STATISTICAL ANALYSIS PLAN
Viracta Therapeutics, Inc.
VT3996-301
(NCT05166577)

Protocol Title:	An Open-Label, Multicenter Phase 1b/2 Study of Nanatinostat and Valganciclovir in Patients with Advanced Epstein-Barr Virus-Positive (EBV^+) Solid Tumors and in Combination with Pembrolizumab in Patients with Recurrent/Metastatic Nasopharyngeal Carcinoma
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STATISTICAL ANALYSIS PLAN APPROVAL

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ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CI	confidence interval
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EBV^+	Epstein-Barr Virus-Positive
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment
ET	Early Termination
FFPE	formalin-fixed paraffin-embedded
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
iRECIST	Immunologic Response Evaluation Criteria in Solid Tumors
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PD	progressive disease
PD-1	programmed cell death protein 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
Q1	1^{st} quartile (25^{th} percentile)
Q3	3^{rd} quartile (75^{th} percentile)

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
RM-NPC	recurrent/metastatic nasopharyngeal carcinoma
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SI	Système International
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
WHODDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Viracta Therapeutics, Inc. Protocol VT3996-301 (An Open-Label, Multicenter Phase 1b/2 Study of Nanatinostat and Valganciclovir in Patients with Advanced Epstein-Barr Virus-Positive [EBV^+] Solid Tumors and in Combination with Pembrolizumab in Patients with Recurrent/Metastatic Nasopharyngeal Carcinoma). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guidelines *Statistical Principles for Clinical Trials (E9)* (1998) and *Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (E9[R1])* (2021).

This SAP will be finalized prior to data analysis and before database lock to provide comprehensive details of the tables, figures, and listings to be presented in the Clinical Study Report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

2. STUDY OBJECTIVES

2.1 Primary Study Objectives

The primary objectives of this study include the following:

- Phase 1b: To determine the recommended Phase 2 dose (RP2D) of nanatinostat in combination with valganciclovir; and
- Phase 2:
    - To confirm the RP2D of nanatinostat in combination with valganciclovir;
    - To estimate the objective response rate (ORR) of nanatinostat and valganciclovir alone and in combination with pembrolizumab.

2.2 Secondary Study Objectives

The secondary objectives of this study include the following:

- To characterize the safety and tolerability of nanatinostat and valganciclovir alone and in combination with pembrolizumab;
- To characterize the pharmacokinetic (PK) properties of nanatinostat in combination with valganciclovir; and

- To evaluate additional preliminary efficacy parameters of nanatinostat and valganciclovir alone and in combination with pembrolizumab.

2.3 Exploratory Study Objective

The exploratory objectives of this study include the following:

- Evaluate potential biomarkers of activity of nanatinostat and valganciclovir alone and in combination with pembrolizumab; and

- Evaluate the safety, tolerability, PK, pharmacodynamic (PD), and antitumor activity of nanatinostat in combination with valganciclovir in patients with non-NPC EBV^+ solid tumors.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is a Phase 1b/2, open-label, multicenter study designed to evaluate the safety and preliminary efficacy of oral nanatinostat and valganciclovir alone and in combination with IV pembrolizumab in patients with EBV^+ recurrent/metastatic nasopharyngeal carcinoma (RM-NPC). The safety and tolerability of study drug treatments will be evaluated by means of adverse event (AE) reports, laboratory safety evaluations, vital sign measurements, 12-lead resting electrocardiograms (ECGs), physical examinations, and Eastern Cooperative Oncology Group (ECOG) performance status. The efficacy of study drug treatments will be evaluated for Phase 2 patients per tumor response measurements. Pharmacokinetic and pharmacodynamic assessments are also planned.

Phase 1b

A traditional 3+3 dose escalation design will be used to determine the RP2D of nanatinostat and valganciclovir; approximately 27 to 60 patients with RM-NPC will be enrolled; cohorts of 3 to 6 patients with RM-NPC will be enrolled sequentially at escalating nanatinostat doses starting with 20 mg daily on Days 1 to 4 per week (intermittent dosing) with valganciclovir 900 mg daily. Any patients in screening when the last patient is enrolled in a cohort may also be enrolled if eligible. Dose escalation of nanatinostat will continue as described below until the RP2D is identified:

- Total daily nanatinostat dose of 30 and 40 mg daily administered as a single dose on Days 1 to 4 per week with valganciclovir 900 mg once daily; or

- Divided nanatinostat dose twice daily on Days 1 to 4 per week with valganciclovir 900 mg once daily or valganciclovir 900 mg twice daily for 21 days followed by a subsequent dose reduction to 900 mg once daily; or

- Split daily dose of nanatinostat starting at 20 mg with valganciclovir 450 mg twice daily, 4 hours apart on Days 1 to 7 per week.

Because plasma EBV deoxyribonucleic acid (DNA) levels correlate closely together with the presence of disease and response to therapy in RM-NPC, these data will be considered together with safety data in the selection of the RP2D.

Phase 2

Following dose escalation, Phase 2 will begin with a dose optimization cohort to assess the safety, tolerability, PK, PD, and antitumor activity of nanatinostat and valganciclovir and to confirm its RP2D in patients with RM-NPC.

Patients will be randomly assigned 1:1 to each treatment group (up to 20 patients in each treatment group for approximately 40 patients total) during the dose optimization cohort period. The starting doses of nanatinostat for the treatment groups will be the RP2D and another dose level below the RP2D (<RP2D) plus valganciclovir 450 mg twice daily, based on the Safety Monitoring Committee's (SMC's) review of the totality of the data from the previous Phase 1b cohorts. After the nanatinostat and valganciclovir RP2D is confirmed by the SMC based on the results of the dose optimization cohorts, up to 60 patients with RM-NPC will be randomly assigned 1:1 to receive that RP2D of nanatinostat and valganciclovir with or without concomitant pembrolizumab to assess the preliminary antitumor activity, safety, and tolerability of each regimen in the Phase 2 dose expansion period. Randomization will be stratified by prior anti programmed cell death protein 1(PD-1) treatment exposure.

Pembrolizumab will be dosed at 200 mg intravenous(ly) (IV) every 3 weeks for those patients randomly assigned to the nanatinostat, valganciclovir, and pembrolizumab group. An early safety analysis will be performed after the first 6 patients are randomized to receive nanatinostat and valganciclovir in combination with pembrolizumab and have been followed for at least 2 cycles (7 weeks) of treatment as described in Section 5.5.3.3 of the clinical study protocol.

