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

Protocol Number:	VT3996-301 (NCT05166577)
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Investigational Drugs:	Nanatinostat, VRx-3996 Valganciclovir Pembrolizumab
Short Title:	Nanatinostat and Valganciclovir in EBV$^+$ Solid Tumors
Regulatory Agency Identifying Number(s):	IND Number 154400
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Amendment 3:	Version 4.0; 22 Sep 2023

This study will be conducted according to the principles of Good Clinical Practice as described in International Council for Harmonisation guidelines, including the archiving of essential documents.

SPONSOR'S PROTOCOL SIGNATURE PAGE

By signing below, the Sponsor declares that this study will be conducted in accordance with current International Council for Harmonisation (ICH) Guidelines, Good Clinical Practice (GCP) standards, the Declaration of Helsinki, and local ethical and legal requirements.

This protocol has been reviewed and approved by:

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25 SEPTEMBER 2023
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25 SEPTEMBER 2023
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INVESTIGATOR'S AGREEMENT

By signing below, the Investigator agrees to adhere to the protocol as written and agrees that any changes to the protocol must be approved by Viracta Therapeutics, Inc. before seeking approval from the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC).

The study will be conducted in accordance with the current International Council for Harmonisation (ICH) Guidelines, the Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, national and local ethical and legal requirements.

The information contained in this protocol is proprietary and provided to the Investigator in confidence, and may not be disclosed to any other party, in any form, without prior authorization from Viracta Therapeutics, except to the extent necessary for the conduct of the study at this investigational site.

Printed Name of Investigator

Signature of Investigator

Date

Institution

PROTOCOL SYNOPSIS

Protocol Number	VT3996-301
Study 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
Sponsor	Viracta Therapeutics, Inc.
Investigational Drugs	Nanatinostat (VRx-3996) Valganciclovir Pembrolizumab
Study Phase	Phase 1b/2
Primary objectives	**Phase 1b**: • To determine the recommended Phase 2 dose (RP2D) of nanatinostat in combination with valganciclovir **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
Secondary objectives	• 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 • To evaluate additional preliminary efficacy parameters of nanatinostat and valganciclovir alone and in combination with pembrolizumab
Exploratory objectives	• To evaluate potential biomarkers of activity of nanatinostat and valganciclovir with or without pembrolizumab • To evaluate the safety, tolerability, PK, pharmacodynamics, and antitumor activity of nanatinostat in combination with valganciclovir in patients with non-nasopharyngeal (NPC) EBV^+ solid tumors
Primary endpoints	**Phase 1b:** • Incidence of dose-limiting toxicities (DLTs) during the DLT evaluation period **Phase 2:** • Incidence of DLTs plus other safety parameters, tolerability, PK, and plasma EBV DNA concentrations at the RP2D and <RP2D of nanatinostat in combination with valganciclovir • ORR - defined as the percentage of patients with a complete response (CR) or partial response (PR) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (v1.1)
Secondary endpoints	• Incidence and severity of treatment-emergent adverse events per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 • PK parameters (eg, time to maximum plasma concentration, maximum plasma concentration, and area under the plasma concentration-time curve) of nanatinostat, its metabolites, and ganciclovir (primary active hydrolytic product of valganciclovir) • Duration of response (DOR) - defined as the interval from date of first observed CR or PR to the date of documented disease progression or death due to any cause, whichever occurs first

	• Disease control rate (DCR)- defined as the percentage of patients having a CR, PR, or stable disease at any time during treatment • Progression-free survival (PFS) - defined as the interval from the start of study drug treatment to the date of first documented disease progression or death from any cause, whichever occurs first • Overall survival (OS) - defined as the interval of time from the start of study drug treatment to date of death for any reason
Exploratory endpoints	• Plasma Epstein-Barr virus (EBV) DNA levels (real-time quantitative polymerase chain reaction [PCR]) • Expression of EBV gene products (ie, lytic cycle antigens) in both pre-study and during study tumor biopsies • Programmed cell death-ligand 1 expression on tumor cells and tumor-infiltrating immune cells • Histone H3 acetylation • Incidence of DLTs plus other safety parameters, tolerability, PK, and plasma EBV DNA concentrations of nanatinostat in combination with valganciclovir in non-NPC solid tumors
Study Design	Phase 1b/2, open-label, multicenter study. **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 recurrent and/or metastatic nasopharyngeal carcinoma (RM-NPC) will be enrolled; cohorts of 3 to 6 patients with RM-NPC will be enrolled sequentially at escalating nanatinostat doses starting with a 20 mg once daily dose on Days 1 to 4 per week (intermittent dosing) with valganciclovir 900 mg daily. Dose escalation of nanatinostat will continue with i) a total daily dose of 30 and 40 mg 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 split daily dose (SDD) of nanatinostat starting at 20 mg and valganciclovir at 450 mg twice daily 4 hours apart on Days 1 to 7 per week (continuous daily dosing) until the RP2D is determined. **Phase 2**: Phase 2 will begin with a randomized dose optimization lead-in cohort to assess the safety, PK, pharmacodynamics, and antitumor activity of nanatinostat and valganciclovir and 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’) together with valganciclovir 450 mg twice daily based on the Safety Monitoring Committee’s (SMC) review of the totality of data from the previous Phase 1b cohorts. After the nanatinostat and valganciclovir RP2D has been confirmed by the SMC based on the results of the dose optimization cohort, up to 60 patients with RM-NPC will be randomly assigned 1:1 to receive nanatinostat and valganciclovir at that RP2D with or without pembrolizumab (n = 30 per cohort) 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 1 (PD-1) treatment exposure. Pembrolizumab will be administered at 200 mg intravenously every 3 weeks for those patients randomly assigned to the nanatinostat, valganciclovir, and pembrolizumab group. An early safety analysis after the first 6 patients randomized to this treatment group and followed for at least 2 cycles (7 weeks) will be performed.

	In addition, up to 10 patients with advanced EBV$^+$ non-nasopharyngeal carcinoma (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 this 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. 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 RECIST v1.1. A scan to confirm an unconfirmed PR or unconfirmed CR ≥4 weeks later may also be performed. Patients will continue to receive study treatment 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 (maximum treatment duration of pembrolizumab is 24 months). Upon discontinuation of the protocol-specified treatments, patients will enter the Follow-up period. All patients must complete safety follow-up assessments at 30 and 90 days after receiving their last dose of study treatment (permanent discontinuation). All AEs for patients treated with nanatinostat, valganciclovir, and pembrolizumab and only serious adverse events (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. All patients enrolled in the study will be followed for survival.
Population	**Phase 1b**: Patients with EBV$^+$ RM-NPC and EBV$^+$ non-NPC solid tumors (exploratory proof-of-concept cohort only) **Phase 2**: Patients with EBV$^+$ RM-NPC
Inclusion Criteria	1. Adult patients age ≥18 years. 2. Willing and able to give informed consent. 3. Histologically or cytologically documented EBV$^+$ tumor cells by Epstein-Barr virus encoded RNA – in situ hybridization (EBER-ISH) or latent membrane protein (LMP) -1 (according to local guidelines) per an archival tumor sample taken within 2 years prior to screening otherwise a de novo biopsy may be required. Formalin fixed, paraffin embedded (FFPE) tissue block(s) or at least 10 unstained slides are requested. It is encouraged (but not required) that patients with a site of disease accessible to biopsy and who are candidates for tumor biopsy according to local practice guidelines undergo a new tumor biopsy at baseline and during treatment. 4. Patients with recurrent or metastatic nasopharyngeal carcinoma (RM-NPC) (excluding patients in the Phase 1b exploratory proof-of-concept cohort) for whom no potentially curative options are available, who have received at least 1 prior line of platinum-based chemotherapy, and no more than 3 prior lines of therapy for RM-NPC. Note: The following clinical scenarios are not considered to be separate lines of therapy: a. Maintenance therapy: drug therapy (including chemotherapy, targeted therapy, or immunotherapy including vaccines, cellular therapy, and checkpoint inhibitors) that is started with maintenance intent in patients who have recently completed one line of chemotherapy without experiencing disease progression b. Drug rechallenge: patients who have been "rechallenged" with the same drug therapy(s) previously used to treat recurrent or metastatic NPC. 5. Patients who developed recurrent or metastatic disease within six months following radical concurrent chemoradiotherapy in combination with neoadjuvant and/or adjuvant therapy for non-metastatic NPC are eligible as long as no potentially curative options are available.

	6. **For Phase 1b exploratory proof-of-concept cohort only:** Patients with advanced/metastatic EBV$^+$ non-NPC solid tumors (gastric cancer, lymphoepithelioma-like carcinoma, leiomyosarcoma) that have progressed despite standard therapy for which no effective therapies exist. 7. Radiologically measurable disease per RECIST v1.1. 8. All acute toxic effects of any prior anti-neoplastic therapy resolved to at least Grade 1 before initiation of study treatment (excluding alopecia, and Grade 2 sensory neuropathy, hypothyroidism [stable on thyroid hormone supplementation], chronic/stable xerostomia, hearing loss, lymphedema, and taste changes [all Grade 2]). 9. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. 10. Life expectancy ≥3 months. 11. Adequate laboratory parameters (in the absence of transfusion or growth factor support within 3 weeks of Screening) including: a. Absolute neutrophil count (ANC) ≥1500/mm^3. b. Platelet (PLT) count ≥100,000/mm^3. c. Hemoglobin ≥9.0 g/dL. d. Aspartate aminotransferase (AST)/serum glutamine oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic- pyruvic transaminase (SGPT) ≤2.5 × upper limit of normal (ULN) (≤5 × ULN if known liver involvement by tumor). e. Total bilirubin ≤2.0 × ULN unless considered due to Gilbert's syndrome in which case, ≤3.5 × ULN. f. Estimated glomerular filtration (eGFR) rate ≥60 mL/min by Cockcroft-Gault equation (see Section 5.6.2 for formula to calculate creatinine clearance). g. Prothrombin time (PT) or international normalized ratio (INR) ≤1.5 × ULN. h. Serum potassium and magnesium should be within normal limits for institution or treatment to correct out of range values should be instituted. 12. For human immunodeficiency virus (HIV) positive patients: a. CD4 count ≥350 cells/μL. b. On an established antiretroviral therapy (ART) for ≥4 weeks. c. An undetectable HIV viral load. d. No prior acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections within the past 12 months. 13. Willingness to comply with study requirements. 14. Women of childbearing potential (ie, reached menarche, and not post-menopausal [no menses for 12 months without an alternative medical cause] or surgically sterile) must have the following: a. Understand that the study medication is expected to have teratogenic risk. b. Have a negative serum beta human-chorionic gonadotropin (β-hCG) pregnancy test at screening. c. Commit to continued abstinence from heterosexual intercourse (excluding periodic abstinence or the withdrawal method) or commit to the use of 2 forms of birth control with at least one highly effective method of birth control with a Pearl-Index <1%, and one effective barrier method such as a male condom, female condom, cervical cap, diaphragm, or contraceptive sponge with spermicide, without interruption, throughout the study dosing period and for 6 months after the last dose of study treatment. Apart from abstinence, highly effective methods of birth control include the following: i. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (ie, intravaginal, transdermal). Please note: Although the potential for drug interactions and risk of venous

	thromboembolism is low (see Section 5.7.2.3), the use of an alternative method of contraception is recommended. ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable). iii. Intrauterine device (IUD). iv. Intrauterine hormone-releasing system (IUS). v. Bilateral tubal occlusion. vi. Vasectomized partner. 15. Male patients must agree to use condoms during intercourse throughout the study dosing period and for 90 days after the last dose of study treatment.
Exclusion Criteria	1. Anti-tumor treatment with cytotoxic drugs, biologic therapy (eg, monoclonal antibody), immunotherapy or other investigational drugs within 4 weeks or >5 half-lives, whichever is shorter. 2. Corticosteroids within 7 days prior to dosing (unless ≤10 mg/day of prednisone or equivalent). 3. **For NPC:** a. Active parenchymal or leptomeningeal metastases. b. Base of skull disease that poses a risk of significant bleeding (eg, proximity to carotid artery) as judged by the Investigator. c. Invasive disease for which there is a potential risk of significant bleeding as judged by the Investigator. 4. **For non-NPC cancers:** Active central nervous system disease (CNS)/metastases. 5. Nasopharyngeal cancer patients who have received prior therapy with an anti-PD-1 agent are not excluded, except for those who experienced prior Grade 3 or higher immune-related toxicity that resulted in permanent drug discontinuation (patients with prior temporary drug interruptions due to endocrinopathies etc. are eligible). 6. Less than 14 days from prior locoregional radiotherapy. Palliative radiotherapy outside the head and neck is allowed as long as the lesions are not target lesions. 7. Tumor mutational burden (TMB) -high advanced malignancies and/or microsatellite instability (MSI) -high malignancies who would otherwise be eligible for pembrolizumab (unless patients have progressed on pembrolizumab) in accordance with local standards (ie, only if such biomarkers are performed as standard of care in the participating center). 8. Major surgery, open biopsy, or significant traumatic injury within 28 days prior to starting study treatment. In case of recent major surgery, the patient must have recovered adequately from the procedure and/or any complications prior to starting study treatment. 9. Is currently participating in or has participated in an interventional study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. Note: Individuals who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent. 10. Diagnosis of any other malignancy within 3 years prior to enrollment, except for the following if adequately treated: • local basal cell or squamous cell carcinoma of the skin, or related localized non-melanoma skin cancer. • carcinoma in situ of the breast or of the cervix. • superficial bladder cancer. • Low grade (Gleason 6 or below) prostate cancer undergoing surveillance with no plans for treatment intervention or previously fully resected.

	11. Gastrointestinal abnormalities including the following: • Inability to take oral medication. • Malabsorption syndrome or any other gastrointestinal condition (nausea, diarrhea, vomiting) that may impact the absorption of nanatinostat and valganciclovir. • Prior surgical procedures affecting absorption including total gastric resection. • Active gastrointestinal bleeding (hematemesis, hematochezia, or melena) in the past 3 months without documentation of resolution by endoscopy/colonoscopy. 12. Positive surface antigen unless quantitative DNA PCR is undetectable, and patient is stable on antiviral prophylaxis against hepatitis B virus (HBV) reactivation. Patients who are hepatitis B core antibody positive must have undetectable quantitative DNA PCR and be monitored according to the local standard-of-care/institutional guidelines. 13. Positive hepatitis C virus (HCV) on RNA PCR. 14. Known SARS-CoV-2 positivity at time of screening (patients can be re-screened once negative by PCR). 15. History of allergic reactions attributed to compounds of similar chemical or biologic composition to valganciclovir or nanatinostat. 16. Active infection requiring systemic therapy. 17. Prolongation of corrected QT interval using Fridericia's formula (QTcF) to >480 msec, requires the coadministration of drugs known to prolong QT (Class Ia [disopyramide, quinidine, procainamide] and Class III [sotalol, dofetilide, ibutilide] antiarrhythmic agents) (Drew 2010), and/or has a history of Torsades de Pointes (TdP). 18. Receiving potentially nephrotoxic drugs (eg, cyclosporin) 19. Receiving concomitant drugs that are inhibitors of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) , unless they can be held for 2 weeks or 5 half-lives, whichever is longer, prior to administration of nanatinostat. See Appendix 1, Table 2 for a list of drugs. 20. Receiving tenofovir (unless can be switched to an alternative ART). 21. Psychiatric illness/social situations/substance abuse disorder that would interfere with compliance with study requirements. 22. Active autoimmune disease that has required systemic therapy with modifying agents, corticosteroids, or immunosuppressive agents. 23. Prior or ongoing clinically significant illness, medical condition, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the Investigator's opinion, could affect the safety of the patient, impair the assessment of study results, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate. 24. Females who are pregnant or breastfeeding or expecting to conceive children within the projected duration of the study, starting with the screening visit through 6 months after the last dose of study treatment.
Sample Size, Location	**Sample size**: up to a maximum of 170 patients For Phase 1b, approximately 27 to 60 patients total will be enrolled during the dose escalation period. An additional 100 patients may be enrolled in Phase 2; up to 40 patients will be enrolled during the dose optimization cohort period and up to 60 patients in the dose expansion period with or without pembrolizumab. Up to an additional 10 patients total will be enrolled in the exploratory proof-of-concept cohort of other EBV^+ solid tumors. The reported ORR for PD-1 inhibitors in RM-NPC patients has ranged from 20% to 30%. Assuming that the pembrolizumab ORR for RM-NPC patients in this study will be around 25%, a sample size of 30 patients would provide a 95% 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 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 using the nQuery Advisor tool (www.statsols.com; Statistical Solutions, Ltd, Cork, Ireland). **Location**: Global
Study Treatments, Dose, Route of Administration, Treatment Regimen	Nanatinostat (VRx-3996) oral – Starting dose: 20 mg once daily on Days 1 to 4 per week; Dose escalation: up to a total daily dose of 40 mg (Days 1 to 4 per week), then from 40 mg to 80 mg as a SDD twice daily 4 hours apart (Days 1 to 7) (RP2D to be determined during the study) Valganciclovir 900 mg oral once daily or twice daily for 21 days followed by a subsequent dose reduction to 900 mg once daily when administered with nanatinostat on Days 1 to 4 per week (intermittent dosing) and 450 mg twice daily when administered with nanatinostat on Days 1 to 7 per week (split daily dosing). (RP2D to be determined during the study) Pembrolizumab 200 mg IV every 3 weeks (See Section 3, Study Design for additional details on dosing regimens to be evaluated) For Phase 2 dose expansion, pembrolizumab will be administered initially 7 days after the start of nanatinostat and valganciclovir, and thereafter every 3 weeks. (Dosing schemas are provided in Section 5.3.3). **Dosing Cycles**: Cycle 1: 28 days. Cycles 2+: 21 days.
Efficacy Assessment(s)	**ORR**: defined as the percentage of patients with a CR or PR within the first 26 weeks (6 months) of treatment as assessed by the Investigator using RECIST v1.1. ORR will be summarized by dosing regimen with 95% confidence interval (CI) obtained by Clopper-Pearson Exact methods and stratified by prior anti-PD-1 treatment exposure. **DOR**: defined as the interval from date of first observed CR or PR to the date of documented disease progression, or death due to any cause, whichever occurs first. All patients who have not progressed will be censored at the last non-missing tumor assessment. Estimates of median DOR with 95% CI will be determined by dosing regimen using Kaplan-Meier methods. **DCR**: defined as the percentage of patients having a CR, PR, or stable disease at any time during treatment, as assessed by the Investigator using RECIST v1.1. DCR will be summarized by dosing regimen with 95% CI obtained by Clopper-Pearson Exact methods. **PFS**: defined as the interval from the start of study drug treatment to the date of first documented disease progression or death from any cause, whichever occurs first. Responding patients and patients who are lost to follow-up will be censored at their last tumor assessment date. Estimates of median PFS with 95% CI will be determined by dosing regimen using Kaplan-Meier methods. The 95% CI around the PFS and OS rates at 12 months (56 weeks) will also be presented. **OS**: defined as the interval from the start of study drug treatment to date of death for any reason. Surviving patients and patients who are lost to follow-up will be censored at their contact date. Estimates of median OS with 95% CI will be determined by dosing regimen using Kaplan-Meier methods.
Safety Assessment(s)	The safety and tolerability of study drug treatments will be evaluated by means of adverse event (AE) reports (number and severity); dose holds, modifications, or discontinuations; laboratory safety evaluations; vital sign measurements; 12 lead resting ECGs; physical examinations; and ECOG performance status. Laboratory and AE toxicities will be graded according to NCI CTCAE v5.0.
Pharmacokinetics	• PK sampling for nanatinostat and its metabolites • PK sampling for ganciclovir (primary active hydrolytic product of valganciclovir)
Biomarker Assessments	The exploratory biomarker analyses outlined in this study are intended to foster an understanding of how baseline expression of certain pharmacodynamic markers may impact the activity of combination therapy with nanatinostat, valganciclovir and pembrolizumab, and how pharmacodynamic markers, such as plasma EBV DNA levels, may correlate with

