and OS will be conducted once all patients are treated and followed for a minimum of 3 months (2 radiologic scans). The final analysis for PFS and OS will be conducted after all patients have been followed for a minimum of 15 months, unless the study is deemed futile at the interim or primary ORR analysis stage.

5.12.4.1 Disease Control Rate and Complete Response Rate

Disease control rate (DCR) is defined as the proportion of patients with a best overall response of CR, PR, or SD. Confirmation by repeat assessments is required for a BOR of CR or PR.

Complete response rate (CRR) is defined as the proportion of patients with a best overall response of CR. Confirmation by repeat assessments is required.

The statistical analysis of DCR and CRR will be the same as performed for ORR described in Section 5.12.2.

5.12.4.2 Duration of Response

Duration of response (DOR) is defined as the date of the patient's first BOR of CR or PR to the earliest date of documented progression or to death if no prior evidence of disease progression. DOR will be calculated as follows for all patients in the FAS population with a confirmed objective response. The date of the first confirmed response is based on the first instance of CR or PR that is confirmed by repeat assessments at least 4 weeks later.

$$DOR\ (Months) = \frac{(Date\ of\ PD, Death, or\ censoring - Date\ of\ 1^{st}\ confirmed\ CR\ or\ PR) + 1}{30.4375}$$

DOR may be censored to a stop date other than PD or death, as described in the censoring rule table of Section 5.12.4.5.

Kaplan-Meier estimates of 25th, 50th and 75th percentiles for DOR will be presented. Corresponding 95% confidence intervals using Greenwood's formula will be provided. Minimum and Maximum DOR will be presented.

The following SAS code will be used.

```
proc lifetest data=adtte timelist=3 6 9 12 reduceout outsurv=<outdata>;
      time aval*cnsr(1);
      by trt01pn;
run;
```

5.12.4.3 Progression Free Survival

PFS is defined as the time from date of randomization to first progression of disease (PD) or death due to any cause, whichever occurred first, where the disease progression will be determined based on RECIST v1.1 criteria. The analysis of this endpoint will be based on FAS population.

$$PFS\ (Months) = \frac{(Date\ of\ PD\ or\ Death\ or\ Censoring - Date\ of\ randomization) + 1}{30.4375}$$

PFS may be censored to a stop date other than PD or death, as described in the censoring rule table of Section 5.12.4.5.

PFS median follow-up time (MFT) is defined as the time from date of randomization until the time where a subject is censored based on censoring rules for PFS. In the calculation for PFS MFT, documented PD or death will be considered censored events, rather than events.

Kaplan-Meier estimates of 25th, 50th and 75th percentiles for PFS and PFS MFT will be presented. Corresponding 95% confidence intervals using Greenwood's formula will be provided. Minimum and Maximum PFS will be presented.

A Stratified Log-Rank test will be conducted, stratified for Baseline CPS category, to compare both treatment arm and the p-value will be provided. The following SAS code will be used:

```
ods output homtests=<outdata>;
proc lifetest data=adtte;
      time aval*cnsr(1);
      strata cpsgr1 / group=trt01pn;
run;
```

Probability of progression-free survival for at least 3 months, 6 months, 9 months, and 12 months along with corresponding 95% confidence intervals using the Kaplan-Meier method will be provided for the Overall column.

The hazard ratio of PFS, comparing the combination arm to Pembrolizumab, will be estimated using a Cox Proportional-Hazard model. The model will adjust for Baseline CPS category, and a corresponding 95% confidence interval will be provided. The following SAS code will be used:

```
ods output parameterestimates=<outdata>;
proc phreg data=adtte
      class trt01pn(ref='2');
      model aval*cnsr(1)=trt01pn / r1 ties=exact;
      strata cpsgr1;
      hazardratio trt01an;
run;
```

5.12.4.4 Overall Survival

Overall survival (OS) is defined as the time from randomization to death from any cause.

$$OS\ (Months) = \frac{(Date\ of\ Death\ or\ Censoring - Date\ of\ randomization) + 1}{30.4375}$$

OS may be censored to a stop date other than PD or death, as described in the censoring rule table of Section 5.12.4.5.