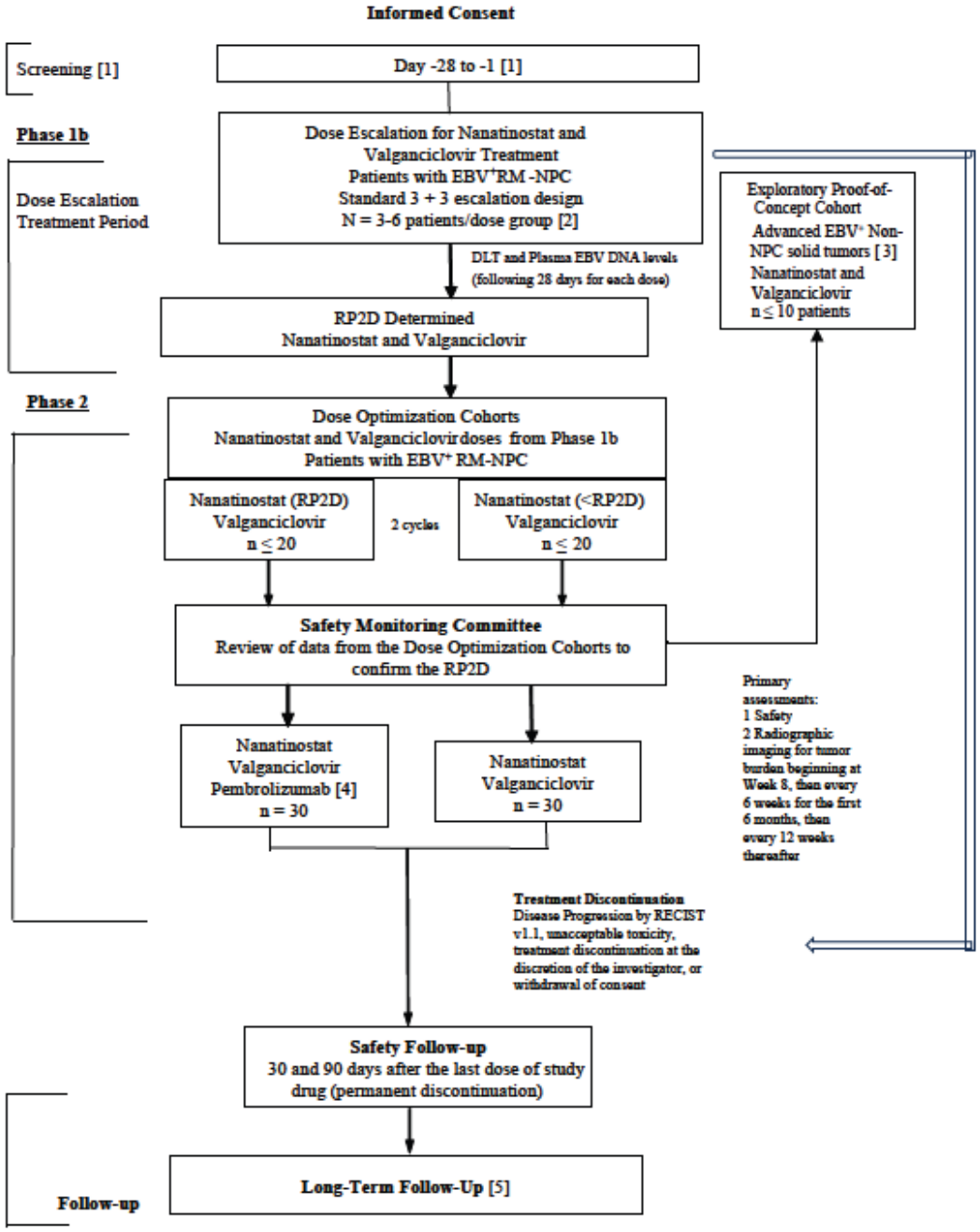
In addition, up to 10 patients with advanced EBV^+ non-NPC solid tumors (gastric cancer, lymphoepithelioma-like carcinoma, and leiomyosarcoma) will be enrolled in a Phase 1b exploratory proof-of-concept cohort to characterize the safety and PK of the nanatinostat and valganciclovir combination in other solid tumors. Enrollment in this proof-of-concept cohort will begin when the appropriate RP2D for this population is determined in consultation with the SMC, while enrollment in the proof-of-concept cohort may be stopped before 10 patients are treated if a) evidence of safety or tolerability issues arise or b) Phase 2 of the study completes enrollment.

All patients will be monitored at weekly intervals for the first 6 weeks, and then at 3-week intervals thereafter starting at Week 8. Tumor responses will be assessed at Week 8 and then every 6 weeks for the first 26 weeks (6 months) and every 12 weeks thereafter by the Investigator per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). A scan to confirm an unconfirmed partial response (PR) or unconfirmed complete response (CR) ≥4 weeks later may also be performed.

Patients will continue to receive study drug until the development of progressive disease (per Investigator assessment), unacceptable toxicity, withdrawal of consent, Investigator's discretion, initiation of new antineoplastic therapy, or study termination by the Sponsor. The maximum treatment with pembrolizumab is 24 months.

The study design is summarized in Figure 1 on the next page.

Figure 1 Study Design



CT = computed tomography; DLT = dose-limiting toxicity; EBV = Epstein-Barr virus; MRI = magnetic resonance imaging; NPC = nasopharyngeal carcinoma; RECIST v 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; RM = recurrent and/or metastatic; RP2D = recommended Phase 2 dose; SDD = split daily dose

[1] Patients must have a histologically confirmed diagnosis of EBV+ recurrent or metastatic NPC or other solid tumor type and received previous systemic therapy for their cancer; have measurable disease determined by magnetic resonance imaging (MRI) or computed tomography with contrast at screening; and have adequate bone marrow, liver, and renal function.

[2] Starting nanatinostat dose is 20 mg once daily on Days 1 to 4 per week with valganciclovir 900 mg daily. Dose escalation of nanatinostat will continue with i) a total daily dose of 30 and 40 mg daily administered as a single dose on Days 1 to 4 per week with valganciclovir 900 mg once daily, ii) as a divided nanatinostat dose twice daily on Days 1 to 4 per week with valganciclovir 900 mg once daily or twice daily for 21 days followed by a subsequent dose reduction to 900 mg once daily, then iii) as a SDD of nanatinostat starting at 20 mg and valganciclovir at 450 mg twice daily 4 hours apart on Days 1 to 7 per week until the RP2D is determined.