	clinical efficacy. Potential predictive markers will be studied to identify patients with optimal responses to nanatinostat and valganciclovir. The impact of study drug administration on B-cell/T-cell/NK cell/myeloid cell populations will be evaluated over time.
Statistical Methods and Data Analysis	**Safety Analysis**: The safety analysis population will include all patients who received at least one dose of any study drug. Safety analysis will be based on all patients in the Safety population and will be summarized overall, by dosing regimen, and by any other relevant subgroup (eg, solid tumor type). AEs will be summarized using System Organ Class and Preferred Term. Tabulations and listings of values for laboratory safety evaluations, vital signs, and ECGs, will be presented. Any abnormal or out-of-range values from laboratory safety evaluations or physical examinations will be presented in data listings. **Efficacy Analysis**: The Full Analysis Set population will consist of 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 to which they have been assigned. The full analysis set will be used for summaries of tumor response and survival metrics. The modified Intent-to-Treat (mITT) population is defined as all RM-NPC patients who have received at least one dose of study treatment (nanatinostat, valganciclovir, or pembrolizumab), have a confirmed diagnosis of EBV^+ by central pathology review, met all inclusion criteria, and have baseline (screening) and at least one post-baseline tumor assessment for efficacy. The number and percentage of patients with each response and overall (CR and PR) will be presented for each time point for the Full Analysis Set population with Clopper-Pearson Exact 95% CIs. The results from this study will be presented using descriptive statistical methods. Kaplan-Meier statistics will be used to display DOR, PFS and OS; Clopper-Pearson Exact methods will be used to display DCR.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
AE	adverse event
Ag	antigen
AIDS	acquired immunodeficiency syndrome
AITL	angioimmunoblastic T-cell lymphoma
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BUN	blood urea nitrogen
CBC	complete blood count
CMV	cytomegalovirus
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRT	chemoradiation therapy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP, CYP450	cytochrome P450
DCR	disease control rate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
EBER	Epstein-Barr virus-encoded RNA
EBER-ISH	Epstein-Barr virus encoded RNA – in situ hybridization
EBV	Epstein-Barr virus
EBV^+	Epstein-Barr virus positive
EBV-CTL	Epstein-Barr virus-specific cytotoxic T lymphocyte
EBV-PK	Epstein-Barr virus-encoded protein kinase
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Abbreviation	Definition
ENKTL	Extranodal NK/T-cell lymphoma
EOT	End of Treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
G-CSF	granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage-colony stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HDAC	histone deacetylase
IA-LPD	immunodeficiency-associated lymphoproliferative disorders
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
iCPD	immune confirmed progressive disease
iCR	immune complete response
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
iPR	immune partial response
IR	immediate-release
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune-modified Response Evaluation Criteria in Solid Tumors
iSD	immune stable disease
iUPD	immune unconfirmed progressive disease
IV	intravenous(ly)
LELC	lymphoepithelioma-like carcinoma
LMP	latent membrane protein
MDR1	multidrug resistance 1
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer
NPC	nasopharyngeal carcinoma
NSAID	non-steroidal anti-inflammatory drug

Abbreviation	Definition
NSCLC	non-small cell lung cancer
NTL	nontarget lesion
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD-1	programmed cell death-1
PD	progressive disease
PD-L1	programmed cell death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PLELC	pulmonary lymphoepithelioma-like carcinoma
PR	partial response
PT	prothrombin time
PTCL-NOS	peripheral T-cell lymphoma not otherwise specified
qPCR	quantitative polymerase chain reaction
QTcF	corrected QT interval using Fridericia's method
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RM-NPC	recurrent and/or metastatic nasopharyngeal carcinoma
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SDD	split daily dose
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SJS	Stevens-Johnson Syndrome
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
$t_{1/2}$	terminal elimination half-life
TdP	Torsades de Pointes
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TIL	tumor-infiltrating lymphocyte
TL	target lesion
t_{max}	time to maximum plasma concentration
TMB	tumor mutational burden
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cells
WHO	World Health Organization

1. INTRODUCTION

1.1. EBV and Cancer

Epstein-Barr virus (EBV), a member of the γ-herpesvirus family, was the first virus directly implicated in the development of a human tumor (Epstein 1964) and is formally classified as a carcinogenic agent by the World Health Organization (WHO). Primary infection with EBV typically occurs in childhood and is generally asymptomatic; however, infection later in life may manifest as infectious mononucleosis (Thompson 2004). Once infected, individuals remain lifelong carriers of the virus, with >90% of the world's population asymptomatically infected with EBV.

Latent infection and intermittent reactivation are 2 important characteristics of the EBV lifecycle. The maintenance of latent EBV infection requires the expression of a small subset of genes. Specific expression patterns (Types I – III) of these genes are associated with specific EBV-driven malignancies (Saha 2011). EBV is associated with a wide spectrum of lymphoid malignancies, including B-cell, T/natural killer (NK)-cell and Hodgkin lymphomas, and solid tumors such as nasopharyngeal carcinoma (NPC), gastric cancer (and other lymphoepithelioma-like cancers [LELCs] involving the lung and other organs), and leiomyosarcomas (Li 2018, Neparidze 2014).

1.2. Overview of EBV-positive (EBV$^+$) Solid Tumors and Current Treatments

1.2.1. EBV$^+$ Nasopharyngeal Carcinoma

NPC is one of the most commonly reported cancers of the head and neck worldwide. While it is prevalent in Southeast Asian countries and in native populations of the Artic region, North Africa, and the Middle East, with incidence rates of 15 to 50 per 100,000 in southern China and East Malaysia (Du 2020, Hutajulu 2014), NPC represents a rare disease in the Western countries (such as Europe and USA), Latin America and Japan, affecting less than 1 in 100,000 people (Perri 2019, Carioli 2017). Using the Global Cancer Observatory database, 129,079 new cases of NPC and 72,987 NPC-related deaths globally were estimated in 2018 (Bray 2018). The WHO has categorized NPC into 3 histopathologic subtypes: keratinizing squamous cell carcinoma (WHO type I), with varying degrees of differentiation; nonkeratinizing squamous cell carcinoma (WHO type II), retaining epithelial cell shape and growth pattern; and undifferentiated carcinoma (WHO type III), which does not produce keratin and lacks a distinctive growth pattern (Hutajulu 2014). Contributors to the etiology of NPC include genetic background (one-third of patients harbor major histocompatibility complex [MHC] class I gene aberrations), environmental factors such as diet (salt preserved fish), tobacco, alcohol consumption, and EBV infection. Males are 2 to 3 times more likely to develop NPC than females. The peak age of incidence is between 50 and 60 years. Non-keratinizing NPC is consistently associated with EBV and accounts for the majority of NPC cases in endemic areas (Wu 2018).

The main prognostic factor affecting the overall survival (OS) of NPC is the stage of the disease at presentation (Sun 2014), with 5-year OS rates for Stage 1 disease reported at 95% compared with 60% for Stage 4 disease (Li 2014). Because NPC is frequently asymptomatic, most patients (80%) present with advanced stage disease at diagnosis (Li 2014).

Circulating cancer-derived EBV DNA is a well-established tumor marker for NPC, with a sensitivity of 96% and a specificity of 93% (Leung 2014, Lo 1999). Plasma EBV DNA is detected in >95% of patients with advanced stage disease and is recognized as an independent prognostic biomarker in NPC (Lo 2000a, Ma 2018, Kim 2017), with high pre-treatment levels of EBV DNA correlating with a high risk of disease recurrence and distant metastasis (Chan 2002, Lo 2000b). In addition, patients with detectable plasma EBV DNA following chemoradiotherapy are at high risk of locoregional treatment failure (Chan 2018).

EBV is considered the primary etiologic agent in the pathogenesis of NPC; both EBV DNA and EBV gene expression are detected in precursor lesions and tumor cells (Raab-Traub 2002). NPC cells express a type II latency pattern in which Epstein-Barr virus-encoded RNA 1/2 (EBER1/2), Epstein-Barr nuclear antigen 1 (EBNA1), and 2 integral membrane proteins, latent membrane protein (LMP)-1 and LMP-2, along with the BamHI-A fragment of the EBV genome are expressed (Tsao 2015). The diagnosis of EBV^+ NPC is based on histologic examination and Epstein-Barr virus encoded RNA – in situ hybridization (EBER-ISH) or immunohistochemical staining for LMP (National Comprehensive Cancer Network [NCCN] Guidelines, Head and Neck Cancers 2021).

EBV-associated NPC typically presents with an enhanced degree of lymphocyte infiltration and overexpression of programmed cell death-ligand 1 (PD-L1) (Zhang 2015), which initiated the clinical treatment evaluation of various checkpoint inhibitors in early phase clinical trials for recurrent and/or metastatic nasopharyngeal cancer (RM-NPC), with objective response rates (ORRs) reported in the range of 20% to 30% (Wang 2021, Ma 2018, Hsu 2017).

The standard first-line treatment for NPC is radiotherapy for early-stage disease and chemoradiotherapy for more advanced disease (including cisplatin plus gemcitabine induction therapy for patients with high risk, locally advanced or metastatic disease) (Zhang 2019, Neparidze 2014). Neoadjuvant chemotherapy is sometimes used to down-stage locally advanced NPCs for radiotherapy. Although response rates to concurrent chemoradiotherapy with cisplatin-based regimens are high and result in 5-year OS rates of approximately 85% (Yang 2015), disease subsequently relapses locally or more commonly with distant metastases in 30% to 40% of patients. No standard treatment options exist for second or later lines of therapy; treatment options are based on the general status of the patient and prior therapies received. The preferred initial regimen for patients with prior chemoradiation therapy (CRT) is gemcitabine/cisplatin, with a reported median progression-free survival (PFS) of 7.0 months (Zhang 2016). Single-agent options for RM-NPC include capecitabine, paclitaxel, docetaxel, and carboplatin (NCCN Guidelines, Head and Neck Cancers 2021). In addition, many patients in communities without access to chemotherapy in advanced medical facilities could benefit by alternative safe and effective treatment options that improve disease-free survival.

As EBV is present in virtually all poorly differentiated and undifferentiated NPC, targeting EBV may be a potential therapeutic option (Chow 2019, Hong 2018). Various EBV-targeted treatment approaches have been evaluated in patients with recurrent or metastatic NPC, including inducing EBV lytic activation with gemcitabine and valproic acid followed by treatment with ganciclovir, an antiviral drug (Wildeman 2012), and adoptive transfer of EBV-specific cytotoxic T lymphocytes (EBV-CTLs) (Huang 2017, Louis 2010, Comoli 2005), with some clinical responses reported. For EBV-CTL therapy, modest clinical response rates of 10% to 20% were

observed in a limited number of patients with metastatic disease reporting a median PFS in the range of 2 to 3 months (Huang 2017, Louis 2010).

Because PD-L1 is highly expressed by NPC cells and a correlation exists between tumor PD-L1 expression with shorter OS, recurrence-free survival, and treatment failure (Hsu 2010), anti-programmed cell death-1 (PD-1) antibodies have been evaluated for the treatment of patients with RM-NPC. An ORR of 25.9% with a median PFS of 6.5 months was reported in a Phase 1b/2 trial (Keynote-028) in 27 patients with relapsed or metastatic PD-L1$^+$ NPC treated with pembrolizumab (Hsu 2017). A Phase 2 trial evaluating nivolumab in 45 patients with RM-NPC who were not selected for PD-L1 expression reported an ORR of 20.5% (median PFS 2.8 months) (Ma 2018). More recently, an ORR of 20.5% with a median duration of response (DOR) of 12.8 months (median PFS of 1.9 months) was reported for a Phase 2 study of toripalimab, a humanized IgG4 monoclonal antibody against PD-1, in 190 patients with RM-NPC (Wang 2021). A decrease of 50% or more in the plasma EBV DNA copy number on Study Day 28 was associated with a significantly improved ORR (P=0.0001); tumor mutation burden had no predictive value for response. Therefore, combining a PD-1 inhibitor with EBV-targeted therapy may have the potential to augment anti-tumor activity for the treatment of RM-NPC.

1.2.2. Other EBV$^+$ Solid Tumors

1.2.2.1. EBV$^+$ Gastric Cancer

Gastric cancer is the second leading cause of cancer death worldwide. Although relatively uncommon in the United States (US) with an estimated 27,600 new cases and 11,010 deaths in 2020 (American Cancer Society 2020) and an overall incidence of 5.6 per 100,000 in North America, a high incidence is reported in East Asia, with an average incidence of 32.1 per 100,000 (males) and 13.2 per 100,000 (females) (Rawla 2019, Van Cutsem 2016). Gastric cancer is classified into 4 subtypes according to its molecular biology in the Cancer Genome Atlas: EBV-positive, microsatellite instability, genomically stable, and chromosomal instability (Wang 2019). EBV-associated gastric carcinoma results from clonal growth of EBV-infected gastric epithelial cells and is characterized by atrophic gastritis in the background mucosa (Abe 2015). EBV$^+$ gastric cancer is traditionally identified by the EBER-ISH assay (Sun 2020). The frequency of EBV infection in gastric carcinoma varies from 2% to 20% with an average of 10% (Camargo 2011). Two subtypes of EBV-associated gastric carcinoma are recognized including LELC and conventional gastric adenocarcinoma (Nepardize 2014). EBV-associated gastric carcinoma is more common in males, is predominantly located in the proximal and middle regions of the stomach (Corvalan 2001, Takada 2000), and has a younger onset of disease (40 years [range: 21-45 years]) compared with 69 years (range: 50-90 years) for EBV-negative gastric cancer (Moore 2020). Risk factors include *Helicobacter pylori* infection and smoking.

Surgical resection is the only curative therapy for localized gastric cancer; however, many patients have recurrence afterwards. EBV$^+$ gastric carcinoma is associated with a significantly lower frequency of lymph node metastasis compared with EBV-negative gastric cancer and a more favorable survival. A recent retrospective analysis of 4599 gastric cancer patients diagnosed between 1976 and 2010 from 13 international centers reported a median OS of 8.5 years for patients with EBV$^+$ tumors compared with 5.3 years for patients with EBV-negative tumors (Carmargo 2014). Recently, nivolumab in combination with chemotherapy was approved by the FDA for the first-line treatment of gastric cancer. Median survival was 13.8 months for

patients who received nivolumab plus chemotherapy compared with 11.6 months for patients who received chemotherapy alone. In addition, pembrolizumab received accelerated approval in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma with an ORR of 74%. Advanced gastric cancer has a poor prognosis despite the availability of chemotherapy, targeted therapies such as trastuzumab, ramucirumab, apatinib, and more recently, PD-1 inhibitors. Pembrolizumab showed an ORR of 11.6% for the treatment of patients with third-line gastric cancer (not selected for PD-L1) (Fuchs 2018). However, many patients relapse after these treatments (Zhao 2019), additional therapies are needed.

1.2.2.2. EBV$^+$ Lymphoepithelioma-like Carcinomas

LELCs are rare tumors with morphologic and genetic features similar or identical to those of undifferentiated NPC that occur outside of the nasopharynx, and have been described in several different organs, with lung, stomach, thymus, and salivary gland LELCs being most consistently associated with EBV infiltration (Iezzoni 1995). Pulmonary lymphoepithelioma-like carcinoma (PLELC) accounts for <1% of all lung cancers and is more prevalent in Asia, primarily affecting younger non-smoking individuals (Li 2020); over 90% of cases are EBV$^+$. No clinical practice guideline specifically for the treatment of PLELC exists owing to its rarity (Hu 2020). In general, treatment is similar to that of non-small cell lung cancer (NSCLC). Surgical resection with or without adjuvant chemotherapy is recommended by some clinicians. For resectable cases with and without standard adjuvant NSCLC chemotherapy, the 36-month recurrence-free survival is 73%, and for those with stage III to IV disease at presentation, a median OS of >3 years has been reported after multimodality therapy (Lin 2016, Huang 2012). However, patients with locally advanced stage PLELC may benefit from a more aggressive multimodality approach (Hu 2020).

Like NPC, plasma EBV DNA levels have been reported to reflect tumor burden in PLELC and may be useful for predicting outcome (eg, risk of disease progression) and monitoring (Li 2020). LELCs of the thymus and salivary glands are very rare, the latter being reported primarily in China (Saw 1986).