OS median follow-up time (MFT) is defined as the time from date of randomization until the time where a subject is censored based on censoring rules for OS. In the calculation for OS median follow-up time, documentation of death will be considered a censored event, rather than an event, and a censored OS will be considered an event.

OS and OS MFT will be analyzed the same as done for PFS. Kaplan-Meier estimates will only be calculated for the probability of survival for at least 12 month or 24 months. Hazard ratio and 95% confidence interval will be provided.

5.12.4.5 Censoring Rules for Time-to-Event Parameters

Progression-Free Survival and Duration of Response Censoring			
#	**Event Description**	**Stop Date Used**	**Outcome**
1	Documented radiological PD before initiation of non-study anti-cancer treatment	Date of the first tumor assessment that determined PD	Event
2	Death during the study with no prior PD and no prior initiation of non-study anti-cancer treatment	Date of death	Event
3	Radiographic PD or death after a missed (or not available / not evaluable) tumor response assessment**	Date of last adequate tumor assessment prior to missed tumor assessment	Censored
4	Patient administered new anticancer therapy prior to disease progression	Date of last valid disease assessment prior to start of new anticancer therapy	Censored
5*	No evaluable post-Baseline tumor assessment	Date of first dose	Censored
6*	Patient without documented progression or death	Date of the last valid disease assessment date	Censored
7*	Patient withdrawal or lost to follow-up	Date of the last valid disease assessment	Censored

Overall Survival Censoring			
#	**Event Description**	**Stop Date Used**	**Outcome**
1	Death from any cause	Date of death	Event
2	Patient withdrawal or lost to follow-up	Date of the last contact	Censored
3	Patient without documentation of death as of the data cutoff	Date of last contact where subject known to be alive.	Censored

*Not applicable to Duration of Response

**A tumor response assessment is considered missed if more than 13 weeks (91 days) has elapsed since the last image-based tumor response assessment. If a subject develops progressive disease or dies directly after this interval, the tumor response assessment will be excluded from analysis and censored to the last evaluable assessment. However, if a response assigned as CR, PR, or SD is obtained after more than 13 weeks, then the tumor response will not be excluded.

5.12.5 Sensitivity Analysis

Sensitivity analysis will be conducted to evaluate the effect of requiring a confirmed objective response for ORR and DOR derivations. The sensitivity analyses for ORR and DOR will be the same as performed for the primary and secondary efficacy analyses, except confirmation of CR and PR by repeat assessments will not be required.

5.12.6 Subgroup Analyses

Subgroup analyses will be performed for the primary and secondary efficacy endpoints for the FAS population. This includes analysis for ORR, DOR, PFS, and OS. The following subgroups will be used.

- Baseline Combined Positive Score Category (CPS < 20, CPS >= 20)
- Sex at Birth (Male, Female)
- Age Group (< 65, >=65)
- ECOG PS (0, 1)
- HPV Status (Positive, Negative)
- Region (US, Non-US)

For subgroup analysis of PFS by Baseline CPS category, Baseline CPS category will be removed as a stratification factor from the Cox Proportional Hazard Model. All subgroup analyses are considered descriptive, and no hypothesis testing will be performed.

5.12.7 Multiplicity

All secondary endpoints and these supportive analyses will be considered as descriptive evidence of efficacy and will be analyzed without any procedures to account for multiple comparisons.

5.12.8 Additional Efficacy Plots

Supportive efficacy data will be plotted for the FAS based on planned treatment.

A forest plot will be provided, presenting the risk difference between treatment arms for ORR and DCR, by Baseline CPS, Baseline ECOG, sex at birth, age group, and overall. Forest plots for PFS and OS will also be provided to present the hazard ratio between combination arm to Pembrolizumab, by the same subgroups.

A waterfall plot presenting the best percent change from baseline in sum of target lesions (mm) will be provided. Each bar will represent one subject and will be color-coded based on that subject's BOR.

A spider plot presenting the percent change from baseline in the sum of target lesions (mm) versus time (analysis visits) will be provided. Each line path will represent one subject and will be color-coded based on the subject's BOR.

A Swimmer's plot for duration of treatment (months) by subject will be provided, presenting overall response at each visit. Each bar will be color-coded by BOR.

5.13 Safety Analyses

All safety analyses will be presented by actual treatment for the Safety Analysis Set.