[3] EBV^+ non-NPC solid tumors may include gastric cancer, lymphoepithelioma-like carcinoma, and leiomyosarcoma - dosing regimen for the proof-of-concept cohorts will be determined on data collected and analyzed at or after the RP2D from Phase 1b is determined.
[4] Pembrolizumab: Standard 200 mg IV every 3 weeks.
[5] Long-term follow-up assessments include tumor evaluation and EBV DNA viral levels (for patients who discontinued treatment for reasons other than disease progression), survival assessment until lost to follow-up, death, or withdrawal of consent, and subsequent anti-neoplastic therapies.

Screening Period

At screening, the patient will provide a signed informed consent form prior to any study-related activities. Collection and shipment of a formalin-fixed paraffin-embedded (FFPE) tumor sample (archived tissue or new biopsy specimen) to the central pathology laboratory should occur as early as possible, and no later than 8 weeks following Cycle 1 Day 1. The tumor sample will be used for central confirmation of EBV status and exploratory assessments as described in Table 3 of the clinical study protocol. For tumor specimens >2 years old, the Sponsor's Medical Monitor should be consulted to discuss eligibility. Additional screening evaluations must be performed within 28 days or 21 days before treatment start (Cycle 1 Day 1) as defined in the Schedule of Events (Table 11). At the time of screening, male patients should be informed about their options to store germ cells in advance of study treatment.

Treatment Period

The treatment period will begin on Cycle 1 Day 1. Cycle 1 will be 28 days; all subsequent cycles will be 21 days. Patients will be treated until unacceptable toxicity, death, progressive disease, treatment discontinuation at the discretion of the Investigator, or withdrawal of consent (maximum treatment duration with pembrolizumab is 24 months). Patients with first evidence of progressive disease and no clinical deterioration may continue study treatment until a repeat scan within 4 to 6 weeks confirms disease progression. To account for atypical disease response to immune therapy, Investigators are encouraged to follow immune-modified Response Evaluation Criteria in Solid Tumors (iRECIST) criteria (criteria based on RECIST v 1.1 for response and progressive disease, but adapted to account for the tumor response seen with immunotherapeutic drugs as described in Appendix 3 of the clinical study protocol) for treatment decision making, including confirmation of unconfirmed progressive disease with additional imaging.

Safety Follow-Up Period

Upon discontinuation of the protocol-specified treatments, patients will enter the Follow-up period. All patients must complete a safety follow-up assessment at 30 and 90 days after receiving their last dose of study drug. All AEs for patients treated with nanatinostat, valganciclovir, and pembrolizumab and only serious AEs (SAEs) for all other patients will be collected up to and including 90 days after the last dose of study treatment or until the start of a new antineoplastic therapy, whichever occurs first. The 90-day safety follow-up assessment may coincide with the first Long-Term Follow-Up visit.

Information related to concomitant medications used to treat AEs and any anti-neoplastic therapies taken following permanent discontinuation of study treatment will be collected for 90 days after the last dose of study treatment for all patients. If a new

antineoplastic treatment is initiated before the 30-day safety evaluation, safety follow-up will occur immediately before starting the new treatment. If a patient withdraws consent after the End of Treatment (EOT) visit, but prior to the 30-day safety evaluation, safety data should be collected on the patient up to the date of consent withdrawal.

Long-Term Follow-Up Visit

All patients enrolled in the study will be followed for survival every 12 weeks (or more frequently if a survival update is required for safety or regulatory reasons) until withdrawal of consent, death, loss to follow-up, completion of 3 years of follow-up, completion of 1 year after the last patient discontinues study treatment, or the study is terminated by the Sponsor, whichever occurs first. Patients will also be followed during this period for disease progression (for those who discontinued treatment for reasons other than disease progression), overall survival, and subsequent anti-neoplastic therapies, including response.

Patients enrolled in the study who discontinue study treatment for any reason other than disease progression will have a tumor assessment every 12 weeks (±7 days), up to 1 year from the date of the last dose of study treatment, until disease progression, the initiation of subsequent anti-cancer therapies, withdrawal of consent, loss to follow up, or end of the study, whichever occurs first. Any newly started anti-neoplastic therapies should be recorded on the *Antineoplastic Therapy Since Discontinuation* electronic case report form (eCRF) page.

End of Study

The end of the study occurs when all patients have either progressed, discontinued, died, become lost to follow-up, or have maintained a complete response, partial response, or stable disease for at least 3 years, or when the trial is terminated by the Sponsor. Patients continuing to derive benefit from study treatment in the opinion of the Investigator at the end of the study may be able to continue receiving study treatment on an individual basis (e.g., by separate protocol or post-trial access plan) with Sponsor's Medical Monitor approval.

3.2 Schedule of Assessments

For the complete schedule of assessments, refer to Section 6 (Schedule of Events) in the clinical study protocol.

3.3 Treatments

3.3.1 Treatments Administered

3.3.1.1 Nanatinostat (VRx-3996)

Nanatinostat (VRx-3996) is a hydroxamic acid-based histone deacetylase inhibitor and is available as 10-mg tablets.

All patients will receive nanatinostat orally once or twice daily (at breakfast or at breakfast and lunch, respectively) on Days 1 to 4 per week (i.e., 4 days on, 3 days off),

or Days 1 to 7 per week. Following the completion of the 28-day Cycle 1, patients will continue dosing in 21-day cycles until discontinuation.

3.3.1.2 Valganciclovir

Valganciclovir is a cytomegalovirus nucleoside analogue DNA polymerase inhibitor and is available as 450-mg tablets packaged in bottles.

The daily oral dose of valganciclovir is 900 mg once daily; 900 mg twice daily for 21 days (at breakfast and dinner) followed by a subsequent dose reduction to 900 mg once daily; or 450 mg twice daily at breakfast and lunch, in combination with nanatinostat. Following the completion of the 28-day Cycle 1, patients will continue to receive the combination of nanatinostat and valganciclovir in 21-day cycles until discontinuation.

Valganciclovir doses should be adjusted for patients who develop an elevated creatinine level while on study.

3.3.1.3 Pembrolizumab

Pembrolizumab is a humanized monoclonal PD-1 inhibitor antibody (IgG4/kappa isotype with a stabilizing sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology. Pembrolizumab is available for injection in 100 mg/4 mL (25 mg/mL) in a single-dose vial.

The starting provisional dose of pembrolizumab is 200 mg IV every 3 weeks.

3.3.1.4 Sequence of Study Drug Administration

Patients will be administered study drugs on a treatment schedule determined by study phase and dose level. For a detailed description of different dosing administration schedules for each dose level, refer to Section 5.3.3 (Sequence of Study Drug Administration) of the clinical study protocol.