1.2.2.3. EBV$^+$ Leiomyosarcoma

EBV-associated leiomyosarcomas are very rare neoplasms that are generally seen in immunocompromised (HIV-positive or post-transplant) patients, reported to occur primarily in the liver, brain, gastrointestinal, and respiratory tracts (Boman 1997). A recent review reported on 64 cases of AIDS-associated smooth muscle tumors from 53 articles (Purgina 2011). Clinical outcome was variable and included surgical resection primarily with radiotherapy, chemotherapy, and highly active retroviral therapy as less frequently used options. Surgical resection was more recently reported to be the preferred treatment option, as these tumors tend to be resistant to chemotherapy (Hussein 2014).

1.3. Purpose of the Study

Although response rates to CRT for first-line EBV$^+$ NPC are high, patients tend to relapse with advanced disease, and no standard treatment options are available beyond the first-line setting for patients with platinum-refractory RM-NPC. The combination of histone deacetylase (HDAC)

inhibitors and ganciclovir has been reported to inhibit tumor growth in murine xenograft models of EBV$^+$ nasopharyngeal and gastric cancer (Hui 2016).

Nanatinostat (also known as VRx-3996 and CHR-3996) is an orally administered hydroxamic acid-based, selective and potent inhibitor of histone deacetylase (HDAC) Class I enzymes, originally discovered and developed by Chroma Therapeutics. Nanatinostat is currently being developed by Viracta Therapeutics, Inc (Sponsor) in combination with valganciclovir, an oral prodrug of ganciclovir, in patients with EBV-associated lymphoma. Nanatinostat and valganciclovir have been safely co-administered to more than 90 heavily pre-treated recurrent EBV$^+$ lymphoma patients with complete and partial responses reported in a variety of B- and T/NK non-Hodgkin lymphoma (NHL) subtypes (summarized in Section 1.5.1.1). Therefore, nanatinostat and valganciclovir hold promise for the treatment of patients with EBV$^+$ solid tumors. Phase 1b of this study will identify the recommended Phase 2 dose (RP2D) for nanatinostat in combination with valganciclovir in patients with recurrent or metastatic EBV$^+$ NPC which will be confirmed in Phase 2.

NPC cells highly express PD-L1, and response rates of 20 to 30% have been reported with PD-1 inhibitors for the treatment of advanced NPC, including an ORR of 25.9% for pembrolizumab and an ORR of 20.5% for toripalimab in PD-1 positive RM-NPC (Wang 2021, Ma 2018, Hsu 2017). Pembrolizumab has been safely combined with various cytotoxic chemotherapies as well as HDAC inhibitors (Gray 2019).

As discussed in Section 1.5.2, there is a compelling rationale to suggest that exposure to nanatinostat will result in enhancement of immune destruction of EBV-positive solid tumors. In order to explore the hypothesis that concurrent treatment with a PD-1 inhibitor together with an EBV-targeted treatment regimen may result in potentially greater anti-tumor activity for the treatment of RM-NPC, pembrolizumab will be administered concomitantly with nanatinostat and valganciclovir and compared with nanatinostat and valganciclovir alone during Phase 2 of the study.

1.4. Overview of Investigational Treatment

1.4.1. Nanatinostat (VRx-3996)

Nanatinostat (VRx-3996) is a selective and potent HDAC Class I inhibitor with activity against HDAC1, HDAC2, and HDAC3. Nanatinostat is also a potent inducer of EBV protein kinase and tyrosine kinase. In tumor cell lines and tumor xenograft models, nanatinostat inhibited tumor growth across a wide spectrum of human tumor types and demonstrated synergistic activity in combination with agents such as erlotinib, decitabine, and tosedostat (Banerji 2012).

1.4.1.1. Nonclinical Experience with Nanatinostat Monotherapy

1.4.1.1.1. Nonclinical PK and Metabolism of Nanatinostat

Nonclinical studies have shown that nanatinostat, as a single agent, has good oral bioavailability in rats and dogs (30% to 40%), and demonstrates good tissue penetration in rat models. Nanatinostat metabolism is not cytochrome P450 (CYP)-mediated, does not induce CYP450 isoforms, and appears to be a poor inhibitor of CYP450 isoforms, using model substrates and inhibitors across all studies.

1.4.1.1.2. Pharmacodynamics of Nanatinostat

The pharmacodynamics of nanatinostat, as a single agent, were evaluated by acetylation of histone H3 in peripheral blood mononuclear cells (PBMCs). An increase in acetylation was seen by 4 hours and returned towards baseline by 24 hours. Data suggest both a dose relationship and then a plateau in biologic response, with increased acetylation apparent at the 20 mg/day dose level and plateauing at levels ≥40 mg/day.

1.4.1.2. Clinical Experience with Nanatinostat Monotherapy

The safety and preliminary efficacy of nanatinostat as a single agent were evaluated in a Phase 1 study in 39 patients with refractory solid tumors (Banerji 2012). Nanatinostat was administered orally once daily as single doses of 5 mg (n=3), 10 mg (n=4), 20 mg (n=3), 40 mg (n=10), 80 mg (n=10), 120 mg (n=4), and 160 mg (n=5) on a 28-day cycle. Dose-limiting toxicities (DLTs) reported (by nanatinostat dose) included thrombocytopenia (160 mg), fatigue (80 and 120 mg), elevations in serum creatinine (80 mg and 120 mg), and atrial fibrillation (40 mg). The maximum tolerated dose (MTD) was determined to be 80 mg/day, and the RP2D was 40 mg daily. Most adverse events (AEs) were low grade (Grade 1 or 2); the most commonly reported AEs were fatigue and nausea. One partial response (PR) was seen in the 160 mg dose group in a patient with metastatic acinar pancreatic carcinoma.

Nanatinostat was rapidly absorbed with a median time to maximum plasma concentration (t_{max}) of 1 hour (range 1 to 4 hours). Although there was pronounced variability in exposure across the dose levels, area under the plasma concentration-time curves (AUCs) were broadly proportional over the administered dose range. The median terminal elimination half-life ($t_{½}$) was 1.8 hours. No clear differences were observed between Day 1 and Day 28 in pharmacokinetic (PK) parameters, suggestive of no apparent accumulation.

Additional details regarding clinical and nonclinical experience with nanatinostat, are provided in the latest version of the nanatinostat Investigator's Brochure (IB).

1.4.2. Valganciclovir

Valganciclovir (VALCYTE®), an oral prodrug of ganciclovir, is approved internationally for treatment of cytomegalovirus (CMV) retinitis in adult patients with AIDS and prevention of CMV disease in kidney, heart, and kidney-pancreas high-risk transplant patients, including treatment of high-risk pediatric kidney and heart transplant patients.

The recommended adult dosage of valganciclovir for treatment of CMV retinitis is 900 mg orally twice daily for 21 days followed by a maintenance dose of 900 mg once daily. Oral valganciclovir is well absorbed (approximately 60%) and converted to ganciclovir by first-pass intestinal or hepatic metabolism with peak plasma concentrations achieved in 1 to 3 hours. The major elimination pathway is renal excretion through glomerular filtration and active tubular secretion. Dose reductions based on creatinine clearance are recommended for patients with renal impairment. Reported AEs of note related to valganciclovir include cytopenias (leukopenia, neutropenia, anemia, thrombocytopenia) and acute renal failure. Elderly patients, patients receiving nephrotoxic drugs, and inadequately hydrated patients are at higher risk for renal dysfunction (Valcyte [valganciclovir] Prescribing Information, 2021).

1.4.3. Pembrolizumab

Pembrolizumab (KEYTRUDA®) is a potent humanized IgG_4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on nonclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies and is currently approved in more than 90 countries for one or more advanced malignancies (Merck & Co., Inc Corporate Responsibility Report, 2019/2020). Notable toxicities associated with the use of pembrolizumab as a single agent or in combination treatment include a variety of immune-mediated adverse reactions such as pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, and skin and infusion reactions (Keytruda [pembrolizumab] Prescribing Information, 2023). Modest responses to PD-1-targeted monotherapy with pembrolizumab have been reported in patients with RM-NPC. In a recent Phase 2 study evaluating pembrolizumab in patients with PD-L1-positive RM-NPC, patients received pembrolizumab 10 mg/kg every 2 weeks up to 2 years or until disease progression or unacceptable toxicity (Hsu 2017). The primary endpoint was ORR. In 27 patients evaluable for efficacy, the ORR was 25.9% (no patient had a complete response [CR]). Drug-related AEs occurred in 20 patients (74.1%); the most commonly reported were rash and pruritis (25.9% each), pain (22.2%), fatigue (18.5%), and hypothyroidism (18.5%). Grade 3/4-related AEs occurred in 8 patients; only pneumonitis was reported in 2 or more patients. Ten patients were reported to have immune-related AEs, including hepatitis (n=4), hypothyroidism (n=2), and pneumonitis (n=2).

When used as part of combination therapy, the recommended dosage of pembrolizumab is 200 mg IV every 3 weeks or 400 mg IV every 6 weeks until disease progression, unacceptable toxicity or up to 24 months across the approved indications (Keytruda [pembrolizumab] Prescribing Information, 2023).

1.5. Rationale for the Choice of Combination Treatments

The rationale for the proposed combination treatment approach with nanatinostat and valganciclovir for EBV^+ solid tumors in this study is based upon both nonclinical and clinical data supporting the complementary activities of class I HDAC inhibitors and the antiviral ganciclovir in EBV^+ malignancies. Nanatinostat, a Class I-selective oral hydroxamate HDAC inhibitor active against HDAC1, HDAC2, and HDAC3, induces the expression of EBV protein kinases that activate the anti-viral nucleoside analogue ganciclovir via mono- and tri-phosphorylation. This leads to inhibition of both viral and cellular DNA synthesis in EBV^+ tumor cells and potentially in surrounding EBV^- tumor cells as well (bystander effect), causing apoptosis.

Clinical efficacy has previously been reported in patients with a variety of relapsed/refractory EBV^+ lymphomas in early phase clinical studies using the combination of the HDAC inhibitor arginine butyrate with ganciclovir (Perrine 2007) and more recently with nanatinostat in combination with valganciclovir (Porcu 2020; reviewed in Section 1.5.1.1). Several of these EBV lymphoma subtypes shown to be susceptible to this combination therapy in clinical trials express the same EBV latency patterns found in NPC and gastric carcinoma (latency patterns II and III). This same expression indicates nanatinostat should be capable of inducing the EBV in NPC and gastric cancers out of the latent stage, resulting in expression of the target gene/enzyme

EBV-encoded protein kinase (EBV-PK). This inducement has been demonstrated in nonclinical studies using NPC and gastric carcinoma cell lines (data on file). Expression of EBV-PK is sufficient to render cells sensitive to ganciclovir. Ganciclovir triphosphate, the active metabolite of ganciclovir produced by EBV-PK, is toxic to all replicating mammalian cells. EBV-specific killing of NPC and gastric carcinoma cell lines was demonstrated in nonclinical studies using the combination of nanatinostat and ganciclovir (data on file).

In addition, the plasma EBV DNA level has been reported to be closely correlated with survival and the response to therapy in patients with RM-NPC (Wang 2021, Wang 2010). A recent study evaluating the PD-1 inhibitor toripalimab as monotherapy in patients with previously treated RM-NPC reported the association of a significantly higher overall response rate in patients with a ≥50% vs <50% reduction in the plasma EBV DNA copy number on day 28 (Wang 2021). Therefore, dynamic monitoring of the plasma EBV DNA level may be a useful adjunct to determining a dosing regimen for further evaluation.

1.5.1. HDAC Inhibitors and Antiviral Agents for EBV$^+$ Malignancies

EBV exists in a latent form in EBV$^+$ NPC; induction of the viral lytic phase renders the tumor cells susceptible to antiviral therapy. Typically, in a latent tumor, ganciclovir has no antiviral or cytotoxic activity; however, induction of the lytic cycle using an HDAC inhibitor triggers expression of EBV-PK, the enzyme responsible for phosphorylating ganciclovir into its active cytotoxic form.

Inhibition of class I HDACs (HDAC-1, -2, or -3) is sufficient to disrupt EBV latency and activate expression of EBV-PK. In published time-course experiments, discontinuous exposure to the HDAC inhibitor sodium butyrate was found to induce viral gene expression and be sufficient for synergistic tumor cell killing with ganciclovir in the EBV$^+$ Burkitt lymphoma cell line P3HR1 (Ghosh 2007). In vitro exposure of P3HR1 cells to the HDAC inhibitor sodium butyrate induced measurable EBV- thymidine kinase gene expression at 6 hours. Intermittent exposure of P3HR1 cells to sodium butyrate (6 hours daily for 3 days followed by 3 days with no treatment) was as effective as continuous exposure in sensitizing the lymphoma cells to ganciclovir, with significantly greater cytotoxicity observed with the combination compared with either butyrate or ganciclovir alone. Furthermore, intermittent dosing reduces the potential toxicities resulting from the continuous HDAC inhibitor treatment.

Nonclinical proof of concept for combining an HDAC inhibitor (romidepsin) with an anti-viral drug (ganciclovir) was initially established in murine xenograft models of EBV$^+$ NPC and gastric cancer, whereby the combination reduced tumor volume compared with either agent alone (Hui 2016). Similarly, the combination of gemcitabine, the HDAC inhibitor valproic acid, and ganciclovir was reported to exhibit a strong synergistic effect on cytotoxicity in NPC cell lines and clinical responses were noted in 3 patients with RM-NPC who received this regimen (Wildeman 2012).

Nanatinostat is a highly potent inhibitor of Class I HDACs (half-maximal inhibitory concentration = 3, 4, and 7 nM for HDACs 1, 2 and 3, respectively). As a monotherapy, nanatinostat in vitro induces cytotoxicity in P3HR1 cells after 6 days of exposure at or above 320 nM. While these concentrations can be achieved in vitro, preliminary PK data from the ongoing Phase 1b/2 dose escalation/expansion study VT3996-201 (NCT03397706) demonstrate that while nanatinostat may reach these concentrations in human plasma at the doses tested, it is

rapidly eliminated from the circulation ($t_{1/2}$ <2 hours). As a single agent in patients with advanced malignancies (n=39), nanatinostat was well-tolerated, but demonstrated only limited activity at daily doses up to 160 mg (one PR was reported in a patient with metastatic pancreatic cancer receiving 160 mg daily) (Banerji 2012, CHROMA CHR-3996-001 Clinical Study Report). To date, no HDAC inhibitor has been approved in solid tumor indications. While the in vitro data suggest that nanatinostat may induce tumor cell death as a single agent with prolonged exposure, the intermittent administration of nanatinostat four days per week in doses of 20 to 40 mg daily is unlikely to do so.

In vitro studies using EBV^+ Burkitt lymphoma HH514-16 cells demonstrated induction of the EBV lytic cycle after approximately 8 hours of exposure to 50 nM of nanatinostat (corresponding to approximately 20 ng/mL). A murine PK study demonstrated that administering a divided dose of nanatinostat 4 hours apart increased the duration of exposure to nanatinostat >50nM by up to 40%. Treatment of NPC-43 cells, an EBV^+ NPC-derived cell line, with varying concentrations of nanatinostat (5 to 500 nM) efficiently induced the virus lytic cycle (data on file).

Taken together, these data support the conclusion that the activity of nanatinostat in combination with ganciclovir is dependent on their coadministration and is superior to that of either compound alone, particularly at nanatinostat concentrations below those capable of inducing direct HDAC inhibitor-mediated cytotoxicity. In addition, the use of nanatinostat monotherapy (at the same doses/concentrations as used in the combination therapy) as a tumoricidal agent would be ineffective in the clinical setting.

1.5.1.1. Clinical Experience with Nanatinostat and Valganciclovir in EBV^+ Lymphoma

The investigation of nanatinostat in combination with valganciclovir for the treatment of relapsed/refractory EBV^+ lymphoid malignancies was designated as a Fast Track Development Program by the United States (US) Food and Drug Administration (FDA) on 06 Nov 2019. The combination treatment of nanatinostat with valganciclovir is currently being evaluated in patients with EBV^+ relapsed/refractory lymphoma in a single arm Phase 1b/2 dose escalation/expansion study (Study VT3996-201). Patients ≥18 years of age with EBV^+ lymphoma per local laboratory and ≥1 prior therapy are eligible. Baseline hematology labs required for enrollment were a hemoglobin ≥8.0 g/dL, absolute neutrophil count (ANC) ≥1000/mm^3 and platelet count ≥50,000/mm^3.

The following regimens were evaluated in the completed Phase 1b dose-escalation phase (n=25):

- Cohort 1 (n = 7): Nanatinostat 10 mg oral twice daily + valganciclovir 900 mg oral twice daily (20 mg + 1800 mg)
- Cohort 2a (n = 5): Nanatinostat 5 mg oral twice daily + valganciclovir 450 mg oral twice daily (10 mg + 900 mg)
- Cohort 2b (n = 4): Nanatinostat 10 mg oral once daily + valganciclovir 450 mg oral twice daily (10 mg + 900 mg)
- Cohort 2c (n = 4): Nanatinostat 10 mg oral once daily + valganciclovir 900 mg oral once daily (10 mg + 900 mg)

- Cohort 3 (n = 5): Nanatinostat 20 mg oral once daily, Days 1 to 4 per week + valganciclovir 900 mg oral once daily (20 mg + 900 mg)

In Cohort 1, 3 of the first 4 patients enrolled experienced DLTs (Grade 4 neutropenia × 29 days, Grade 3 thrombocytopenia × 6 days, Grade 3 thrombocytopenia × 13 days) and developed Grade 1/2 creatinine elevations. The reported cytopenias and creatinine elevations prompted a 50% dose reduction in valganciclovir to 450 mg twice daily; 3 more patients were subsequently enrolled into the cohort. Following the dose reduction, 1 patient experienced a DLT (uncomplicated Grade 3 thrombocytopenia × 7 days); therefore, Cohort 1 was considered to have exceeded the MTD. In Cohort 2, no DLTs were reported across the 3 sub cohorts (2a, 2b, 2c; n = 13). In Cohort 3, an intermittent dosing schedule was used for nanatinostat administration (20 mg daily, Days 1 to 4 per week) with valganciclovir 900 mg daily based on the recommendation of the study Safety Committee; no subsequent DLTs were reported; these doses were declared the RP2D.