5.13.1 Adverse Events

Treatment-emergent adverse events (TEAE) are reported according to protocol as any AE that has an onset on or after the first dose of study drug or any pre-existing condition that has worsened on or after the first dose of study drug up to the subject completion of the study.

A treatment-related AE is defined as an AE as being definitely, possibly, or probably, related to the study drug.

All TEAE summaries will include the number and percentage of subjects experiencing each adverse events as well as the total number of events. The following TEAEs will be summarized separately by system organ class and preferred term, as coded by MedDRA dictionary.

- Any TEAE
- Any TEAE (PT only)
- Related to Any Study Treatment
- Related to Danvatirsen
- Serious
- Serious Related to Any Study Drug
- Leading to Discontinuation of All Study Drugs
- Leading to Discontinuation of Danvatirsen only
- Leading to Discontinuation of Pembrolizumab only
- Leading to Dose Delays or Reductions of Any Study Drug
- Leading to Dose Delays or Reductions of Danvatirsen
- Leading to Death
- Leading to Death Related to Any Study Drug
- Toxicity Grade 3 or Higher
- By Maximum Toxicity Grade

An overall TEAE summary table will be provided separately, tabulating the number of subjects and events for any adverse event for the above categories. The following summaries will also be provided.

- Listing of Serious TEAEs
- Listing AEs Leading of Deaths
- TEAE by Preferred Term
- TEAE Related to Any Study Drug by Preferred Term

All adverse events will be listed. Listings of AEs leading to death will include a flag for on-treatment deaths. An on-treatment death is defined as death occurring from date of first dose of any study drug to 30 days after last dose of Danvatirsen or 90 days after last dose of Pembrolizumab, whichever is later.

Adverse event incidence is counted only once per system organ class and once per preferred per patient term. The number and percent of patients experiencing events are reported. Outputs reported at maximum severity show the highest severity reported by a patient per system organ class and preferred term. TEAE tables for system organ class, preferred term will be presented in alphabetically order to SOC and decreasing order of frequency for PT based on the Overall column.

5.13.2 Laboratory Data

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and subject data listings will be presented in the International System of Units (SI units; Système International d'Unités).

Laboratory parameters will be programmatically graded according to NCI-CTCAE v5.0 toxicity grading, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the local laboratory will be used to determine programmatically if a laboratory parameter is below, within or above the normal range for the subject's age and sex. In this case, values low, normal, or high will be assigned.

All laboratory result summaries will be presented separately for chemistry, hematology, coagulation, and urinalysis.

Change from Baseline of numerical laboratory results will be summarized at each visit. A separate summary for categorical urinalysis parameters will be provided.

Shift tables will be provided, showing change in CTCAE toxicity grade from Baseline to last visit as well as Baseline to worst post-Baseline grade. For parameters for which a CTCAE scale does not exist, the shift tables will instead present low, normal, or high, based on provided reference ranges of normal. Only patients with both a Baseline and post-Baseline assessment will be included in the analysis. Scheduled visits, unscheduled visits, and repeat assessments will be considered for worst post-Baseline grade.

In the event that a subject has post-Baseline lab results for the same parameter both above and below the range of normal, the record with the value that is the furthest from the reference range will be considered as the worst. If they are equidistant from the reference range, the worst post-Baseline will be assigned as high.

All hematology, chemistry, coagulation, and urinalysis data will be listed separately. An additional listing will be provided for abnormal laboratory values.

5.13.3 Vital Signs

Descriptive statistics for observed values and changes from Baseline in the following vital signs will be presented by study treatment arm and timepoint:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (degrees Celsius)
- Oxygen Saturation (%)
- Weight (kg)

All vital signs data will be listed.

5.13.4 Electrocardiogram Data

Descriptive statistics for observed values and changes from Baseline in the following ECG variables will be tabulated at each follow-up. Average of the triplicate will be used for the summaries.

- Heart rate (bpm)
- PR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTc interval (ms)
- QTcF interval (ms)
- QTcB interval (ms)
- RR interval (ms)

Shift tables will be provided, showing the shift from Baseline to each scheduled visit in overall interpretation of the ECG. Overall Interpretation includes normal, abnormal and not clinically significant, and abnormal and clinically significant. Only patients with both a Baseline and post-Baseline assessment will be included in the analysis. Scheduled visits, unscheduled visits, and repeat assessments will be considered for worst post-Baseline grade.