3.3.2 Method of Assigning Patients to Treatment Groups

Patients with EBV^+ RM-NPC will be enrolled in groups of 3 to 6 in the Phase 1b escalating nanatinostat dose cohorts to determine the RP2D of nanatinostat in combination with valganciclovir. Patients in screening when the last patient is enrolled in a cohort may also be enrolled if eligible.

For Phase 2, following determination of the RP2D, approximately 40 patients will be randomized into one of two dose optimization cohorts receiving nanatinostat at the RP2D or at the '<RP2D' and valganciclovir twice daily.

Following confirmation of the RP2D, patients with EBV^+ RM-NPC will be randomly assigned 1:1 using a centralized interactive randomization system to either nanatinostat and valganciclovir treatment or nanatinostat and valganciclovir in combination with pembrolizumab treatment in the Phase 2 dose expansion period. Randomization will be stratified by prior anti-PD-L1 treatment exposure. Pembrolizumab will be administered at 200 mg IV every 3 weeks for those patients randomly assigned to the nanatinostat, valganciclovir, and pembrolizumab arm. An early safety analysis after the first 6

patients are randomized to this treatment arm and followed for at least 2 cycles (7 weeks) of treatment will be performed.

In addition, up to 10 patients with EBV^+ non-NPC solid tumors will be enrolled into an exploratory proof-of-concept cohort. The dose and regimen will be based on data collected and analyzed from prior cohorts after an RP2D is determined in consultation with the SMC to predict the appropriate recommended dose for the non-NPC solid tumor population prior to commencing enrollment.

3.3.3 Blinding Procedures

This is an open-label study so treatment assignments will not be blinded.

3.4 Efficacy and Safety Variables

3.4.1 Efficacy Variables

3.4.1.1 Primary Efficacy Variable

Tumor responses will be assessed by the Investigator per RECIST v1.1 using MRI or CT scan assessments. For patients receiving pembrolizumab, tumor responses will also be assessed per immunologic RECIST (iRECIST). Tumor imaging will be repeated to confirm disease progression using iRECIST.

The primary efficacy endpoint is ORR, defined as the percentage of patients with a CR or PR as assessed by RECIST v1.1 within the first 26 weeks (6 months) of treatment. The ORR will also be calculated using iRECIST for patients receiving pembrolizumab.

3.4.1.2 Secondary Efficacy Variables

Secondary efficacy endpoints include the following:

- Time to response (TTR) – defined as the interval from the start of study drug treatment to the date of first documented CR or PR per RECIST or iRECIST.
- Duration of response (DOR) – defined as the interval of time from the date of first observed CR or PR to the date of documented disease progression or death due to any cause, whichever occurs first. Dates of progression and censoring will be determined as described in Section 4.5.5.2;
- Disease control rate (DCR) – defined as the percentage of patients having a CR, PR, or stable disease (SD) at any time during treatment;
- Progression-free survival (PFS) – defined as the interval of time from the start of study drug treatment to the date of first documented disease progression, initiation of new antineoplastic therapy, withdrawal of consent, loss to follow-up, or death due to any cause, whichever occurs first. Dates of progression and censoring will be determined as described in Section 4.5.5.2; and
- Overall survival (OS) – defined as the interval of time from the start of study drug treatment to the date of death due to any cause. Patients without

documentation of death at the time of analysis will be censored at the date the patient was last known to be alive.

3.4.2 Safety Variables

3.4.2.1 Adverse Events

An AE is any untoward medical event that occurs to a patient following the start of administration of the study treatment, whether or not the event is considered study drug related. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

For all patients (excluding those in Phase 2 receiving nanatinostat, valganciclovir, and pembrolizumab), AEs will be recorded from the signing of the informed consent form (ICF) up to and including 30 days (90 days for SAEs) after the last dose of study treatment or until the start of subsequent anticancer therapy, whichever occurs first. For patients in Phase 2 who receive nanatinostat, valganciclovir, and pembrolizumab, AEs will be recorded from the signing of the ICF up to and including 90 days after the last dose of study treatment or until a new anticancer treatment is started, whichever is first.

3.4.2.2 Laboratory Parameters

Laboratory tests will be collected and analyzed in central or local laboratories. Assessments include hematology, coagulation, serum chemistry, urinalysis, viral levels, and pregnancy testing (only for females of childbearing potential). Specific parameters include the following:

- Hematology: Hemoglobin, platelets, and white blood cell count with differential (absolute neutrophils, absolute monocytes, absolute eosinophils, absolute lymphocytes, absolute basophils);

- Coagulation: prothrombin time or international normalized ratio, and activated partial thromboplastin time;

- Serum Chemistry: aspartate aminotransferase, alanine aminotransferase, albumin, total bilirubin, sodium, potassium, magnesium, total protein, alkaline phosphatase, bicarbonate, blood urea nitrogen, creatinine, glucose (non-fasting), chloride, calcium, phosphate, uric acid, and thyroid function tests (Phase 2 only [thyroid-stimulating hormone, free T3, free T4])

- Urinalysis (Dipstick): pH, specific gravity, glucose, bilirubin, ketones, blood, protein, urobilinogen, nitrite/nitrate, leukocytes/leukocyte esterase; and

- Viral: Hepatitis B virus (HBV) surface antigen, HBV core and surface antibody, HBV DNA polymerase chain reaction (for patients with positive HBV core antibody or surface antigen), Hepatitis C virus (HCV) antibody (for patients with positive HCV antibody), and EBV DNA, cytomegalovirus, and human immunodeficiency virus levels (HIV), for HIV^+ patients only.

3.4.2.3 Other Safety Variables

All 12-lead ECGs will be conducted in triplicate. Triplicate 12-lead ECGs will be performed separated by approximately 1 minute at screening, on Cycle 1 Day 1 (Phase 1b, all dose levels, and Phase 2), Cycle 2 Day 1 (Phase 1b dose levels 8 through 13 and Phase 2 only) and at the EOT visit. Prior to each ECG, the patient will lie in a supine position in a calm environment for at least 5 minutes.

When performed in concert with serial PK collection on Cycle 1 Day 1 (for Phase 1b dose levels 1 through 7), two ECGs will be performed pre-dose (within 1 hour of dose, separated by at least 15 minutes). Post-dose ECGs will be performed prior to and as close as possible to each PK sample collection at approximately maximum plasma concentration (1 and 2 hours), 4 hours, and 6 hours.