As of 27 Oct 2021, 55 patients (10 patients with B-cell NHL [B-NHL], 21 patients with T-cell NHL [T-NHL]), 11 patients with Hodgkin lymphoma, 13 patients with other lymphomas) were enrolled and followed for DOR for almost 12 months from the first dose of study treatment; 25 patients in Phase 1b and 30 patients in the Phase 2 expansion cohort (7 additional patients enrolled to receive the nanatinostat tablet formulation in an ongoing PK cohort were not part of this analysis). Lymphoma subtypes (N=55) were diffuse large B-cell lymphoma (DLBCL; 7 patients), extranodal NK/T-cell lymphoma (ENKTL; 9 patients), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS; 5 patients), angioimmunoblastic T-cell lymphoma (AITL; 6 patients), cutaneous T-cell lymphoma (1 patient), Hodgkin lymphoma (11 patients), other B-cell (3 patients), and immunodeficiency-associated lymphoproliferative disorders (IA-LPD; 13 patients), including post-transplant lymphoproliferative disorder (PTLD; 4 patients), HIV-associated (5 patients), and other (4 patients: systemic lupus erythematosus [2 patients], common variable immunodeficiency/primary immunodeficiency [2 patients]). Patients had a median of 2 prior therapies (range 1 to 11); 77% had received ≥2 prior therapies, 75% were refractory to their most recent prior therapy, and 96% had exhausted all standard therapies in the judgment of the Investigator. Forty-three patients were evaluable for efficacy. For T-NHL (n = 15), the ORR was 60% (9 of 15 patients); 4 patients had CRs (27%). All T/NK-NHL patients were refractory to their most recent prior therapy. ORR/CR rates by T-NHL subtype were as follows: ENKTL 63% (5 of 8 patients)/ 13% (1 of 8 patients) and PTCL (including PTCL-NOS, AITL) 67% (4 of 6 patients)/ 50% (3 of 6 patients). Two patients (1 ENKTL and 1 PTCL) were withdrawn at 3.5 and 5.8 months, respectively, by the investigators to undergo SCT. For the other 3 responding PTCL patients, one remains in a CR (16.6 months), one remained in a CR for 20.7 months after stopping study drug treatment, and one had a PR lasting 10.6 months.

For B-NHL overall (n = 8), the ORR/CR rates were 50% (4 of 8 patients)/ 25% (2 of 8 patients). Four of 6 DLBCL patients responded (2 CRs in patients with primary refractory DLBCL and 2 PRs). For Hodgkin lymphoma (n=10), PR was the best response in 1 patient (5 stable disease; 4 progressive disease), and for IA-LPD (n=10), responses included 2 patients with CRs and 1 patient with a PR. The median DOR was 10.4 months (Haverkos 2021).

The most frequently reported Grade 3/4 treatment-emergent adverse events (TEAEs) overall by study phase are presented in Table 1.

Table 1: Study VT3996-201: Grade 3/4 Treatment-Emergent Adverse Events Experienced by ≥3 (5%) Patients (as of 27 Oct 2021)

	Phase 1b (n=25)	Phase 2 (n=30)
Thrombocytopenia	13 (52%)	7 (23%)
Neutropenia	10 (40%)	9 (30%)
Anemia	9 (36%)	8 (27%)
Lymphopenia	6 (24%)	4 (13%)
Leukopenia	5 (20%)	5 (17%)
Acute kidney injury	4 (16%)	2 (7%)
GI hemorrhage	2 (8%)	2 (7%)
Febrile neutropenia	1 (4%)	3 (10%)

In total, 42 patients received study treatment at the RP2D (nanatinostat 20 mg daily, Days 1 to 4 per week plus valganciclovir 900 mg daily) including 5 patients from Cohort 3 of Phase 1b, 30 patients from the Phase 2 expansion cohort, and 7 patients in the tablet PK cohort. At the RP2D, the most commonly reported TEAEs (≥20% of patients) were nausea (43%), anemia and neutrophil count decreased (31% each), constipation and fatigue (26% each), and diarrhea (21%). In general, the RP2D had a favorable safety and tolerability profile.

In summary, the combination of nanatinostat and valganciclovir has been associated with a favorable safety and tolerability profile at the RP2D and showed preliminary efficacy in a population of heavily pretreated patients with a variety of EBV^+ lymphomas, the majority of whom had refractory disease to their last therapy prior to entering the study. Further information about the safety profile of nanatinostat in combination with valganciclovir can be found in the current version of the IB.

1.5.2. Rationale for Adding Pembrolizumab to Nanatinostat and Valganciclovir

As described in Section 1.2.1, NPC cells are high expressors of PD-L1, and response rates of 20 to 30% have been reported with PD-1 inhibitors for the treatment of advanced NPC, including an ORR of 25.9% for pembrolizumab in PD-1 positive RM-NPC (Wang 2021, Ma 2018, Hsu 2017). Pembrolizumab has been safely combined with various cytotoxic chemotherapies as well as HDAC inhibitors (Gray 2019).

While some HDAC inhibitors have been approved for treating hematopoietic malignancies (romidepsin, vorinostat, panobinostat, belinostat), they are generally ineffective as single agents for the treatment of solid tumors (Anne 2013, Siegel 2009, Whitehead 2009, Steele 2008, Stadler 2006). Class I HDAC inhibitors have been reported in vitro and in vivo to increase PD-L1 and programmed cell death-ligand 2 (PD-L2) expression in nonclinical melanoma models (Woods 2015) and enhance the activity of PD-1 inhibitors. Furthermore, the induction of EBV out of latency by nanatinostat, and the resulting expression of highly immunogenic EBV proteins/antigens on the tumor cells, should serve to enhance the recognition and destruction of EBV^+ solid tumors by T-lymphocytes (the evolutionary rationale for establishment of latency by EBV after infection of cells is to avoid expression of viral antigens, thereby escaping recognition and destruction by T-lymphocytes). Taken together, the dual activities of nanatinostat on the enhancement of PD-1 inhibitor activity and the induction of viral antigen expression suggest that

combining anti-PD-1 therapy with the EBV-targeted regimen of nanatinostat and valganciclovir may have the potential for synergistic antitumor activity in EBV-associated NPC.

1.5.3. Rationale for the Doses of Nanatinostat, Valganciclovir, and Pembrolizumab in this Study

1.5.3.1. Nanatinostat Dose

In the Phase 1b part of this study, the nanatinostat starting dose will be 20 mg once daily on Days 1 to 4 per week with food. This nanatinostat dose was determined to be the RP2D in combination with valganciclovir 900 mg once daily in patients with relapsed/refractory EBV^+ lymphomas in the Phase 1b/2 VT3996-201 study. Preliminary data has shown a favorable safety and tolerability profile at that dose.

Administering nanatinostat as a divided dose may allow for the administration of a higher total daily dose of valganciclovir for the first 21 days improving tolerability and increasing the potential activity. Furthermore, dividing the nanatinostat dose may prolong the duration of nanatinostat exposure above the experimentally determined threshold required for EBV lytic reactivation (see Section 1.5.1). Forty mg daily was identified as the RP2D and 80 mg daily the MTD for single agent treatment in a Phase 1 study in patients with advanced cancers (Banerji 2012, CHROMA CHR-3996-001 Clinical Study Report). Because 40 mg per dose on Days 1 to 4 was well-tolerated with no DLTs to date, the current planned dose escalation is up to a maximum daily dose of 80 mg in divided doses on Days 1 to 7 per week until the RP2D is identified with an allowance for dose reduction cohorts in the case of DLTs.

1.5.3.1.1. Rationale for Split Daily Dosing of Nanatinostat

One of the main rate-limiting steps for the mechanism of action of nanatinostat and valganciclovir is EBV lytic reactivation from latency. This step results in expression of the viral protein kinase, BGLF4, which phosphorylates the pro-prodrug valganciclovir into its active cytotoxic form. To maximize EBV lytic reactivation, in vitro studies were performed to assess the impact of nanatinostat exposure duration on expression of BZLF1, the principal lytic cycle switch protein. The experiment was performed in EBV-infected gastric cancer cells (SNU-719) and revealed that a minimum of 8 to 10 hours is necessary to achieve proper activation of the EBV lytic cycle.

Considering the PK of nanatinostat and its rapid clearance from the circulation (~4 hours), it was hypothesized that splitting the daily dose of nanatinostat into 2 sequential doses would provide adequate exposure to the drug and effective EBV reactivation. To test this hypothesis, a PK study was conducted in a murine model to examine the potential of splitting the single daily dose of nanatinostat into two daily doses that were administered 2 or 4 hours apart. Splitting the nanatinostat dose successfully increased its exposure time by up to 40%. Additionally, modeling of the human PK data from the Phase 1b/2 EBV^+ lymphoma trial (NCT03397706) suggested that splitting the nanatinostat dose into 2 doses 4 hours apart would likely increase exposure to nanatinostat above the experimentally determined threshold required for lytic reactivation (20 ng/mL) by 3 hours relative to the same dose administered as a single dose (6 hours for single dose exposure in 55% of patients versus 9 hours for split dose exposure in 99% of patients) as shown in Table 2.

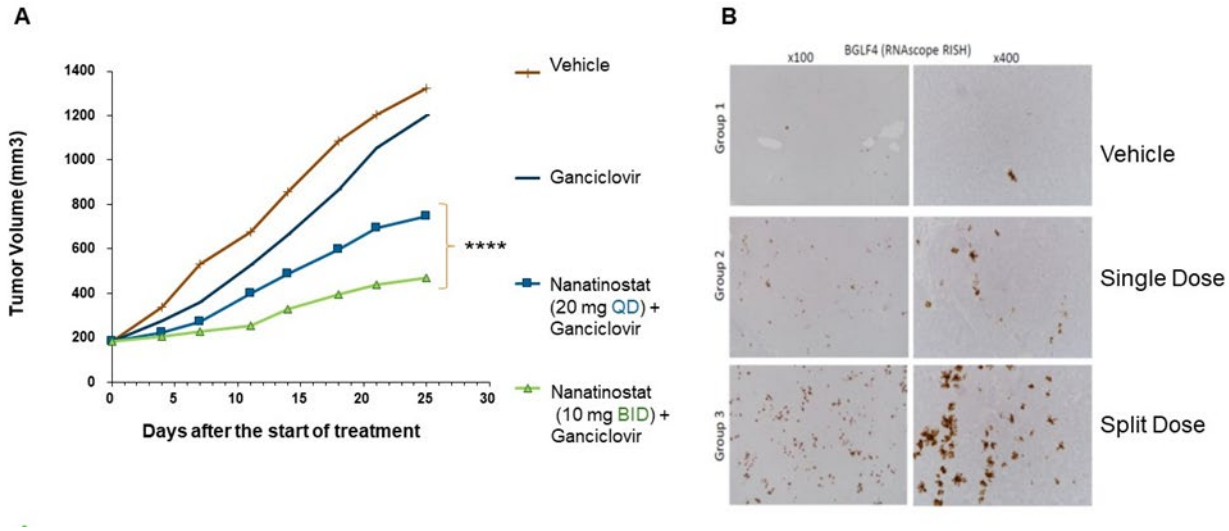
Table 2: Percent of Subjects With Response to Nanatinostat for ≥ 6 Hours Based on Dosing Regimen

Nanatinostat Dosing Regimen	Duration (hours)		Subjects with Duration ≥ 6 hours (%)
	Median	5th percentile, 95th percentile	
30 mg single dose	6.18	4.55, 11.9	55.0
20 mg + 10 mg divided dose (4 hours)	8.55	6.96, 13.7	99.0
15 mg + 15 mg divided dose (4 hours)	9.09	6.98, 14.3	99.0

The effect of splitting the dose of nanatinostat on tumor reduction was assessed in an EBV^+ gastric cancer xenograft murine model. SNU-719 cells were inoculated subcutaneously in the right flank of nude mice (n=10 per group). Once the tumor reached an average of 100 mm^3, the mice were treated with vehicle (0.001 N HCl), ganciclovir (30 mg/kg), and nanatinostat (20 mg/kg) plus ganciclovir. The nanatinostat dose was administered as a single dose or as a split dose 4 hours apart. The animals were dosed 4 consecutive days each week for 4 weeks. No marked weight loss was observed during treatment. Tumor volume was measured twice weekly. Suppression of tumor growth was observed in animals treated with the combination of nanatinostat and ganciclovir. Splitting the dose of nanatinostat resulted in significantly enhanced antitumor activity relative to the single dose (Figure 1A).

In a follow-up experiment, animals were treated for 6 days only, sacrificed on the seventh day, and tumors were resected to study the level of the BGLF4 protein kinase transcripts. Using RNA-scope, splitting the dose of nanatinostat yielded a definite increase in the expression level of BGLF4 transcript compared to the single dose (Figure 1B). These results strongly suggest that administering nanatinostat as 2 sequential doses 2 to 4 hours apart daily markedly increases the expression of the viral protein kinase and significantly enhances the antitumor activity of nanatinostat and valganciclovir.

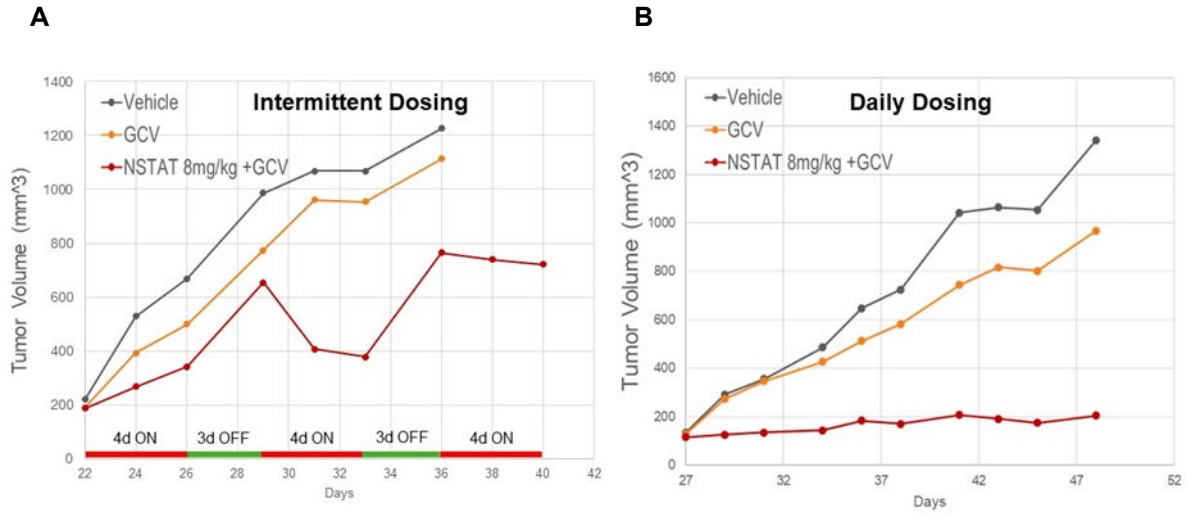
Figure 1: Comparing the Antitumor Activity and Expression of vPK (BGLF4) in EBV+ Gastric Cancer Tumor Samples with Split Daily Dose vs. Single Daily Dose of Nanatinostat in Combination with Ganciclovir



**** p=0.0001

To achieve better tumor growth inhibition, a comparison was conducted to determine the antitumor activity of nanatinostat and valganciclovir in animals treated 4 days a week (Figure 2A) versus animals treated daily (Figure 2B). Treating the animals with the combination of nanatinostat and valganciclovir 4 days per week resulted in less antitumor activity than with uninterrupted daily dosing.

Figure 2: Continuous Daily Dosing of Nanatinostat Provides Better Antitumor Activity Relative to 4 Days On/3 Days Off



Altogether, these results suggest that splitting the dose of nanatinostat in the nanatinostat and valganciclovir combination and continuous daily dosing of nanatinostat rather than intermittent dosing 4 days on/3 days off represent two novel approaches that are likely to improve the efficacy of nanatinostat and valganciclovir in solid tumors.

1.5.3.2. Valganciclovir Dose

For Phase 1b, valganciclovir will be administered at a dose of 900 mg once or twice daily with food. Once and twice daily dosing (900 mg/dose) are consistent with the labeled indication for the prevention and treatment, respectively, of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk (Valcyte [valganciclovir] Prescribing Information, 2020). Once daily dosing was associated with a favorable safety and tolerability profile from the ongoing Phase 1b/2 VT3996-201 study in relapsed/refractory EBV^+ lymphoma in combination with nanatinostat.

Twice daily dosing of valganciclovir for the first 21 days starting on Cycle 1 Day 1 with a subsequent reduction to 900 mg once daily will be introduced in dose level 6 (Table 4), in concert with a divided dose of nanatinostat starting at 10 mg twice daily. Although this dosing regimen was observed to have exceeded the MTD in the Phase 1b/2 VT3996-201 study in patients with relapsed/refractory lymphoma with 2 DLTs of grade 3 thrombocytopenia and 1 grade 4 neutropenia (Section 1.5.1.1), baseline hematology laboratory levels required for eligibility (hemoglobin ≥8.0 g/dL, absolute neutrophil count ≥1000/mm^3, platelet count ≥ 50,000/mm^3) were lower than those required for the current study (VT3996-301**:** Hemoglobin ≥9.0 g/dL, absolute neutrophil count ≥1500/mm^3, platelet count ≥ 100,000/mm^3). Therefore, the previous toxicity observed with these doses of nanatinostat and valganciclovir may not manifest in a different patient population with higher baseline hematology values required for eligibility. Twice daily dosing of 450 mg valganciclovir (900 mg/day; each dose 4 or 8 hours apart) together with twice daily dosing of nanatinostat (each dose 4 hours apart) will be explored in dose levels 6 and 7 and 8 – 13, to assess the impact of short-term "dose intensification" of valganciclovir upon safety, tolerability, and plasma EBV DNA levels.

1.5.3.3. Pembrolizumab Dose

In the Phase 2 dose expansion part of this study, the dose of pembrolizumab will be 200 mg IV every 3 weeks, initially beginning 7 days following the start of administration of nanatinostat and valganciclovir (coinciding with Cycle 1 Day 8). Although the Keynote-028 study evaluated pembrolizumab at a dose of 10 mg/kg administered every 2 weeks (Hsu 2017), early PK and pharmacodynamic data supported using either a once every 2 weeks or once every 3 weeks dosing schedule. In addition, this dose of pembrolizumab has been safely combined with a number of cytotoxic chemotherapy regimens, with a recommended dosage of pembrolizumab across the approved indications of 200 mg IV every 3 weeks or 400 mg IV every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months when used as part of combination therapy (Keytruda [pembrolizumab] Prescribing Information, 2023).