A summary of ECG abnormalities will be provided for both the patient's last visit. The following categories for QTc/QTcF value (msec) will be summarized.

- > 450 and ≤ 480
- > 480 and ≤ 500
- > 500
- > 30 and ≤ 60 Increase from Baseline
- > 60 Increase from Baseline

All ECG data, including details of any abnormalities, will be listed.

5.13.5 Other Safety Assessments

The following data will be listed but not summarized.

- Physical Examination
- Endocrine Hormones
- Thyroid Function Test
- Non-Pharmacological Procedures
- Pregnancy Test
- Social History (Tobacco)
- Tumor Tissue Collection

6 BIOMARKER ANALYSIS

Biomarker analyses will be subject to a separate analysis plan and report, with the exception of HPV status that will be presented in the summary of baseline characteristics and as a subgroup factor for efficacy analyses.

7 IMMUNOGENICITY ANALYSIS

Immunogenicity analyses will be subject to a separate analysis plan and report.

8 INTERIM ANALYSIS

An interim futility analysis is planned for when ORR can be assessed for the first 39 patients. Tumor assessment data for the interim analysis will be restricted to up until the earliest date in which all 39 patients have received at least one dose of study drug. All demographic and safety data reported until the time of the datacut will be included in the report.

The final ORR analysis is planned after 81 patients are followed for a minimum of 3 months (2 radiologic scans). A 2:1 combination: control randomization will be used for the 2 arms and the

(Futility stopping) stop enrolling patients and claim that the experimental arm is unacceptable if:

$$Pr(ORR_{comb} > ORR_{con}|data) < \lambda(n/N)\alpha,$$

Where λ=0.96 and α=0.94 are design parameters optimized to maximize the power under *H0*: *ORRcon* = 0.15 and *ORRcomb* = 0.43, while controlling the type I error rate at 0.05 under *ORRcon* = *ORRcomb* = 0.15. This optimization is performed assuming a vague prior Beta(0.5,0.5) for *ORRcon* and *ORRcomb*.

Based on the above decision rule, to reject the null hypothesis and conclude that the combination arm is superior compared to the control:

At the interim analysis: $Pr(ORR_{comb} > ORR_{con}|\ data) > 0.5$, and

At the final analysis: $Pr(ORR_{comb} > ORR_{con}\ |data) > 0.96$

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

The final analysis analysis will occur prior to the conditions outlined in Section 8, due to early termination of the study.

10 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA
2. Guidance for Industry; E9 Statistical Principles for Clinical Trials; www.fda.gov/media/71336/download
3. E.A. Eisenhauer, et al.: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)
4. Common Terminology Criteria for Adverse Events (CTCAE) v5.0 https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.
5. FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (December 2018); https://www.fda.gov/media/71195/download.

11 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. TFL titles and numbers may vary and are found in the TFL Shell document. The eCTD section is shown in bold. The following validation methods will used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)