When performed in concert with serial PK collection on Cycle 1 Day 1 (for Phase 1b dose levels 8 through 13 and Phase 2), two ECGs will be performed pre-dose (within 1 hour of dose, separated by at least 15 minutes) and one set of triplicate 12-lead ECGs will be performed on Cycle 1 Day 1 at 2-hours post-dose. When performed in concert with serial PK collection on Cycle 2 Day 1 for these patients, two ECGs will be performed pre-dose (within 1 hour of dose, separated by at least 15 minutes). Post-dose ECGs will be performed prior to and as close as possible to each PK sample collection at approximately maximum plasma concentration (1 and 2 hours), 3 hours, 4 hours, 5 hours, and 6 hours.

At screening and at the EOT visit, the ECG may be performed at any time during the clinic visit. ECGs may also be performed when clinically indicated, irrespective of the time of study drug dosing.

Vital signs (temperature, blood pressure, and heart rate) will be collected at the screening visit (Day -28 to Day -1), on Day 1 of each cycle, and at the EOT visit. On visit days requiring serial PK collection, vital signs will be collected just prior to the first dose of valganciclovir and nanatinostat, and in concert and just prior to PK blood draws. On other indicated visit days, vital signs will be collected once (prior to dosing of study treatment if administered in clinic).

A physical examination will be conducted at the screening visit, at the beginning of each cycle, at the EOT visit, and at any additional times deemed necessary by the Investigator. Height and weight will be measured at the screening visit and weight will be subsequently measured on Day 1 of each cycle and at the EOT visit.

The ECOG performance status will be assessed at the screening visit, on Cycle 1 Day 1, and at the EOT visit.

3.4.3 Pharmacokinetic Variables

Pharmacokinetic endpoints include observed plasma concentrations and estimated PK parameters for nanatinostat and ganciclovir, and these will be described in a separate analysis plan.

3.4.4 Pharmacodynamic Variables

Pharmacodynamic endpoints include selected biomarkers of nanatinostat and valganciclovir activity with or without pembrolizumab (e.g., plasma EBV DNA levels), and these will be described in a separate analysis plan.

3.5 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

4. STATISTICAL METHODS

4.1 General Methodology

Data will be analyzed by Emanate biostatistics personnel. Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the Electronic Common Technical Document Specification (Apr 2003).

4.1.1 Reporting Conventions

The Phase 1b and Phase 2 portions of the study will be analyzed separately. Tables and figures will be summarized by dosing regimen. In general, all data collected, and any derived data will be presented in patient data listings, for all enrolled patients. Listings will be ordered by phase, site, patient number, treatment regimen, and assessment or event date. The dosing regimen presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of patients with available data (n), mean, SD, median, first (Q1) and third (Q3) quartiles, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of patients with available data (n), number of patients in each category, and the percentage of patients in each category. Unless otherwise noted, and in order to determine the percentage of patients in each category, the denominator will be based on the number of patients with available data.

Select ordinal data may be summarized using both descriptive statistics and counts and percentages of patients in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the electronic case report form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., standard deviation, standard error) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above or assessed for the most appropriate presentation based on the underlying data.

No formal statistical analysis will be performed to compare treatment regimens. This study is exploratory in nature; descriptive statistics will be tabulated by treatment regimen and reviewed to evaluate all study endpoints.

4.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF. Data collected for the last patient visit completed will be summarized separately, and this summary will be labeled as “End of Treatment.”

Data collected at unscheduled visits will not be included in by-visit summaries but will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in patient listings.

4.1.3 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (e.g., “< 1.0”) will be summarized with the sign suppressed in summary tables and figures, using the numeric value reported. Data will display on patient listings to include the sign.

4.1.4 Baseline Value

Unless otherwise noted, the baseline value will be defined as the last value reported prior to first dose of any study drug.

4.1.5 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on patient data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose of study drug, if the assessment/event date is prior to the date of first dose; and
- The assessment/event date minus the date of first dose of study drug, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:
    - Later date – earlier date + 1, if the earlier date is on or after the date of first dose of study drug; or
    - Later date – earlier date, if the earlier date is prior to the date of first dose of study drug.
- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12).
- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25.
- **Change from Baseline:** Change from baseline will be calculated as the post baseline value minus the baseline value.
- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

4.2 Analysis Sets

The analysis sets are defined as follows:

- Safety Analysis Population: Includes all patients who receive at least one dose of study treatment (nanatinostat, valganciclovir, or pembrolizumab). The Safety Analysis Population will be used for all summaries of safety, demographic, and baseline summaries.
- Full Analysis Set: Includes all patients with measurable disease at baseline who receive at least one dose of nanatinostat and valganciclovir with or without pembrolizumab and who have at least one post-baseline tumor assessment. Patients will be analyzed according to the dosing regimen for which they have been assigned. The Full Analysis Set will be used for summaries of tumor response and survival metrics.

Modified Intent-to-Treat Population: Includes all RM-NPC patients who receive at least one dose of study treatment (nanatinostat, valganciclovir, or pembrolizumab), have a confirmed diagnosis of EBV^+ by central pathology review, met all eligibility criteria, and have baseline (screening) and at least one post-baseline tumor assessment for efficacy.

4.3 Study Patients

4.3.1 Disposition of Patients

Patient disposition will be summarized for all enrolled patients by dosing regimen and over all patients combined. Summaries will include the number and percentage of patients in each analysis set as well as the number and percentage of patients discontinuing the treatment or study by the primary reason for discontinuation.

4.3.2 Protocol Deviations

Important protocol deviations will be summarized by dosing regimen and over all patients combined for the Full Analysis Set. Important protocol deviations are protocol deviations captured on study that are deemed by the Sponsor to potentially impact the safety or efficacy conclusions of the study.

Any important protocol deviations will be determined and appropriately categorized prior to database lock. The number and percentage of patients with any important protocol deviations as well as the number and percentage of patients with deviations within each category will be presented. Corresponding patient listings will be provided.

4.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Analysis Population, Full Analysis Set, and modified Intent-to-Treat Population by dosing regimen and over all patients combined.

Demographic variables include age as collected on the eCRF, age category (<65 or $\geq$ 65 years), sex at birth, childbearing potential (if female), ethnicity, and race. Age will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the number and percentage of patients in each parameter category.

Baseline characteristics include height, weight, body mass index (BMI), medical history, ECOG performance status, primary cancer diagnosis at study entry, time since initial primary cancer diagnosis, stage of disease at study entry, histology, and number of prior systemic therapies. Body mass index will be calculated as: weight (kg) / [height (cm) / 100]^2.