Section 5.3.2 describes specific information regarding the administration of pembrolizumab in combination with nanatinostat and valganciclovir.

1.6. Potential Benefits and Risks

1.6.1. Potential Benefits

As described in Section 1.5.1.1, preliminary data from the Phase 1b/2 VT3996-201 study indicate that at the RP2D, the combination of nanatinostat and valganciclovir was well tolerated and demonstrated clinical activity in a population of heavily pretreated patients with a variety of

recurrent EBV$^+$ lymphomas. The oral administration of both nanatinostat and valganciclovir is an added benefit to patients, allowing them to take their study treatment at home.

Targeting EBV has been reported to improve clinical outcomes of patients with both EBV-associated lymphomas (Porcu 2020, Perrine 2007) and NPC (Section 1.2.1). Therefore, the combination of nanatinostat and valganciclovir may have clinically relevant activity for patients with EBV$^+$ NPC and other tumors.

1.6.2. Potential Risks

HDAC inhibitors are potent inducers of the EBV lytic cycle; the production of infectious virus by virtue of HDAC inhibitor-mediated induction of the tumor lytic cycle is a clinically documented AE described in a monotherapy clinical trial with the HDAC inhibitor romidepsin (ISTODAX® [romidepsin] Prescribing Information 2021). However, this potential safety issue can be abrogated by the coadministration of ganciclovir. In the Phase 1b/2 VT3996-201 study, patients' EBV genome levels are monitored in a serial fashion. No cases of EBV reactivation have been reported to date, indicating that this combination is preventing EBV viremia.

Pertaining to the coadministration of nanatinostat and valganciclovir, both drugs exhibit overlapping toxicities (ie, thrombocytopenia and renal dysfunction) that may be increased in frequency or severity in combination. In addition, other toxicities were reported in prior clinical studies for one or both agents including fatigue, atrial fibrillation, nausea/vomiting, anemia, leukopenia, and neutropenia.

Toxicities reported for other HDAC inhibitors include thrombocytopenia, QTc prolongation, neutropenia, anemia, fatigue, and diarrhea (Gryder 2012). Medications with a known risk of prolonging the QT interval should be avoided (Section 5.7.4).

Toxicities reported for pembrolizumab include immune-mediated adverse reactions (irAEs) such as pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, and dermatologic adverse reactions, as well as gastrointestinal events (nausea, decreased appetite, constipation, and abdominal pain). Patients receiving nanatinostat and valganciclovir in combination with pembrolizumab will be closely monitored for any evidence of irAEs as well as renal dysfunction and enhanced gastrointestinal toxicity.

Further information about the safety profile of nanatinostat as a single agent and in combination with valganciclovir can be found in the current IB. For pembrolizumab, please consult the prescribing information (Keytruda [pembrolizumab] Prescribing Information 2023).

1.6.3. Risks Related to Study Procedures

Potential study-related risks include (but are not limited to) collection of new tumor samples, blood draws, radiologic assessments, and concomitant medications in case of AEs. More information is provided in the consent form.

1.6.4. Risk Management Strategies

The risks to patients in this study will be minimized by compliance with the eligibility criteria (eg, use of an eligibility checklist to approve enrollment) and study procedures, attentive medical monitoring, use of concomitant medications appropriate for the situation (eg, to manage AEs), and following guidance for dose adjustments (outlined in Section 5.6).

The benefit-risk balance of the oral treatment regimen with nanatinostat and valganciclovir alone and with intravenous pembrolizumab is anticipated to be positive for the target study population of patients with advanced incurable EBV^+ solid tumors.

2. OBJECTIVES AND ENDPOINTS

The study objectives and related endpoints are presented in Table 3.

Table 3: Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	**Refer to Section 9.6.1 for methods of analysis.**
Phase 1b: To determine the recommended phase 2 dose (RP2D) of nanatinostat in combination with valganciclovir 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	Phase 1b: Incidence of dose-limiting toxicities (DLTs) during the DLT evaluation period Phase 2: • Incidence of DLTs plus other safety parameters, tolerability, PK and plasma EBV DNA concentrations at the RP2D and <RP2D of nanatinostat in combination with valganciclovir • Objective response rate (ORR) defined as the percentage of patients with a complete response (CR) or partial response (PR) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (v1.1)
Secondary	**Refer to Section 9.6.2 and Section 9.7 for methods of analysis.**
To characterize the safety and tolerability of nanatinostat and valganciclovir alone and in combination with pembrolizumab	Incidence and severity of treatment-emergent adverse events (TEAEs) per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
To characterize the pharmacokinetic (PK) properties of nanatinostat in combination with valganciclovir	PK parameters (eg, time to maximum plasma concentration [t_{max}], maximum plasma concentration [C_{max}], and area under the plasma concentration-time curve [AUC]) of nanatinostat, its metabolites, and ganciclovir (primary active hydrolytic product of valganciclovir)
To evaluate additional preliminary efficacy parameters of nanatinostat and valganciclovir alone and in combination with pembrolizumab	• Duration of response (DOR) – defined as the interval 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 • Disease control rate (DCR) – defined as the percentage of patients having a CR, PR, or stable disease at any time during treatment • Progression-free survival (PFS) – defined as the interval from the start of study drug treatment to the date of first documented disease progression or death from any cause, whichever occurs first • Overall survival (OS) – defined as the interval of time from the start of study drug treatment to date of death for any reason

Objective(s)	Endpoint(s)
Exploratory	**Refer to Section 9.6.3 for methods of analysis.**
To evaluate potential biomarkers of activity of nanatinostat and valganciclovir with or without pembrolizumab	• Plasma Epstein-Barr virus (EBV) DNA levels (real-time quantitative polymerase chain reaction [PCR]) • Expression of EBV gene products (ie, lytic cycle antigens) in both pre-study and during-study tumor biopsies • Programmed cell death-ligand 1 (PD-L1) expression on tumor cells and tumor-infiltrating immune cells • Histone H3 acetylation
To evaluate safety, tolerability, PK, PD, and antitumor activity of nanatinostat in combination with valganciclovir in patients with non-NPC EBV^+ solid tumors	Incidence of DLTs plus other safety parameters, tolerability, PK and plasma EBV DNA concentrations of nanatinostat in combination with valganciclovir in non-NPC solid tumors

3. STUDY DESIGN

3.1. Description of 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^+ RM-NPC (Figure 3).

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 a 20 mg once daily dose 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 will continue with i) a 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, ii) as a 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 iii) as a 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 until the RP2D is determined. Because plasma EBV DNA levels correlate closely 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, pharmacodynamics, 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-PD-1 treatment exposure.

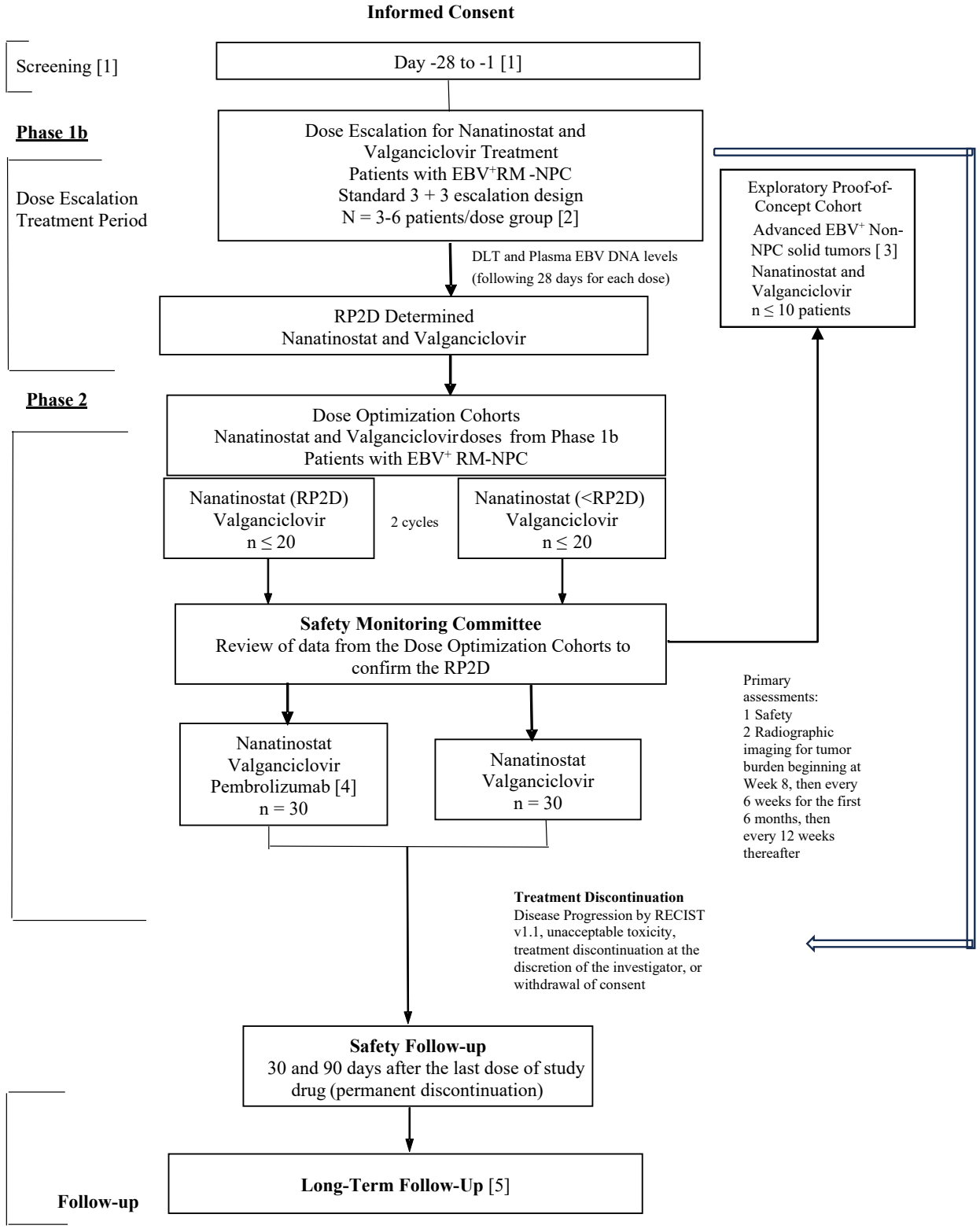
Pembrolizumab will be dosed at 200 mg IV every 3 weeks for those patients randomly assigned to the nanatinostat, valganciclovir, and pembrolizumab group.
An early safety analysis will be performed after the first 6 patients are randomized to receive nanatinostat and valganciclovir in combination with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

In addition, up to 10 patients with advanced EBV^+ non-NPC solid tumors (gastric cancer, LELC, 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 (RECIST) version 1.1 (v1.1). A scan to confirm an unconfirmed PR or unconfirmed CR ≥4 weeks later may also be performed.

Patients will continue to receive study treatment 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 duration with pembrolizumab is 24 months.

Figure 3: 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 and/or metastatic NPC or other solid tumor type and received previous systemic therapy for their cancer; have measurable disease determined by MRI or CT 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, 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

3.1.1. 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 lab 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. 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.

3.1.2. 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) for treatment decision making, including confirmation of unconfirmed progressive disease with additional imaging.

3.1.3. 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 treatment (permanent discontinuation) as described in Section 7.3.5. All AEs for patients treated with nanatinostat, valganciclovir, and pembrolizumab and only serious adverse events (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.

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 visit, but prior to the 30-day safety evaluation, safety data should be collected on the patient up to the date of consent withdrawal.

3.1.3.1. Disease Progression Follow-up Period

All 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) as detailed in Table 11, up to 1 year from the date of the last dose of study treatment, disease progression, the initiation of subsequent anti-cancer therapies, 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.

3.1.3.2. Survival Follow-up Period

All patients enrolled in the study will be followed for survival as described in Section 7.3.6 (or more frequently if a survival update is required for safety or regulatory reasons) for disease progression (for those who discontinued treatment for reasons other than disease progression), OS and subsequent anti-neoplastic therapies. Survival information can be obtained by phone calls, e-mail, medical records, clinic visits, or public records, such as government census or death records, until the patient is lost to follow-up, death, or withdraws consent.

3.1.4. 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 CR, PR, 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 (eg, by separate protocol or post-trial access plan) with Sponsor's Medical Monitor approval.

3.2. Duration of Study

The study enrollment period is anticipated to be approximately 2 years, and the total duration of the study period is expected to be up to approximately 4 years (maximum treatment duration with pembrolizumab is 24 months).

3.3. Discussion of Study Design

This is a Phase 1b/2, open-label, multicenter, multiple dose study designed to evaluate the safety and preliminary efficacy of nanatinostat and valganciclovir alone and in combination with pembrolizumab in adult patients with recurrent or metastatic EBV^+ NPC and other solid tumors. PK and pharmacodynamic assessments are also planned.

The purpose of Phase 1b is to determine the RP2D of nanatinostat in combination with valganciclovir for treatment in Phase 2. Because this is the first study evaluating the combination of nanatinostat and valganciclovir in patients with solid tumors, determination of the RP2D is necessary for safe dosing in Phase 2.

In Phase 2, a dose optimization cohort period will occur where approximately 40 patients will be randomly assigned to one of two cohorts (up to 20 patients each) at the RP2D and a dose below the RP2D to confirm the recommended nanatinostat and valganciclovir dose for Phase 2. After review of the data by the SMC, up to 60 RM-NPC patients will be randomly assigned to receive nanatinostat and valganciclovir at the confirmed RP2D with or without pembrolizumab, and an

early safety analysis will be performed after the first 6 patients randomized to receive nanatinostat and valganciclovir with pembrolizumab have been followed for at least 2 cycles (7 weeks) of treatment as described in Section 5.5.3.3. Randomization will be stratified for prior exposure to anti-PD-1 agents. In addition, an exploratory proof-of-concept cohort of patients with other non-NPC EBV^+ solid tumors is included for a preliminary analysis of safety of the RP2D in additional EBV^+ tumor types.

Antitumor activity will be assessed by radiologic tumor assessments conducted at baseline, Week 8, then every 6 weeks for the first 26 weeks (6 months), and every 12 weeks thereafter (and at the end-of-treatment visit) using RECIST v1.1 as the primary measure for assessment with the recommendation to employ iRECIST guidelines for treatment decision-making in the Phase 2 pembrolizumab combination group. A scan to confirm an unconfirmed PR or unconfirmed CR ≥4 weeks later may also be performed.

PK assessments will be conducted to evaluate nanatinostat and valganciclovir only; these 2 drugs do not have competing elimination/metabolism pathways with pembrolizumab. For this reason, a 7-day lead-in period for nanatinostat and valganciclovir prior to pembrolizumab administration is included in Phase 2.

The assessments to evaluate safety, tolerability, PK, and antitumor activity planned for this study are commonly used in oncology studies.

An FFPE tumor block or 10 unstained slides of a representative tumor specimen obtained within 2 years prior to screening must be available (otherwise a de novo biopsy may be required) and submitted to the central pathology laboratory within 8 weeks after Cycle 1 Day 1. Central pathology assessment will include EBER-ISH to confirm EBV status and also pharmacodynamic/ biomarker studies as described in Section 7.4.4. Biomarker studies using both archival and optional on-study tumor biopsies (to be performed on Cycle 1 Day 15 and at end of treatment with relapse or progression, if agreed) will be conducted to evaluate the mechanism of action of nanatinostat and valganciclovir with or without pembrolizumab, as well as to understand potential mechanisms of resistance.

3.4. Dosing Considerations

3.4.1.1. Nanatinostat and Valganciclovir

In Phase 1b, the nanatinostat starting dose of 20 mg orally once daily on Days 1 to 4 per week in combination with the standard valganciclovir dose 900 mg orally once daily is based on the preliminary results (as of 27 Oct 2021; n=55) from the Phase 1b/2 VT3996-201 study in patients with EBV^+ relapsed or refractory lymphomas. This patient population was heavily pretreated (77% received ≥2 prior therapies; median number of prior therapies was 2, range 1-11), the majority (75%) of whom had disease that was refractory to their last therapy at study entry. Most patients received repeat cycles of various cytotoxic regimens, including alkylating agents, anthracyclines, vinca alkaloids, and various biologic agents; the majority of these agents are associated with cytopenias. Nanatinostat in combination with valganciclovir has been generally well tolerated in this patient population (Section 1.5.1.1).

Based on the safety data from previous cohorts, dosing with nanatinostat and valganciclovir will continue in single or split daily doses of nanatinostat with single daily or split daily doses of

valganciclovir beginning with intermittent nanatinostat dosing on Days 1 to 4 and escalating to twice daily dosing of nanatinostat and valganciclovir on Days 1 to 7 per week until the RP2D is determined.

3.4.1.2. Nanatinostat, Valganciclovir, and Pembrolizumab

According to the prescribing information, the recommended dose and schedule of pembrolizumab is 200 mg IV every 3 weeks (Keytruda [pembrolizumab] Prescribing Information, 2023). This dose and schedule of pembrolizumab has been safely combined with a number of cytotoxic chemotherapy regimens and biologic agents. For valganciclovir, although most toxicities reported are mild to moderate in nature, the prescribing information carries a warning regarding the development of cytopenia and renal toxicity (Valcyte [valganciclovir] Prescribing Information, 2021).

To date, the most commonly reported toxicities with nanatinostat and valganciclovir at the RP2D (n=42) in the VT3996-201 study include nausea and cytopenias (additional details are provided in the latest version of the nanatinostat IB). The potential for overlapping toxicities with nanatinostat, valganciclovir, and pembrolizumab may be highest for renal function (already mitigated by the frequent monitoring of renal function according to the prescribing information for valganciclovir) and gastrointestinal events such as nausea and vomiting.