Number	Title	Validation Method	Interim Analysis
Tables			
14.1.1.1	Subject Disposition	IP	X
14.1.1.2	Analysis Sets	IP	
14.1.1.3	Major Protocol Deviations	IP	
14.1.1.4	Failure of Randomization Criteria	IP	
14.1.1.2.1	Demographics and Baseline Characteristics	IP	X
14.1.1.3.1	Cancer History	IP	X
14.1.1.3.2	Prior Medical History	IP	
14.1.1.3.3	Medical History Ongoing at Screening	IP	
14.1.1.3.3	Surgical History	IP	
14.1.1.3.4	Prior Cancer Therapy	IP	
14.1.1.3.5	Prior Medication	IP	
14.1.1.3.6	Concomitant Medication	IP	
14.2.1.1	Objective Response Rate and Disease Control Rate	Stat IP	X
14.2.1.2	ORR and DCR by Baseline CPS	Stat IP	X
14.2.1.3	ORR and DCR by Baseline ECOG	Stat IP	
14.2.1.4	ORR and DCR by Sex at Birth	Stat IP	
14.2.1.5	ORR and DCR by Age Group	Stat IP	
14.2.1.6	ORR and DCR by HPV Status	Stat IP	
14.2.1.7	ORR and DCR by Region	Stat IP	
14.2.1.8	ORR and DCR - Sensitivity Analysis Confirmed or Unconfirmed	Stat IP	
14.2.2.1.1	Duration of Response	Stat IP	X
14.2.2.1.2	DOR by Baseline CPS	Stat IP	X
14.2.2.1.3	DOR by Baseline ECOG	Stat IP	
14.2.2.1.4	DOR by Sex at Birth	Stat IP	
14.2.2.1.5	DOR by Age Group	Stat IP	
14.2.2.1.6	DOR by HPV Status	Stat IP	
14.2.2.1.7	DOR by Region	Stat IP	
14.2.2.1.8	DOR - Sensitivity Analysis Confirmed or Unconfirmed.	Stat IP	
14.2.2.2.1	Progression-Free Survival	Stat IP	X
14.2.2.2.2	PFS by Baseline CPS	Stat IP	X
14.2.2.2.3	PFS by Baseline ECOG	Stat IP	
14.2.2.2.4	PFS by Sex at Birth	Stat IP	
14.2.2.2.5	PFS by Age Group	Stat IP	
14.2.2.2.6	PFS by HPV Status	Stat IP	
14.2.2.2.7	PFS by Region	Stat IP	
14.2.2.3.1	Overall Survival	Stat IP	
14.2.2.3.2	OS by Baseline CPS	Stat IP	
14.2.2.3.3	OS by Baseline ECOG	Stat IP	
14.2.2.3.4	OS by Sex at Birth	Stat IP	
14.2.2.3.5	OS by Age Group	Stat IP	
14.2.2.3.6	OS by HPV Status	Stat IP	

14.2.2.3.7	OS by Region	Stat IP	
14.3.1.1.1	Overall Treatment-Emergent Adverse Events	IP	X
14.3.1.2.1	TEAE by SOC and PT	IP	X
14.3.1.2.1.1	TEAE by PT	IP	X
14.3.1.2.2	TEAE by SOC and PT - Related to Any Study Drug	IP	X
14.3.1.2.3	TEAE by SOC and PT - Related to Danvatirsen	IP	X
14.3.1.2.4	TEAE by SOC and PT - Serious	IP	X
14.3.1.2.5	TEAE by SOC and PT - Serious and Related to Any Study Drug	IP	
14.3.1.3.1	TEAE by PT	IP	
14.3.1.3.2	TEAE by PT - Related to Any Study Drug	IP	
14.3.1.4.1	TEAE by SOC and PT - Leading to Discontinuation of All Study Drugs	IP	
14.3.1.4.2	TEAE by SOC and PT - Leading to Discontinuation of Danvatirsen	IP	
14.3.1.4.3	TEAE by SOC and PT - Leading to Discontinuation of Pembrolizumab	IP	
14.3.1.4.4	TEAE by SOC and PT - Leading to Dose Delays or Reductions of Any Study Drug	IP	
14.3.1.4.5	TEAE by SOC and PT - Leading to Dose Delays or Reductions of Danvatirsen	IP	
14.3.1.4.6	TEAE by SOC and PT - Leading to Dose Delays of Pembrolizumab	IP	
14.3.1.4.7	TEAE by SOC and PT - Leading to Death	IP	
14.3.1.4.8	TEAE by SOC and PT - Leading to Death and Related to Any Study Drug	IP	
14.3.1.5.1	TEAE by SOC and PT - Grade 3 or Higher	IP	
14.3.1.5.2	TEAE by SOC, PT, and Maximum Toxicity Grade	IP	X
14.3.2.1	Listing of Deaths	IP	X
14.3.2.2	Listing of Serious AE	IP	
14.3.4.1	Listing of Lab Abnormalities	IP	
14.3.5.1	Hematology	IP	X
14.3.5.2	Hematology Shift	IP	X
14.3.5.3	Chemistry	IP	
14.3.5.4	Chemistry Shift	IP	X (ALT/AST Only)
14.3.5.5	Coagulation	IP	
14.3.5.6	Coagulation Shift	IP	
14.3.6.1	Extent of Exposure to Danvatirsen	IP	X
14.3.6.2	Extent of Exposure to Pembrolizumab	IP	X
14.3.7.1	Vital Signs	IP	
14.3.7.2	12-Lead ECG	IP	
14.3.7.3	12-Lead ECG Shift	IP	
14.3.7.4	12-Lead ECG Abnormalities	IP	
14.3.7.5	ECOG	IP	
14.3.7.6	Post-Treatment Anticancer Therapy	IP	
Figures			
14.2.3.1.1	Duration of Treatment Swimmer's Plot	IP	X
14.2.3.2.1	Waterfall Plot - Max Percent CFB in Tumor Size	IP	
14.2.3.3.1	Spider Plot - Sum of Target Lesions vs Time by CPS	IP	
14.2.3.4.1	Forest Plot - ORR and DCR	IP	
14.2.3.4.2	Forest Plot - PFS	IP	
14.2.3.4.3	Forest Plot - OS	IP	
14.2.3.5.1	Kaplan-Meier Plot - DOR	IP	
14.2.3.5.2	Kaplan-Meier Plot - DOR by CPS	IP	
14.2.3.5.3	Kaplan-Meier Plot - PFS	IP	X
14.2.3.5.4	Kaplan-Meier Plot - PFS by CPS	IP	X
14.2.3.5.5	Kaplan-Meier Plot - OS	IP	
14.2.3.5.6	Kaplan-Meier Plot - OS by CPS	IP	
14.3.1.1	Spider Plot – AST	IP	X