Height, weight, and BMI at baseline will be summarized using descriptive statistics. ECOG performance status will be summarized with the number and percentage of patients in each category.

Medical history conditions will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 27.1).

Frequency counts and percentages to summarize patients reporting abnormal medical history by system organ class will be presented.

For primary cancer history, diagnosis when patient entered the study (RM-NPC, Not NPC [gastric cancer, lymphoepithelioma-like carcinoma, leiomyosarcoma, etc.]), stage at study entry, histology, and number of prior systemic therapies will be summarized with the number and percentage of patients in each category. The time since the date of original primary cancer diagnosis will be summarized using descriptive statistics. All other primary cancer history will be included in patient data listings.

4.5 Efficacy Evaluation

4.5.1 Datasets Analyzed

Efficacy summaries will be produced as described in Section 4.2. Efficacy summaries will be repeated for the modified Intent-to-Treat Population (if meaningfully different than the Full Analysis Set) as supportive evidence and to assess the robustness of efficacy findings. A data listing of patients excluded from the Full Analysis Set and modified Intent-to-Treat Population, to include the reason for exclusion, will be presented.

4.5.2 Measurements of Treatment Compliance

Compliance with both nanatinostat and valganciclovir will be determined as the total number of tablets taken divided by the expected number of tablets taken, multiplied by 100.

The expected number of tablets administered will be determined using the prescribed dosing information contained in Table 4 of the clinical study protocol, where nanatinostat and valganciclovir are dispensed in 10 mg and 450 mg tablets, respectively. The number of tablets expected will be calculated for each cycle and then multiplied by the number of cycles the patient completes.

The total number of tablets taken will be determined using the data recorded on the Study Drug Exposure eCRF pages for nanatinostat and valganciclovir. If a patient is administered study drug as expected (with no changes to dose administered, no interruptions, delays, or missed doses), then the Study Drug Exposure eCRFs will include a record for that cycle that indicates “No Change to Dose.” In this case, the total number of tablets taken in each cycle will be calculated as the number of days in the cycle where the doses were administered (multiplied by two if a divided dose). Missed doses are recorded on the Study Drug Exposure eCRFs as “Missed/Dosing Error.” When calculating the number of missed doses, if a patient reports “Missed/Dosing Error” on the eCRF, it will be assumed no study drug was administered on that date.

Compliance with pembrolizumab will be determined as the total number of infusions received divided by the number of expected infusions, multiplied by 100. The number of expected infusions will be determined using the dosing schedule provided in Figure 10 of the clinical study protocol. The total number of infusions received will be determined using the *Study Drug Administration Log - Pembrolizumab* eCRF.

Dosing compliance will be summarized using descriptive statistics, for each dosing regimen based on the Safety Analysis Population. The number and percentages of patients who are <80% compliant and ≥80% compliant within each dosing regimen will be summarized. Treatment compliance will also be included in a by-patient data listing.

4.5.3 Primary Efficacy Endpoint Analysis Methods

Counts and percentages for each tumor response category assessed by the Investigator per RECIST v1.1 will be presented by dosing regimen. Separate summaries will also be produced by prior anti-PD-1 treatment exposure. Non-evaluable patients are considered non-responders and will be included in the denominator. ORR estimates, from the first post-baseline assessment, with corresponding binomial 95% confidence intervals using the Clopper-Pearson Exact method will also be presented.

For patients receiving pembrolizumab, the analysis will be repeated using iRECIST.

Results from tumor assessments will be provided in separate listings.

4.5.4 Secondary Efficacy Endpoint Analysis Methods

Disease control rate will be analyzed using the same statistical methodologies as applied to the primary efficacy endpoint in Section 4.5.3.

Duration of response, PFS, and OS will be summarized in days using Kaplan-Meier methodology. The number of patients who experienced the event of interest and the number of patients censored will be presented, as will Kaplan-Meier product limit estimates of the 25th, 50th (median), and 75th percentiles with associated CIs (where estimable) using Greenwood's formula. The range for all patients, as well as those who experience the event of interest will also be summarized. Kaplan-Meier estimates of the survival distribution function over time will be generated for all patients receiving study treatment. The PFS and OS at 12 months (56 weeks) with associated 95% CIs will also be presented.

All derived efficacy measures will also be provided in a separate listing.

4.5.5 Statistical/Analytical Issues

4.5.5.1 Adjustments for Covariates

There are no planned applications of covariate adjustments; all statistical results are descriptive in nature.

4.5.5.2 Handling of Dropouts or Missing Data

Objective response rate and disease control rate are based on those patients with available data (baseline and post-baseline response assessment). Non-evaluable patients are considered non-responders and will be included in the denominator. The analysis of PFS and DOR will be right-censored according to the conventions described in Table 2. These conventions are based on the FDA Guidance for Industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (2018) and *Clinical*

Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (2015).

Table 2 Conventions for Censoring for DOR and PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization (if applicable), or enrollment	Censored
New anti-cancer treatment started before documentation of PD or death	Date of last disease assessment without documentation of PD before start of new treatment	Censored
Death or progressive disease (PD) immediately after more than one consecutively missed disease assessment visit	Date of last disease assessment visit without documentation of PD that is before the first missed visit	Censored
Alive and without PD documentation	Date of last disease assessment	Censored
Treatment discontinuation for undocumented progression, toxicity, or other reason	Date of last disease assessment without documentation of PD	Censored
Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Not Censored
Death or PD after more than one missed visit	Date of last disease assessment without documentation of PD	Censored

4.5.5.3 Interim Analyses and Data Monitoring

There are no interim analyses planned for this study.

4.5.5.4 Multicenter Studies

This is a multicenter study with 19 sites participating. Efficacy data collected from all study sites will be pooled for data analysis. The effect of study site on the efficacy analysis results may be explored post-hoc, as needed.

4.5.5.5 Multiple Comparisons/Multiplicity

There will be no adjustments for multiple comparisons in the efficacy analysis for this study. Results are descriptive in nature, and there will be no formal comparisons made between treatment groups.

4.5.5.6 Use of an "Efficacy Subset" of Patients

The primary efficacy analysis will be performed on the Full Analysis Set, and the modified Intent-to-Treat Population will be utilized for sensitivity analyses.

4.5.5.7 Active-Control Studies Intended to Show Equivalence

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

4.5.5.8 Examination of Subgroups

The primary efficacy endpoint may be summarized by various Phase 2 study patient subgroups of interest based on baseline and demographic categories including age (<65 years of age and ≥ 65 years of age), ECOG performance status at study entry (0 and 1), number of prior systemic therapies (1, 2, and 3 lines), gender, and race. Summaries by subgroup will only be produced if there are at least 6 patients in the category of interest. Additional subgroup analyses may be performed post-hoc, as appropriate.