Following dose escalation, two additional cohorts with up to 20 patients each will be randomized to receive nanatinostat and valganciclovir in the dose optimization cohort period at the RP2D and <RP2D to be selected in consultation with the SMC. After a review of the data from the first two cycles of the dose optimization cohort period, enrollment into Phase 2 dose expansion will begin, supported by an early safety analysis of the first 6 patients randomized to receive nanatinostat and valganciclovir with pembrolizumab as described in Section 5.5.3.3.

4. SELECTION OF STUDY POPULATION

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 (CT) with contrast at screening; and have adequate bone marrow, liver, and renal function.

4.1. Patient Population

4.2. Inclusion Criteria

To be eligible for study participation, patients must meet **all** of the following inclusion criteria:

1. Adult patients age ≥18 years.
2. Willing and able to give informed consent.
3. Histologically or cytologically documented EBV^+ tumor cells by EBER-ISH or LMP-1 (according to local guidelines) per an archival tumor sample taken within 2 years prior to screening, otherwise a de novo biopsy may be required. FFPE tissue block(s) or at least 10 unstained slides are requested. It is encouraged (but not required) that patients with a

site of disease accessible to biopsy and who are candidates for tumor biopsy according to local practice guidelines undergo a new tumor biopsy at baseline and during treatment.

4. Patients with RM-NPC (excluding patients in the Phase 1b exploratory proof-of-concept cohort) for whom no potentially curative options are available, who have received at least 1 prior line of platinum-based chemotherapy and no more than 3 prior lines of therapy for RM-NPC.

   Note: The following clinical scenarios are not considered to be separate lines of therapy:

   a. Maintenance therapy: drug therapy (including chemotherapy, targeted therapy, or immunotherapy including vaccines, cellular therapy, and checkpoint inhibitors) that is started with maintenance intent in patients who have recently completed one line of chemotherapy without experiencing disease progression.
   b. Drug rechallenge: patients who have been "rechallenged" with the same drug therapy(s) previously used to treat recurrent or metastatic NPC.

5. Patients who developed recurrent or metastatic disease within six months following radical concurrent chemoradiotherapy in combination with neoadjuvant and/or adjuvant therapy for non-metastatic NPC are eligible as long as no potentially curative options are available.

6. **For Phase 1b exploratory proof-of-concept cohort only:** Patients with advanced/metastatic EBV^+ non-NPC solid tumors (gastric cancer, LELC, leiomyosarcoma) that have progressed despite standard therapy for which no curative therapies exist.

7. Radiologically measurable disease per RECIST v1.1.

8. All acute toxic effects of any prior anti-neoplastic therapy resolved to at least Grade 1 before initiation of study treatment (excluding alopecia, Grade 2 sensory neuropathy, hypothyroidism [stable on thyroid hormone supplementation], chronic/stable xerostomia, hearing loss, lymphedema, and taste changes [all Grade 2]).

9. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

10. Life expectancy ≥3 months.

11. Adequate laboratory parameters (in the absence of transfusion or growth factor support with 3 weeks of Screening) including:

    a. Absolute neutrophil count ≥1500/mm^3.
    b. Platelets count ≥100,000/mm^3.
    c. Hemoglobin ≥9.0 g/dL.
    d. Aspartate aminotransferase (AST)/serum glutamine oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic- pyruvic transaminase (SGPT) ≤2.5 × upper limit of normal (ULN) (≤5 × ULN if known liver involvement by tumor).
    e. Total bilirubin ≤2.0 × ULN unless considered due to Gilbert's syndrome in which case, ≤3.5 × ULN.
    f. Estimated glomerular filtration rate ≥60 mL/min by Cockcroft-Gault equation (see Section 5.6.2 for formula to calculate creatinine clearance).

g. Prothrombin time (PT) or international normalized ratio ≤1.5 × ULN.
h. Serum potassium and magnesium should be within normal limits for institution or treatment to correct out of range values should be instituted.

12. For HIV positive patients:
    a. CD4 count ≥350 cells/μL.
    b. On an established antiretroviral therapy (ART) for ≥4 weeks.
    c. An undetectable HIV viral load.
    d. No prior AIDS-defining opportunistic infections within the past 12 months.
13. Willingness to comply with study requirements.
14. Women of childbearing potential (ie, reached menarche, and not post-menopausal [no menses for 12 months without an alternative medical cause] or surgically sterile) must have the following:
    a. Understand that the study medication is expected to have teratogenic risk.
    b. Have a negative serum beta human-chorionic gonadotropin pregnancy test at screening.
    c. Commit to continued abstinence from heterosexual intercourse (excluding periodic abstinence or the withdrawal method) or commit to the use of 2 forms of birth control with at least one highly effective method of birth control with a Pearl-Index <1%, and one effective barrier method such as a male condom, female condom, cervical cap, diaphragm, or contraceptive sponge with spermicide, without interruption, throughout the study dosing period and for 6 months after the last dose of study treatment. Apart from abstinence, highly effective methods of birth control include the following:
        i. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (ie, intravaginal, transdermal). Please note: Although the potential for drug interactions and risk of venous thromboembolism is low (see Section 5.7.2.3), the use of an alternative method of contraception is recommended.
        ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
        iii. Intrauterine device
        iv. Intrauterine hormone-releasing system
        v. Bilateral tubal occlusion.
        vi. Vasectomized partner.
15. Male patients must agree to use condoms during intercourse throughout the study dosing period and for 90 days after the last dose of study treatment.

4.3. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Anti-tumor treatment with cytotoxic drugs, biologic therapy (eg, monoclonal antibody), immunotherapy, or other investigational drugs within 4 weeks or >5 half-lives, whichever is shorter.

2. Corticosteroids within 7 days prior to dosing (unless ≤10 mg/day of prednisone or equivalent).
3. For NPC:
    a. Active parenchymal or leptomeningeal metastases.
    b. Base of skull disease that poses a risk of significant bleeding (eg, proximity to carotid artery) as judged by the Investigator.
    c. Invasive disease for which there is a potential risk of significant bleeding as judged by the Investigator.
4. **For non-NPC cancers**: Active central nervous system (CNS) disease/metastases.
5. Nasopharyngeal cancer patients who have received prior therapy with an anti-PD-1 agent are not excluded, except for those who experienced prior Grade 3 or higher immune-related toxicity that resulted in permanent drug discontinuation (patients with prior temporary drug interruptions due to endocrinopathies etc. are eligible).
6. Less than 14 days from prior locoregional site radiotherapy. Palliative radiotherapy outside the head and neck is allowed as long as the lesions are not target lesions.
7. Tumor mutational burden -high advanced malignancies and/or microsatellite instability-high malignancies who would otherwise be eligible for pembrolizumab (unless patients have progressed on pembrolizumab) in accordance with local standards, (ie, only if such biomarkers are performed as standard of care in the participating center).
8. Major surgery, open biopsy, or significant traumatic injury within 28 days prior to starting study treatment. In case of recent major surgery, the patient must have recovered adequately from the procedure and/or any complications prior to starting study treatment.
9. Is currently participating in or has participated in an interventional study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

    Note: Individuals who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent.
10. Diagnosis of any other malignancy within 3 years prior to enrollment, except for the following if adequately treated:
    - local basal cell or squamous cell carcinoma of the skin, or related localized non-melanoma skin cancer.
    - carcinoma in situ of the breast or of the cervix.
    - superficial bladder cancer.
    - low grade (Gleason 6 or below) prostate cancer undergoing surveillance with no plans for treatment intervention or previously fully resected.
11. Gastrointestinal abnormalities including the following:
    - Inability to take oral medication.
    - Malabsorption syndrome or any other gastrointestinal condition (nausea, diarrhea,

vomiting) that may impact the absorption of nanatinostat and valganciclovir.
- Prior surgical procedures affecting absorption including total gastric resection.
- Active gastrointestinal bleeding (hematemesis, hematochezia, or melena) in the past 3 months without documentation of resolution by endoscopy/colonoscopy.

12. Positive surface antigen unless quantitative DNA polymerase chain reaction (PCR) is undetectable, and patient is stable on antiviral prophylaxis against hepatitis B virus (HBV) reactivation. Patients who are hepatitis B core antibody positive must have undetectable quantitative DNA PCR and be monitored according to the local standard-of-care/institutional guidelines.
13. Positive hepatitis C virus on RNA PCR.
14. Known SARS-CoV-2 positivity at time of screening (patients can be re-screened once negative by PCR).
15. History of allergic reactions attributed to compounds of similar chemical or biologic composition to valganciclovir or nanatinostat.
16. Active infection requiring systemic therapy.
17. Prolongation of corrected QT interval using Fridericia's formula (QTcF) to >480 msec, requires the coadministration of drugs known to prolong QT (Class Ia [disopyramide, quinidine, procainamide] and Class III [sotalol, dofetilide, ibutilide] antiarrhythmic agents) (Drew 2010), and/or has a history of Torsades de Pointes (TdP).
18. Receiving potentially nephrotoxic drugs (eg, cyclosporin).
19. Receiving concomitant drugs that are inhibitors of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), unless they can be held for 2 weeks or 5 half-lives, whichever is longer, prior to administration of nanatinostat. See Appendix 1, Table 2 for a list of drugs.
20. Receiving tenofovir (unless can be switched to an alternative ART).
21. Psychiatric illness/social situations/substance abuse disorder that would interfere with compliance with study requirements.
22. Active autoimmune disease that has required systemic therapy with modifying agents, corticosteroids, or immunosuppressive agents.
23. Prior or ongoing clinically significant illness, medical condition, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the Investigator's opinion, could affect the safety of the patient, impair the assessment of study results, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate.
24. Females who are pregnant or breastfeeding or expecting to conceive children within the projected duration of the study, starting with the screening visit through 6 months after the last dose of study treatment.

5. STUDY TREATMENT INFORMATION

For this study, the term "study treatment" refers to the combination of nanatinostat and valganciclovir in Phase 1b and nanatinostat and valganciclovir with or without pembrolizumab in Phase 2 only.

5.1. Nanatinostat

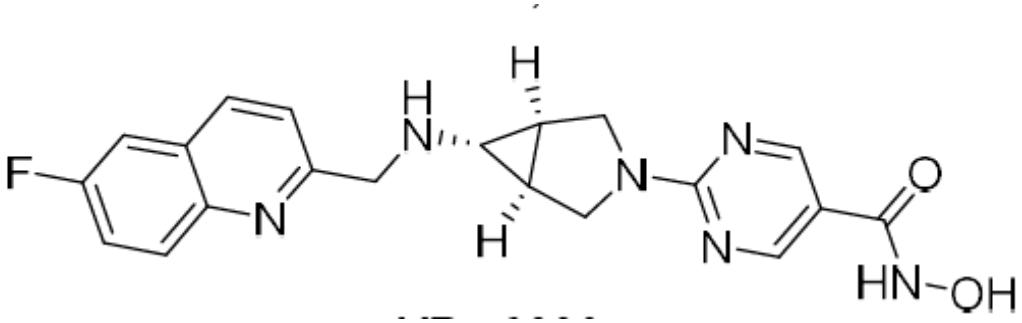
5.1.1. Dosage Form, Composition, and Packaging

Nanatinostat is available as 10 mg tablets. Instructions for requesting and receiving nanatinostat from the Sponsor will be included in the Study Manual.

Nanatinostat (VRx-3996) is a hydroxamic acid-based HDAC inhibitor (Moffat 2010). As is typical of this class, the structure of nanatinostat has 3 main components: a hydroxamic acid that coordinates with the Zn^{2+} ion in the active pocket of the enzyme, a spacer (azabicyclo pyrimidine) that fills out the narrow channel of the binding site, and a hydrophobic head group, amino methyl(fluoroquinoline), that interacts with the rim surrounding the pocket of the active site.

Nanatinostat is an off-white to pale orange solid with a molecular formula of $C_{20}H_{19}FN_6O_2$, and a molecular weight of 394.41 Da. The structural formula is presented in Figure 4.

Figure 4: Structural Formula and Key Features of Nanatinostat



Nanatinostat film-coated immediate-release (IR) 10 mg tablets consisting of the active nanatinostat (VRx-3996), and inactive excipients (ie, mannitol, microcrystalline cellulose, croscarmellose sodium, and sodium stearyl fumarate). The tablets are film coated with non-functional Opadry II white.

All inactive ingredients in the drug product meet compendial requirements of the United States Pharmacopeia and/or National Formulary.

5.1.2. Nanatinostat Study Drug Storage

Nanatinostat should be stored at controlled room temperature (20 to 25ºC, 68 to 77ºF) in a secure location. Excursions are permitted to 15ºC to 30ºC (59ºF to 86ºF). Once the bottle seal is broken, bottles should be stored tightly capped.

5.1.3. Nanatinostat Administration

All patients will receive nanatinostat orally once or twice daily (at breakfast or breakfast and lunch, respectively) on Days 1 to 4 per week (ie, 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 as described in Section 7.3.3.

Because valganciclovir tablets should be taken with food per prescribing information (Valcyte [valganciclovir] Prescribing Information, 2021), patients should be instructed to take both valganciclovir and nanatinostat with food and not fasting.

See Appendix 1 for medications to be used with caution with nanatinostat.

5.2. Valganciclovir

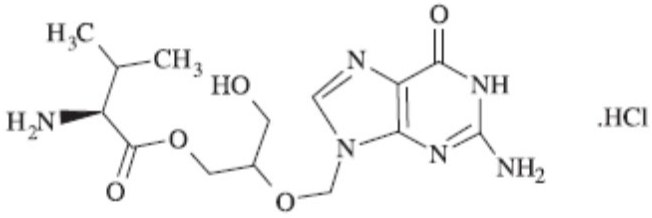
Valganciclovir is a cytomegalovirus nucleoside analogue DNA polymerase inhibitor.

5.2.1. Dosage Form, Composition, and Packaging

Valganciclovir is available as 450 mg tablets packaged in bottles.

Valganciclovir hydrochloride is a white to off-white solid with a molecular formula of $C_{14}H_{22}N_6O_5$. HCl, and a molecular weight of 390.82 g/mol. The structural formula is presented in Figure 5.

Figure 5: Valganciclovir Hydrochloride Structural Formula



Valganciclovir tablets manufactured by Viracta or commercially sourced will be provided to the investigational sites. Valganciclovir film-coated IR 450 mg tablets consist of the active valganciclovir (as hydrochloride) and inactive excipients (ie, microcrystalline cellulose, povidone, crospovidone, and magnesium stearate). The tablets are film coated with a non-functional coating.

Instructions for requesting and receiving valganciclovir will be included in the Study Manual.

5.2.2. Valganciclovir Study Drug Storage

Valganciclovir should be stored at controlled room temperature (20ºC to 25ºC, 68ºF to 77ºF) in a secure location. Excursions are permitted to 15ºC to 30ºC (59ºF to 86ºF). Once the bottle seal is broken, bottles should be stored tightly capped.

5.2.3. Valganciclovir Administration

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 as described in Section 7.3.3.

Valganciclovir doses should be adjusted for patients who develop an elevated creatinine while on study (see Section 5.6).

Because valganciclovir tablets should be taken with food per prescribing information (Valcyte [valganciclovir] Prescribing Information, 2021), patients should be instructed to take both valganciclovir and nanatinostat with food and not fasting.

All dosages of study treatment prescribed and dispensed to the patient, and all dose adjustments made during the study, must be accurately recorded in the eCRFs.

5.3. 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) colorless to slightly yellow solution in a single-dose vial and will be provided from commercial sources. Instructions for pembrolizumab will be included in the Study Manual.

5.3.1. Pembrolizumab Study Drug Storage

Pembrolizumab solution (injection) will be supplied in cartons containing either one or two 100 mg/4 mL (25 mg/mL) vials. Vials should be stored refrigerated (2°C to 8°C, 36°F to 46°F) in the original carton to protect from light.

As described in Section 5.3.2, pembrolizumab solution is diluted in an IV bag of sodium chloride or glucose. The diluted pembrolizumab solution may be stored at room temperature (20ºC to 25ºC, 68ºF to 77ºF) for no more than 6 hours from the time of dilution (this time includes room temperature storage of the diluted solution and the duration of infusion) and refrigerated for no more than 96 hours from the time of dilution. If refrigerated, the IV solution should come to room temperature prior to administration.

5.3.2. Pembrolizumab Administration

Prior to administration, pembrolizumab solution is transferred into an IV bag of sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%). The diluted solution is mixed by gentle inversion; the solution should not be shaken. The final concentration of the diluted solution is between 1 mg/mL to 10 mg/mL. The infusion solution is administered by IV over 30 minutes. Pembrolizumab should not be co-administered with other drugs through the same infusion line.

The dose of pembrolizumab is 200 mg IV every 3 weeks (Section 5.5.1). On treatment days, pembrolizumab should be administered within an hour following nanatinostat and valganciclovir (nanatinostat and valganciclovir are administered first). Additional administration information is provided in the pembrolizumab prescribing information (Keytruda [pembrolizumab] Prescribing Information, 2023).

5.3.3. Sequence of Study Drug Administration

The intermittent weekly dosing sequence for nanatinostat in combination with valganciclovir in Phase 1b dose levels 1 through 3 (defined in Table 4) is presented in Figure 6.

For patients receiving divided dosing of nanatinostat and single dosing of valganciclovir (dose levels 4 and 5 defined in Table 4), the first dose of nanatinostat and the only dose of valganciclovir will be taken at approximately breakfast time; the second dose of nanatinostat 4 hours later will be taken at approximately lunch time. The sequence for intermittent divided dosing of nanatinostat only is presented in Figure 7.

For the first 21 days of Cycle 1, patients receiving divided dosing of both nanatinostat and valganciclovir (dose levels 6 and 7 defined in Table 4) will take the first dose of nanatinostat and valganciclovir at approximately breakfast time, the second dose of nanatinostat 4 hours later at approximately lunch time, and then the second dose of valganciclovir in the evening at approximately dinner time on Days 1 to 4 per week. Patients will continue to receive divided dosing of valganciclovir at breakfast and dinner on Days 5 to 7 per week. Following the first 21 days, these patients will continue to receive divided dosing of nanatinostat on Days 1 to 4 per week, but subsequent valganciclovir dosing will be reduced to once daily at breakfast. The sequence for divided dosing of both nanatinostat and valganciclovir is presented in Figure 8.