14.3.1.2	Spider Plot - ALT	IP	X
14.3.1.3	Spider Plot – Hemoglobin	IP	X
14.3.1.4	Spider Plot – Neutrophils	IP	X
14.3.1.5	Spider Plot - Platelets	IP	X
Listings			
16.2.1.1	Randomization	IP	X
16.2.1.2	Patient Disposition	IP	
16.2.1.3	Screen Failures	IP	
16.2.2.1	Protocol Deviations	IP	
16.2.3.1	Analysis Sets	IP	
16.2.4.1	Demographics	IP	X
16.2.4.2	Medical History	IP	
16.2.4.3	Surgical History	IP	
16.2.4.4	Non-Pharmacological Procedures	IP	
16.2.4.5	Cancer History	IP	X
16.2.4.6	Prior Cancer Therapy	IP	
16.2.4.7	Prior and Concomitant Medications	IP	
16.2.4.8	Tobacco History	IP	
14.3.5.1	Danvatirsen Administration	IP	X
14.3.5.2	Pembrolizumab Administration	IP	X
16.2.6.1	Target Lesions	IP	X
16.2.6.2	Non-Target Lesions	IP	X
16.2.6.3	New Lesions	IP	X
16.2.6.4	Response Assessments and BOR	IP	X
16.2.6.5	DOR	IP	X
16.2.6.6	DOR Unconfirmed	IP	
16.2.6.7	PFS	IP	X
16.2.6.8	OS	IP	
16.2.7.1	Adverse Events	IP	X
16.2.8.1	Hematology	IP	X
16.2.8.2	Chemistry	IP	
16.2.8.3	Coagulation	IP	
16.2.8.4	Urinalysis	IP	
16.2.8.5	Endocrine Hormones	IP	
16.2.8.6	Thyroid Function Test	IP	
16.2.8.7	Pregnancy Test	IP	
16.2.9.1	Vital Signs	IP	
16.2.9.2	ECG Overall Interpretation	IP	
16.2.9.3	ECG Data	IP	
16.2.9.4	Physical Exam	IP	
16.2.9.5	ECOG	IP	
16.2.9.6	Survival Status	IP	
16.2.9.7	Anti-Drug Antibodies	IP	
16.2.9.8	Tumor Tissue Collection	IP	
16.2.9.9	Systemic Anti-Cancer Therapy	IP	

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Signing reason: I approve this document
Signature Date: 2025-08-01 - 10:22:00 PM GMT - Time Source: server

Agreement completed.

2025-08-01 - 10:22:00 PM GMT

drew.denker@flamingotx.com authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2025-08-01 - 10:22:00 PM GMT