4.5.6 Plasma Concentrations

Plasma concentration measurements will be summarized in a separate report and is outside the scope of this SAP.

4.5.7 Pharmacokinetic Analysis

Pharmacokinetic analysis will be summarized in a separate report and is outside the scope of this SAP.

4.5.8 Pharmacodynamic Analysis

Analysis of selected biomarkers (e.g., plasma EBV DNA levels) will be summarized in a separate report and is outside the scope of this SAP.

4.6 Safety Evaluation

Safety analysis will be carried out for the Safety Analysis Population. Patients who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis. Safety analysis will be summarized by dosing regimen and overall patients combined.

4.6.1 Extent of Exposure

Extent of exposure to nanatinostat, valganciclovir, and pembrolizumab will be summarized for the Safety Analysis Population by dosing regimen. The duration of exposure for each drug will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one. Duration of exposure and total dose received will be summarized using descriptive statistics. Patients with dosing interruptions greater than 14 days will be flagged in associated patient data listings.

4.6.2 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those AEs with onset after the first dose of study drug or existing events that worsened after the first dose during the study. Treatment-emergent AEs will be summarized by phase and treatment group. Events reported with a partial onset date (e.g., month and year are reported but the day

is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using MedDRA, version 27.1)

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and patient incidence of TEAEs meeting various criteria;
- Overall summary of number of unique treatment-emergent SAEs (TESAEs) and patient incidence of TESAEs meeting various criteria;
- Patient incidence of TEAEs by MedDRA system organ class and preferred term;
- Patient incidence of the most frequently occurring TEAEs (i.e., TEAEs occurring in ≥ 10% of the Safety Analysis Population) by MedDRA preferred term;
- Patient incidence of TEAEs by Common Terminology Criteria for Adverse Events (CTCAE) grade, MedDRA system organ class, and preferred term;
- Patient incidence of TEAEs by relationship to nanatinostat, MedDRA system organ class, and preferred term;
- Patient incidence of TEAEs by relationship to valganciclovir, MedDRA system organ class, and preferred term;
- Patient incidence of TEAEs by relationship to pembrolizumab, MedDRA system organ class, and preferred term;
- Patient incidence of TEAEs related to nanatinostat by CTCAE grade, MedDRA system organ class and preferred term;
- Patient incidence of TEAEs related to valganciclovir by CTCAE grade, MedDRA system organ class and preferred term;
- Patient incidence of TEAEs related to nanatinostat or valganciclovir by CTCAE grade, MedDRA system organ class and preferred term;
- Patient incidence of TEAEs related to pembrolizumab by CTCAE grade, MedDRA system organ class and preferred term;

- Patient incidence of the most frequently occurring TEAEs related to nanatinostat (i.e., related TEAEs occurring in ≥ 10% of the Safety Analysis Population) by MedDRA preferred term;

- Patient incidence of the most frequently occurring TEAEs related to valganciclovir (i.e., related TEAEs occurring in ≥ 10% of the Safety Analysis Population) by MedDRA preferred term;

- Patient incidence of the most frequently occurring TEAEs related to nanatinostat or valganciclovir (i.e., related TEAEs occurring in ≥ 10% of the Safety Analysis Population) by MedDRA preferred term;

- Patient incidence of the most frequently occurring TEAEs related to pembrolizumab (i.e., related TEAEs occurring in ≥ 10% of the Safety Analysis Population) by MedDRA preferred term;

- Patient incidence of TEAEs leading to dosing interruption of nanatinostat by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs leading to dose reduction of nanatinostat by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs leading to dosing interruption of valganciclovir by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs leading to dose reduction of valganciclovir by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs leading to dosing interruption of nanatinostat or valganciclovir by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs leading to dose reduction of nanatinostat or valganciclovir by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs leading to dosing interruption of pembrolizumab by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs leading to dose reduction of pembrolizumab by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs related to nanatinostat leading to discontinuation of study drug by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs related to valganciclovir leading to discontinuation of study drug by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs related to nanatinostat or valganciclovir leading to discontinuation of study drug by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs related to pembrolizumab leading to discontinuation of study drug by MedDRA system organ class and preferred term;
- Patient incidence of SAEs by MedDRA system organ class and preferred term;
- Patient incidence of SAEs by CTCAE grade, MedDRA system organ class and preferred term;
- Patient incidence of SARs (nanatinostat) by MedDRA system organ class and preferred term;
- Patient incidence of SARs (valganciclovir) by MedDRA system organ class and preferred term;
- Patient incidence of SARs (nanatinostat or valganciclovir) by MedDRA system organ class and preferred term;
- Patient incidence of SARs (pembrolizumab) by MedDRA system organ class and preferred term;
- Patient incidence of dose-limiting toxicities by MedDRA system organ class and preferred term;
- Patient incidence of TEAEs leading to death by MedDRA system organ class and preferred term.

Selected AE summaries may also be repeated for different age subgroups (<65 years old, ≥ 65 years old) if there are at least 5 patients enrolled in each age group.

At each level of summarization (e.g., any AE, system organ class, and preferred term), patients experiencing more than one TEAE will be counted only once. In the summary of TEAEs by severity grade, patients will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, patients will be counted once at the closest relationship to study drug. Related events include those reported as "Possibly Related" or "Definitely Related" to each study drug; events considered not related are those reported as "Not Related" to each study drug

For summaries of treatment-related TEAEs by CTCAE grade, a column summarizing patients with at least one treatment-related Grade ≥3 TEAE will also be presented.

Adverse event data will be presented in data listings by patient, treatment regimen, and event. Serious AEs and AEs leading to permanent discontinuation of the study drugs will also be presented in separate data listings.

4.6.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the post treatment follow-up period, will be listed by patient, to include the primary cause of death. Serious TEAEs and other significant AEs, including those that led to withdrawal, interruption, or dose reduction of each

study drug and those classified as CTCAE Grade 3 or higher will be provided in separate patient data listings.

4.6.4 Clinical Laboratory Evaluation

All descriptive summaries of laboratory results will be based on data analyzed by the central or local laboratory and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). All data will be included in by-patient data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by patient, laboratory test, and unit. In addition, normal ranges provided by the central laboratory will be presented in a separate listing.

Clinical laboratory measurements, including serum chemistry, hematology, and coagulation will be summarized by dosing regimen. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol.