For patients receiving split daily dosing of both nanatinostat and valganciclovir (dose levels 8 through 13 defined in Table 4), the first dose of nanatinostat and valganciclovir will be taken at approximately breakfast time and the second dose of nanatinostat and valganciclovir will be taken 4 hours later at approximately lunch time on Days 1 to 7. The sequence for split daily dosing of both nanatinostat and valganciclovir is presented in Figure 9.

The dosing sequence for nanatinostat and valganciclovir during the two dose optimization cohorts following identification of the RP2D is presented in Figure 10.

The dosing sequence for nanatinostat and valganciclovir in combination with pembrolizumab during Phase 2 is presented in Figure 10. During Cycle 1, pembrolizumab will be administered on Day 8 of the 28-day cycle. This sequence will allow for the collection of PK samples (for nanatinostat and valganciclovir) and may potentiate the efficacy of pembrolizumab based on the rationale provided in Section 1.5. The dosing sequence for nanatinostat and valganciclovir without pembrolizumab during Phase 2 is presented in Figure 9.

Note: Following Cycle 1, pembrolizumab will be administered on Day 1 of each subsequent 21-day cycle. Nanatinostat will continue to be administered on Days 1 to 4 or 1 to 7 per week and valganciclovir will be administered every day.

Figure 6: Dosing Sequence: Nanatinostat and Valganciclovir (Phase 1b Dose Levels 1 through 3)

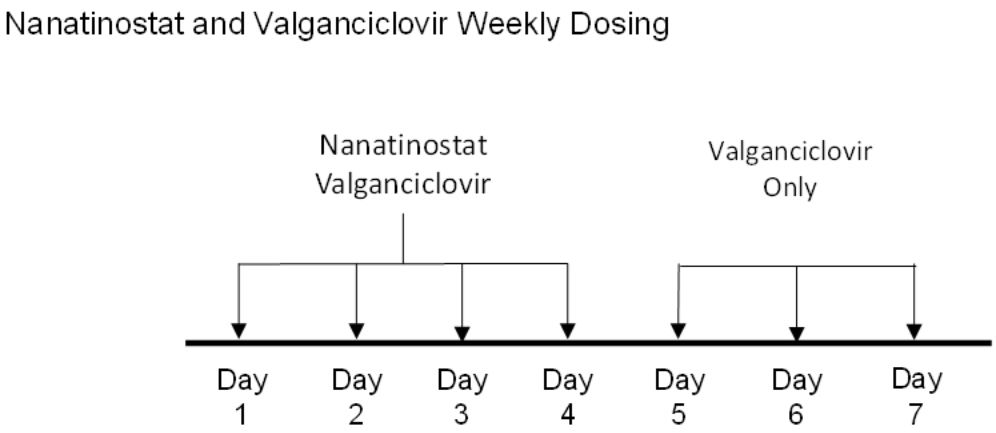
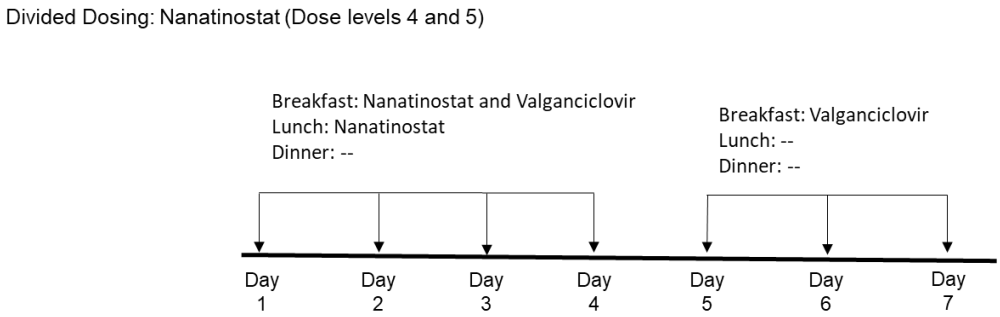
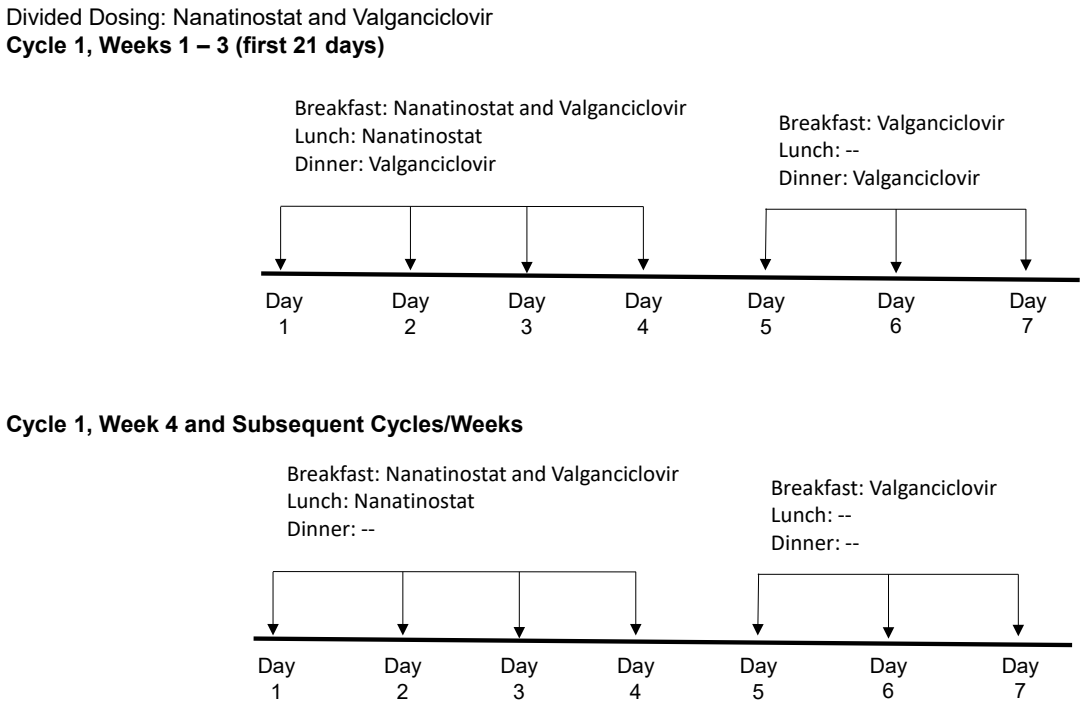


Figure 7: Divided Dosing Sequence: Nanatinostat (Dose Levels 4 and 5)



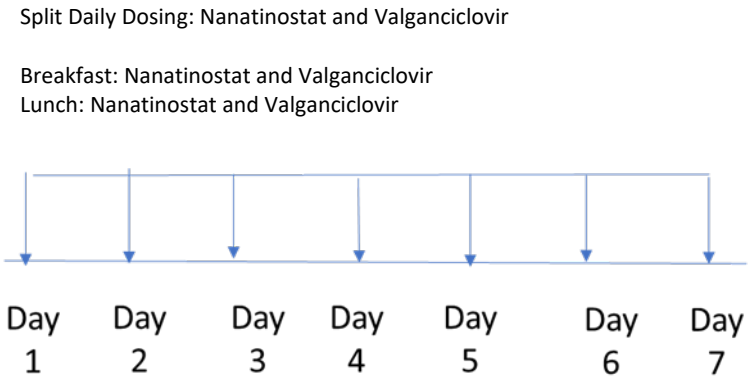
Dose levels defined in Table 4.
Note: If divided dosing for nanatinostat only is determined as the RP2D for Phase 2, pembrolizumab and valganciclovir dosing will not be split and will follow the sequence described in Figure 10.

Figure 8: Divided Dosing Sequence: Nanatinostat and Valganciclovir (Dose Levels 6 and 7)



Dose levels defined in Table 4.
Note: If divided dosing for nanatinostat and valganciclovir is determined as the RP2D for Phase 2, pembrolizumab dosing will not be split and will follow the sequence described in Figure 10.

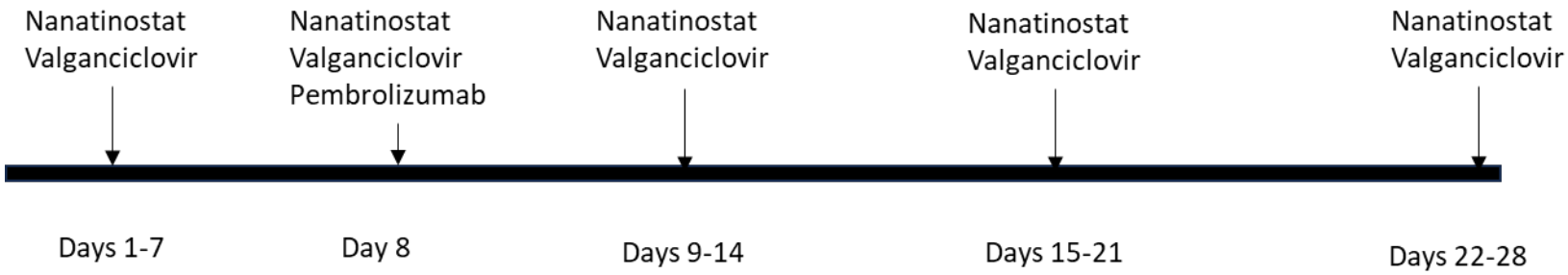
Figure 9: Split Daily Dosing Sequence: Nanatinostat and Valganciclovir (Dose Levels 8 through 13)



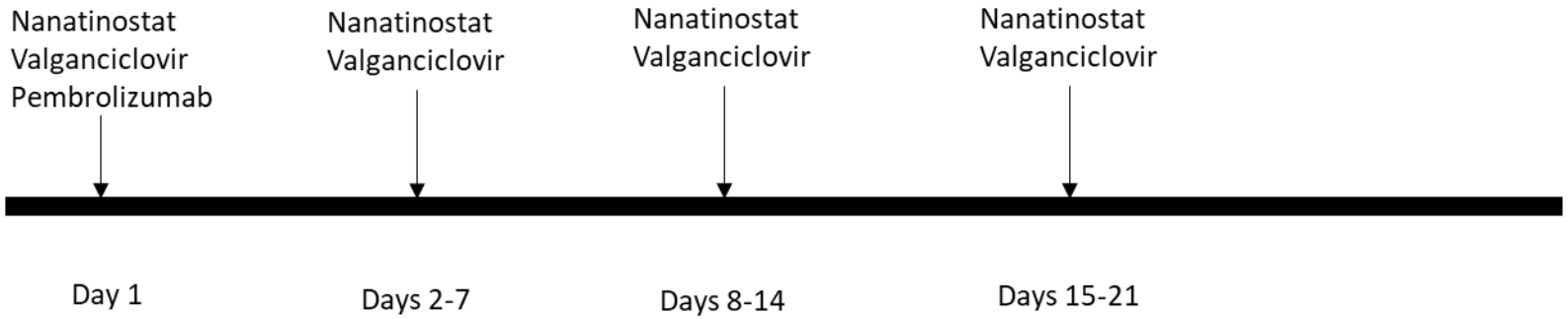
Dose levels defined in Table 4.
Note: refer to Figure 6 through Figure 8 if the dosing schedule returns to intermittent nanatinostat dosing.

Figure 10: Dosing Sequence: Nanatinostat, Valganciclovir, and Pembrolizumab – Phase 2 Dose Expansion

Nanatinostat, Valganciclovir, and Pembrolizumab –Cycle 1 Only



Nanatinostat, Valganciclovir, and Pembrolizumab –Subsequent Cycles



Note: refer to Figure 6 through Figure 8 if the confirmed RP2D returns to intermittent nanatinostat dosing. Pembrolizumab will continue to be administered as illustrated in Figure 10.

5.4. Additional Dosing Guidelines for Pharmacokinetic Sampling

In an effort to standardize food intake for the PK assessments, patients will be asked to consume one can of Ensure® meal replacement shake or equivalent, prior to the dose of study treatment (within 30 minutes) on days with pre- and post-dose PK assessments as outlined in Section 7.4.3. An Ensure equivalent is defined as any liquid nutrition that is at least 8 ounces in size containing at least 8 grams of protein and at least 6 grams of fat. Alternatively, patients may consume a light breakfast in place of consuming an Ensure or equivalent meal replacement shake. The meal should start 30 minutes before administration of valganciclovir and nanatinostat.

Note that nanatinostat and valganciclovir should be taken at the same time, including on Cycle 1 Day 1 (for divided dosing, the first doses of the day should be taken together in the morning at approximately breakfast). For patients receiving divided or split daily dosing of nanatinostat and valganciclovir (dose levels 4-13; Table 4), the 4-hour PK time point samples should be collected prior to administration of the second dose of nanatinostat (ie, at approximately lunch time). For patients receiving divided dosing of valganciclovir (dose levels 6 and 7), the 8-hour PK timepoint should be collected prior to administration of the second dose of valganciclovir (ie, at approximately dinner time).

See Appendix 1 for medications to be used with caution with nanatinostat.

5.5. Dose Escalation Guidelines

5.5.1. Provisional Dose Levels

Table 4 describes the starting doses and the provisional dose levels of nanatinostat and valganciclovir (Phase 1b) and nanatinostat and valganciclovir with pembrolizumab (Phase 2 Dose Optimization and Phase 2 Expansion) to be evaluated. The actual dose levels will be determined based on available data following a discussion with Investigators during dose-escalation teleconferences. No intrapatient dose escalation will be permitted in the Phase 1b dose escalation.

Table 4: Phase 1b: Dose Levels – Nanatinostat and Valganciclovir

Dose Level	Nanatinostat Oral Dose on Days 1-4/Week	Valganciclovir Oral Dose Daily
-1	10 mg once daily	900 mg once daily
1	20 mg once daily	900 mg once daily
2	30 mg once daily	900 mg once daily
3	40 mg once daily	900 mg once daily
4	20 mg and 10 mg divided dose	900 mg once daily
5	20 mg twice daily	900 mg once daily
6	10 mg twice daily	900 mg twice daily × 21 days, then once daily
7	20 mg and 10 mg divided dose	900 mg twice daily × 21 days, then once daily
	Nanatinostat Oral Dose Twice Daily on Days 1-7/Week	**Valganciclovir Oral Dose Twice Daily on Days 1-7/Week**
8[a]	20 mg and 10 mg divided dose	450 mg twice daily

9[a]	20 mg and 20 mg divided dose	450 mg twice daily
10[a]	30 mg and 20 mg divided dose	450 mg twice daily
11[a]	30 mg and 30 mg divided dose	450 mg twice daily
12[a]	40 mg and 30 mg divided dose	450 mg twice daily
13[a]	40 mg and 40 mg divided dose	450 mg twice daily

DLT = dose-limiting toxicity; RP2D = recommended Phase 2 dose
a: Dose levels 9, 11, and 13 are planned dose levels, while dose levels 8, 10, and 12 are planned provisional dose levels for stepping up or down based on the DLT profile to potentially better determine the RP2D. See Table 5 for further details.

5.5.2. Guidelines for Dose Escalation

During the DLT evaluation window of both phases of the study, patients who permanently discontinue study treatment prior to receiving 75% of the planned number of nanatinostat and valganciclovir doses or 2 pembrolizumab doses due to reasons other than study drug-related toxicity will not be considered evaluable for DLT and may be replaced.

Phase 1b

The RP2D of nanatinostat in Phase 1b will be defined as the highest dose administered with standard daily doses of valganciclovir (900 mg once or 450 mg twice daily) for which <33% of patients experience a DLT (defined in Section 5.5.3) during the first treatment cycle (28 days) up to a maximum daily dose of 80 mg administered with food either as a single daily dose administered intermittently (Days 1 to 4 per week) or as a split dose twice daily administered continuously (Days 1 to 7 per week). In addition to toxicity, PK, antitumor activity, plus pharmacodynamic markers of disease response (plasma EBV DNA levels) will be considered in the final determination of the RP2D in consultation with the SMC. Dose escalation rules during Phase 1b are presented in Table 5.

Table 5: Phase 1b Dose Escalation Rules for Nanatinostat in Combination with Valganciclovir*

Dose level	Outcome	Action
-1 Nanatinostat 10 mg daily, Days 1-4/wk Valganciclovir 900 mg daily	If none of the first 3 patients experiences a DLT	Proceed to expansion cohorts.
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level -1
	If 1 of 6 patients experiences a DLT	Declare dose level -1 to be RP2D
	If ≥2/6 patients experience a DLT	Convene safety review to discuss next steps.
1 **Starting dose** Nanatinostat 20 mg daily, Days 1-4/wk Valganciclovir 900 mg daily	If none of the first 3 patients experiences a DLT	Proceed to dose level 2
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 1
	If 1 of 6 patients experiences a DLT	Proceed to dose level 2
	If ≥2/6 patients experience a DLT	Decrease nanatinostat to dose level -1 and proceed.
2 Nanatinostat 30 mg daily, Days 1-4/wk Valganciclovir 900 mg daily	If none of the first 3 patients experiences a DLT	Proceed to dose level 3
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 2.
	If 1 of 6 patients experiences a DLT	Proceed to dose level 3.
	If ≥2/6 patients experience a DLT	Declare dose level 1 the RP2D.