Where applicable, laboratory results will be classified as "low," "normal," or "high" with respect to the parameter-specific reference ranges (i.e., below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-three contingency tables will be presented for each laboratory parameter to summarize the shift from the baseline category to the worst post-baseline measurement, defined as the value numerically farthest outside of the normal range across all post-baseline visits through the end of the study.

Summary results will include the count and percentage of patients within each shift category and treatment group.

The cumulative number and percentage of patients with liver function test abnormalities meeting drug-induced liver injury (DILI) criteria will be summarized by dosing regimen. Patients meeting DILI criteria will also be presented in a patient data listing.

In addition, creatinine clearance will be calculated by the Cockcroft-Gault formula. For males, the creatinine clearance in mL/min is calculated as [(140 - age) × weight (kg)] / [72 ×serum creatinine (mg/dL)]. For females, the creatinine clearance in mL/min is calculated as 0.85 × the male value. The mean change from baseline over time for creatinine and creatinine clearance will be presented graphically over time by dosing regimen and over all patients combined.

Where applicable, hematology, chemistry, and coagulation results for select parameters will be assigned a toxicity grade based on the U.S. Department of Health and Human Services *Common Terminology Criteria for Adverse Events (CTCAE)*, version 5.0 (27 Nov 2017). If the quantitative criteria for grading are equivalent for two grades and the differentiation is described by clinical interventions, the clinical intervention component will not be considered and the highest CTCAE grade will be assigned. Similarly, death related to AE (i.e., Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Laboratory parameters that include multiple sets of criteria for each direction (e.g.,

separate criteria for potassium measures to assess hyperkalemia and hypokalemia) will be summarized separately to reflect each set of criteria.

Five-by-five contingency tables will be presented for laboratory tests where toxicity grading can be applied, to summarize the shift from the baseline grade to the worst post-baseline grade. Grades will be presented as none (Grade 0; i.e., measurements did not meet any CTCAE criteria for Grades 1 through 4), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Summary results will include the count and percentage of patients within each shift category.

4.6.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

4.6.5.1 Vital Signs

Descriptive statistics for vital sign parameter measurements will be presented for results and change from baseline at each visit where parameters were scheduled to be collected.

4.6.5.2 12-Lead Electrocardiogram

Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected. All 12-lead ECGs will be conducted in triplicate. The average of the triplicate ECG interval parameters will be summarized by treatment regimen.

Twelve-lead ECGs will be classified by the investigator as “normal,” “abnormal, not clinically significant,” or “abnormal, clinically significant.” The worst classification for each set of triplicate 12-lead ECGs will be used for analysis. Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of patients within each shift category and treatment group.

Prolonged QTc intervals will be summarized as QTc measurements (msec) that are >450, >480, and >500 msec averaged over each set of triplicate 12-lead ECGs at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent a change >30 or >60 msec relative to the baseline value. Summary results will include the percentage of patients within each category and treatment group.

4.6.5.3 ECOG Performance Status

Performance status will be assessed using the ECOG scale. Descriptive statistics will be presented for observed values and changes from baseline at each visit where assessments were scheduled to be collected per the clinical study protocol. Results will be presented in patient data listings.

4.6.5.4 Prior and Concomitant Medications

Medications will be coded using the latest version of the World Health Organization Drug Dictionary Enhanced (WHODDE). Medications entered on the eCRF will be mapped to Anatomical Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Prior and concomitant medications will be summarized separately, and the categorization of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered prior to the date of the first dose of study drug with an end date prior to date of first dose of study drug. A concomitant medication is defined as any medication administered on or after the date of the first dose of study drug through 90 days after the last dose of study drugs. Any medication whose start date/time cannot be determined due to partial or missing medication start and/or end dates will be considered a concomitant medication.

For both prior and concomitant medications summaries, the number and percentage of patients receiving any medication will be summarized by cohort, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Prior medications will also be summarized over all patients combined. Patients reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. The study phase during which each medication was received (e.g., prior, concomitant, or both) will be presented on the listing of prior and concomitant medications.

4.7 Determination of Sample Size

For Phase 1b, approximately 27 to 60 patients will be enrolled for up to 13 dose escalations of nanatinostat and valganciclovir and up to 10 patients in the exploratory proof-of-concept cohort of other EBV^+ solid tumors.

Assuming the pembrolizumab ORR in RM-NPC patients in this study will be around 25%, a sample size of 30 would provide a 95% confidence interval (CI) that excludes 10% as the lower ORR. A total of 60 patients (30 per randomized treatment group) is sufficient to provide adequate estimates of tumor response for each group and to provide initial indicators of safety and tolerability. These estimates will be utilized in planning for future studies in this patient population. The sample size of N=30 per randomized treatment group was determined from nQuery Advisor tool (www.statsols.com; Statistical Solutions, Ltd, Cork, Ireland).

4.8 Changes in the Conduct of the Study or Planned Analyses

Enrollment into Study VT3996-301 was discontinued after completion of the final Phase 1b dose level for business reasons unrelated to clinical factors or safety concerns. Patients who were receiving study drugs at the time of the study discontinuation notice continued to remain on study treatment as long as they derived clinical benefit, and they were to remain on study including and up to their final Safety Follow-Up Visit. Patients who were in the Long-Term Follow-Up period transitioned to End of Study. Reporting of serious adverse events continued per clinical study protocol Section 8.2.1.

Consequently, study conduct did not proceed to Phase 2 after the recommended Phase 2 dose of nanatinostat and valganciclovir was determined, and thus the Phase 2 study-specific analyses described in this SAP will not be performed. The study will be considered complete when all patients have completed safety follow-up assessments.

The only changes to the study conduct or planned analyses identified within the development of this SAP relative to the descriptions provided within the clinical study protocol are described below:

- Section 2 of the clinical study protocol only specified ORR as a primary efficacy endpoint for Phase 2, while ORR was added as a primary efficacy endpoint for Phase 1b in this SAP.

- Section 9.1 of the clinical study protocol states that all data will be summarized by dosing regimen, disease subtype, and overall, but data summaries by disease subtype are unnecessary since Phase 1b only enrolled patients with RM-NPC, and the study did not proceed to Phase 2.

5. REFERENCE LIST

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) (US). Guidance for industry: *Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics*. April 2015. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-non-small-cell-lung-cancer-drugs-and-biologics

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ICH guideline *Statistical Principles for Clinical Trials (E9)* (1998) and *Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (E9[R1], Rev 1)* (2021).

ICH in Appendix 7 of the *Electronic Common Technical Document Specification (Apr 2003)*

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