Dose level	Outcome	Action
3 Nanatinostat 40 mg daily, Days 1-4/wk Valganciclovir 900 mg daily	If none of the first 3 patients experiences a DLT	Proceed to dose level 6.
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 3.
	If 1 of 6 patients experiences a DLT	Proceed to dose level 6.
	If ≥2/6 patients experience a DLT	Proceed to dose level 4.
4 Nanatinostat 20 mg + 10 mg divided dose, Days 1-4/wk Valganciclovir 900 mg daily	If none of the first 3 patients experiences a DLT	Declare 30 mg nanatinostat the RP2D*
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 4.
	If 1 of 6 patients experiences a DLT	Declare 30 mg nanatinostat the RP2D*
	If ≥2/6 patients experience a DLT	Declare dose level 2 the RP2D.
5 Nanatinostat 20 mg BID, Days 1-4/wk Valganciclovir 900 mg daily	If none of the first 3 patients experiences a DLT	Declare 40 mg nanatinostat the RP2D*
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 5.
	If 1 of 6 patients experiences a DLT	Declare 40 mg nanatinostat the RP2D*
	If ≥2/6 patients experience a DLT	Declare dose level 3 the RP2D.
6 Nanatinostat 10 mg BID, Days 1-4/wk Valganciclovir 900 mg BID for 21 days, then daily	If none of the first 3 patients experiences a DLT	Proceed to dose level 7.
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 6.
	If 1 of 6 patients experiences a DLT	Proceed to dose level 7.
	If ≥2/6 patients experience a DLT	Proceed to dose level 5.
7 Nanatinostat 20 mg + 10 mg divided dose, Days 1-4/wk Valganciclovir 900 mg BID for 21 days, then daily	If none of the first 3 patients experiences a DLT	Proceed to dose level 9.
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 7.
	If 1 of 6 patients experiences a DLT	Proceed to dose level 8 if it has not been previously enrolled, otherwise declare dose level 7 the RP2D.
	If ≥2/6 patients experience a DLT	Step down to dose level 6 and enroll a total of 6 patients there. Alternatively, declare dose level 6 the RP2D if it has already enrolled 6 patients.
8 Nanatinostat 20 mg + 10 mg divided dose, Days 1-7/wk Valganciclovir 450 mg twice daily	If none of the first 3 patients experiences a DLT	Proceed to dose level 9 if it has not been previously enrolled, otherwise declare dose level 8 the RP2D and expand dose level 8 to 6 patients to confirm RP2D determination.
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 8.
	If 1 of 6 patients experiences a DLT	Proceed to dose level 9 if it has not been previously enrolled, otherwise declare dose level 8 the RP2D.
	If ≥2 patients experience a DLT	Step down to dose level 7 and enroll a total of 6 patients there. Alternatively, declare dose level 7 the RP2D if it has already enrolled 6 patients.
9 Nanatinostat 20 mg + 20 mg divided dose, Days 1-7/wk Valganciclovir 450 mg twice daily	If none of the first 3 patients experiences a DLT	Proceed to dose level 11.
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 9.
	If 1 of 6 patients experiences a DLT	Proceed to dose level 10 if it has not been previously enrolled, otherwise declare dose level 9 the RP2D.
	If ≥2 patients experience a DLT	Step down to dose level 8 and enroll a total of 6 patients there. Alternatively, declare dose level 8 the RP2D if it has already enrolled 6 patients.
10 Nanatinostat 30 mg + 20 mg divided dose, Days 1-7/wk	If none of the first 3 patients experiences a DLT	Proceed to dose level 11 if it has not been previously enrolled, otherwise declare dose level 10 the RP2D and expand dose level 10 to 6 patients to confirm RP2D determination.

Dose level	Outcome	Action
Valganciclovir 450 mg twice daily	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 10.
	If 1 of 6 patients experiences a DLT	Proceed to dose level 11 if it has not been previously enrolled, otherwise declare dose level 10 the RP2D.
	If ≥2 patients experience a DLT	Step down to dose level 9 and enroll a total of 6 patients there. Alternatively, declare dose level 9 the RP2D if it has already enrolled 6 patients.
11 Nanatinostat 30 mg + 30 mg divided dose, Days 1-7/wk Valganciclovir 450 mg twice daily	If none of the first 3 patients experiences a DLT	Proceed to dose level 13.
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients in dose level 11
	If 1 of 6 patients experiences a DLT	Proceed to dose level 12 if it has not been previously enrolled, otherwise declare dose level 11 the RP2D.
	If ≥2 patients experience a DLT	Step down to dose level 10 and enroll a total of 6 patients there. Alternatively declare dose level 10 the RP2D if it has already enrolled 6 patients.
12 Nanatinostat 40 mg + 30 mg divided dose, Days 1-7/wk Valganciclovir 450 mg twice daily	If none of the first 3 patients experiences a DLT	Proceed to dose level 13 if it has not been previously enrolled, otherwise declare dose level 12 the RP2D and expand dose level 12 to 6 patients to confirm RP2D determination.
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 12.
	If 1 of 6 patients experiences a DLT	Proceed to dose level 13 if it has not been previously enrolled, otherwise declare dose level 12 the RP2D.
	If ≥2 patients experience a DLT	Step down to dose level 11 and enroll a total of 6 patients there. Alternatively, declare dose level 11 the RP2D if it has already enrolled 6 patients.
13 Nanatinostat 40 mg + 40 mg divided dose, Days 1-7/wk Valganciclovir 450 mg twice daily	If none of the first 3 patients experiences a DLT	Declare dose level 13 the RP2D and expand dose level 13 to 6 patients to confirm RP2D determination
	If 1 of 3 patients experiences a DLT	Enroll 3 more patients into dose level 13.
	If 1 of 6 patients experiences a DLT	Declare dose level 13 the RP2D
	If ≥2 patients experience a DLT	Step down to dose level 12 and enroll a total of 6 patients there. Alternatively declare dose level 12 the RP2D if it has already enrolled 6 patients.

*The RP2D referenced in this table is equivalent to a maximum tolerated dose (MTD) or maximum administered dose, but ultimate determination of the RP2D of nanatinostat will be based on the evaluation of additional parameters such as the incidence and severity of AEs, tolerability, pharmacokinetic data, antitumor activity, and plasma EBV DNA levels in consultation with the Safety Monitoring Committee.
AEs = adverse events; BID = twice daily; DLT = dose-limiting toxicity; EBV = Epstein-Barr virus; RP2D = recommended Phase 2 dose; wk = week

5.5.3. Dose-Limiting Toxicities (DLTs)

A DLT is defined as an AE or clinically significant abnormal laboratory value that is **at least possibly related** to study drugs and is not primarily related to disease, disease progression, concomitant medication(s), or intercurrent illness. DLTs will be assessed for each phase of the study and will include events that meet any of the criteria outlined in Section 5.5.3.1, Section 5.5.3.2, and Section 5.5.3.3. National Cancer Institute (NCI) Common Terminology Criteria for

Adverse Events (CTCAE) version 5.0 (v5.0) will be used for all AE grading for the purpose of dose-escalation decisions.

5.5.3.1. Phase 1b: Nanatinostat and Valganciclovir

The DLT evaluation period is 28 days.

To be considered a DLT, an AE must meet one or more of the following criteria:

1. Hematologic DLTs:
   - Grade 4 neutropenia or thrombocytopenia lasting ≥7 days.
   - Grade ≥3 thrombocytopenia associated with clinically significant bleeding.
2. Non-hematologic DLTs:
   - Grade ≥3 non-laboratory toxicities despite maximum supportive therapy.
   - Grade ≥3 clinically significant laboratory abnormality for which the patient is symptomatic regardless of its duration, requires medical intervention, is not corrected within 72 hours, or leads to hospitalization.
3. Febrile neutropenia, defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
4. Any treatment-related toxicity that results in a dose hold of >7 consecutive days or causes the patient to discontinue treatment.
5. Any Grade 5 toxicity not clearly due to the underlying disease or extraneous causes
6. Any Hy's law case: ALT and/or AST >3 × ULN and total bilirubin >2 × ULN not explained by other causes.

5.5.3.2. Phase 2: Nanatinostat and Valganciclovir With or Without Pembrolizumab

The DLT evaluation period is 7 weeks.

Phase 2 of the study will initially have a dose optimization cohort period to assess the safety of the RP2D and '<RP2D' of nanatinostat and valganciclovir determined by the SMC's review of the totality of the data from the previous Phase 1b cohorts. The dose optimization cohort period will be monitored by the study's SMC composed of the lead study Investigators and the Sponsor's Medical Monitor. The evaluation period will be 2 cycles post-initial study drug administration (7 weeks). When all patients enrolled in the dose optimization cohort have completed 2 cycles (7 weeks) of treatment (or discontinued earlier) recruitment will be paused until a safety data review is performed in the following situations:

1. If treatment was postponed due to the reasons listed below for more than 2 of the first 6 enrolled patients who received at least one dose of any study drug.
2. If treatment was postponed due to the reasons listed below for 4 or more of the first 9 patients who have received at least one dose of any study drug.

The SMC will review the clinical and laboratory data for any DLTs and/or emerging new or unexpected toxicities associated with the nanatinostat and valganciclovir dose to determine the next steps for dosing and continued enrollment.

Following review of the data from the dose optimization cohorts and confirmation of the RP2D, enrollment into the Phase 2 dose expansion will begin, supported by an early safety analysis of the first 6 patients randomized to receive nanatinostat and valganciclovir with pembrolizumab as described in Section 5.5.3.3. Any DLTs and/or emerging new or unexpected toxicities associated with nanatinostat in combination with valganciclovir and pembrolizumab will be evaluated by the SMC who will determine the next steps for dosing and continued enrollment.

To be considered a DLT, an AE must meet one of the following criteria, where the relationship to study drug(s) cannot be ruled out, and the AE is not primarily related to disease, disease progression, concomitant medication(s) or intercurrent illness:

1. Hematologic DLTs:
   - Grade 4 neutropenia or thrombocytopenia lasting ≥7 days.
   - Grade ≥3 thrombocytopenia associated with clinically significant bleeding.
2. Non-hematologic DLTs:
   a. Grade ≥3 non-laboratory toxicities despite maximum supportive therapy.
   b. Grade ≥3 clinically significant laboratory abnormality for which the patient is symptomatic regardless of its duration, requires medical intervention, is not corrected within 72 hours, or leads to hospitalization.
3. Febrile neutropenia defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
4. Any treatment-related toxicity that causes the participant to discontinue treatment.
5. Any Grade 5 toxicity not clearly due to the underlying disease or extraneous causes.
6. Any Hy's law case: ALT and/or AST >3 × ULN and total bilirubin >2 × ULN not explained by other causes.

After the nanatinostat and valganciclovir RP2D is confirmed by the SMC based on the results of the dose optimization cohorts, the study will proceed to the Phase 2 dose expansion period. 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 200 mg IV every 3 weeks to assess the preliminary antitumor activity, safety, and tolerability of each regimen.

5.5.3.3. Assessment of Toxicity During Phase 2 Dose Expansion

Sequential boundaries will be used to monitor the DLT rate during Phase 2 dose expansion (Ivanova 2005). The accrual will be halted if excessive numbers of DLTs (boundary) as defined in Section 5.5.3.2 are seen per arm, and the SMC will have the option of either discontinuing accrual in that arm or reducing the RP2D to reduce the level of toxicity. The boundaries at which accrual is halted or the RP2D is reduced are listed in Table 6. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 5% when the rate of dose-limiting toxicity is equal to the acceptable rate of 30%.

Table 6: Early Stopping Boundaries for Toxicity

Number of Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Boundary	-	-	-	4	5	5	6	6	7	7	8	8	9	9	9
Number of Patients	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Boundary	10	10	11	11	12	12	12	13	13	14	14	14	15	15	15

An early safety analysis of the first 6 patients randomized to receive nanatinostat and valganciclovir with pembrolizumab will be performed, and a more conservative early stopping boundary than is shown in Table 6 above will be applied if appropriate. If at least two of these patients experience DLTs during their first 2 cycles (7 weeks) of treatment, then patient accrual will be halted, and the SMC will have the option of either discontinuing accrual in that arm or reducing the RP2D to reduce the level of toxicity.

5.6. Dose Modification Guidelines for Study Treatment-Related Toxicities

Nanatinostat and Valganciclovir

For patients who do not tolerate the protocol-specified dosing schedule or develop toxicities, dose adjustments of nanatinostat and valganciclovir are permitted. Dose adjustments, except for valganciclovir adjustments based on renal function (Section 5.6.2), must be approved by the Medical Monitor or Sponsor prior to implementing. These changes must be accurately recorded in the eCRFs.

Given the expectation that both study drugs are required for activity, both agents will be held and restarted in parallel. Dose modification guidelines in case of study treatment-related toxicity for nanatinostat, valganciclovir, and pembrolizumab are presented in Table 7.

Unless otherwise indicated in Table 7, any AE that requires a dose hold should resolve to Grade 1 or baseline generally within 14 days before resuming treatment at the current or a reduced dose.

The management of patients requiring more than 2 dose reductions should be discussed with the Sponsor's Medical Monitor.

For patients in Phase 2 treated with nanatinostat and valganciclovir in combination with pembrolizumab, if pembrolizumab treatment is discontinued, nanatinostat and valganciclovir dosing may continue. If nanatinostat or valganciclovir are discontinued, the Sponsor's Medical Monitor should be consulted about pembrolizumab treatment.

Pembrolizumab

Dose reduction of pembrolizumab will not be required in this study. For the management of specific immune-mediated adverse reactions, see Table 8. Otherwise, withhold pembrolizumab for severe (Grade 3) immune-mediated adverse reactions and permanently discontinue pembrolizumab for those that are life-threatening (Grade 4), recurrent Grade 3 that require systemic immunosuppressive treatment, or if not able to reduce corticosteroid dosing to 10 mg per day or less of prednisone or an equivalent within 12 weeks of initiating steroids.

If a patient requires a dose interruption of >6 weeks of pembrolizumab from the intended day of the next scheduled dose, pembrolizumab should be discontinued.

Exceptions following a discussion between the Sponsor's Medical Monitor and the Investigator may be possible. Reasons for a potential exception include, but are not limited to, the following:

1. Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs.
2. Dosing delays lasting >6 weeks from the previous dose that occur for non-drug-related reasons (eg, surgery) may be allowed.

Patients with permanent discontinuation of pembrolizumab due to adverse reactions may continue treatment with nanatinostat and valganciclovir provided that they could still potentially benefit from the treatment (in the opinion of the Investigator) until disease progression, occurrence of intolerable toxicity, death, Investigator's decision, or voluntary withdrawal of the patient from the study.

The Investigator must first discuss any decision about permanent drug discontinuation in advance with the Sponsor's Medical Monitor. All doses of study treatment and all dose interruptions or modifications must be accurately recorded in the eCRFs.

For additional details on pembrolizumab dosing, refer to the current prescribing information (Keytruda [pembrolizumab] Prescribing Information, 2023).

Table 7: Dose Modification Guidelines for Study Treatment-Related Toxicity

NCI CTCAE v5.0 Toxicity Grade	Recommended Dose Modifications for Nanatinostat and Valganciclovir	Recommended Dose Modifications for Pembrolizumab
Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L)	1. Interrupt nanatinostat/valganciclovir dosing. 2. Resume nanatinostat/valganciclovir at the same doses when ANC $\geq 1.0 \times 10^9$/L. 3. If the grade 4 neutropenia lasts more than 7 days or recurs, then decrease valganciclovir dose by 50% daily. For dose levels 6 and 7: decrease twice daily valganciclovir dosing to once daily dosing (take with nanatinostat). 4. If the decreased dose is tolerated for ≥4 weeks, then resume previous daily valganciclovir dose. 5. If Grade 4 neutropenia occurs again following a valganciclovir dose reduction, then interrupt nanatinostat/valganciclovir dosing and discuss with the medical monitor. 6. Use of growth factors (G-CSF, GM-CSF) is permitted per the ASCO 2015 clinical practice guidelines (Smith 2015).	Withhold until resolution to Grade 0 or 1.
Grade 3 neutropenia (ANC 0.5 – $<1.0 \times 10^9$/L)	1. If persistent (>7 days) then interrupt nanatinostat/valganciclovir dosing. 2. Resume nanatinostat/valganciclovir at the same doses when ANC $\geq 1.0 \times 10^9$/L. 3. If recurs and persists >7 days, then consider reducing daily valganciclovir dose by 50%. For dose levels 6 and 7: decrease twice daily valganciclovir dosing to once daily dosing (take with nanatinostat). 4. If persists, then decrease nanatinostat daily dose to the next lowest nanatinostat dose level. 5. Use of growth factors (G-CSF, GM-CSF) are permitted per the ASCO 2015 clinical practice guidelines (Smith 2015).	Maintain dose and schedule.

NCI CTCAE v5.0 Toxicity Grade	Recommended Dose Modifications for Nanatinostat and Valganciclovir	Recommended Dose Modifications for Pembrolizumab
Grade 4 thrombocytopenia (Platelet count <25 × 10^9/L)	1. Interrupt nanatinostat/valganciclovir dosing. 2. If thrombocytopenia resolves to ≤Grade 2 (>50 × 10^9/L), then restart both drugs. 3. If recurs, then decrease daily valganciclovir dose by 50%. For dose levels 6 and 7: decrease twice daily valganciclovir dosing to once daily dosing (take with nanatinostat). If the decreased dose is tolerated for ≥4 weeks, then resume previous daily valganciclovir dose. 4. If Grade 4 thrombocytopenia occurs again following a valganciclovir dose reduction, then interrupt nanatinostat/valganciclovir dosing and discuss with the medical monitor.	If ongoing at time of next scheduled pembrolizumab dose, omit scheduled dose. If asymptomatic, resolved to ≤Grade 2 within ≤7 days and prior to scheduled dose, proceed with pembrolizumab dose.
Grade 3 anemia (Hemoglobin <8.0 g/dL)	1. Continue nanatinostat and decrease valganciclovir dose as follows: from 900 mg twice daily to 900 mg daily; from 900 mg daily to 450 mg daily; from 450 mg daily to 450 mg every 2 days; from 450 mg every 2 days to 450 mg twice weekly. 2. If anemia persists, then decrease nanatinostat daily dose to the next lowest nanatinostat dose level. 3. If anemia resolves to ≤Grade 2 (≥8.0 g/dL), after (1), then increase valganciclovir dose. Increase nanatinostat dose if it was decreased per (2). 4. If anemia recurs, then decrease valganciclovir dose as outlined in (1) and maintain at the lower dose. 5. Transfusion is recommended in patients with a hemoglobin level <7-8 g/d L per institutional guidelines, and/or with symptomatic anemia	Maintain dose and schedule.
Grade 4 anemia	1. Hold both study drugs. 2. Transfuse. 3. Once anemia resolves to ≤Grade 2 (≥8.0 g/dL), resume nanatinostat at the planned dose and valganciclovir at a lower dose as follows: Decrease 900 mg twice daily to 900 mg daily; decrease 900 mg daily to 450 mg daily; decrease 450 mg daily to 450 mg every 2 days; decrease 450 mg every 2 days to 450 mg twice weekly) 4. If anemia persists, then decrease nanatinostat daily dose to the next lowest nanatinostat dose level. 5. If recurs, interrupt both drugs and discuss with the study's Medical Monitor.	Maintain dose and schedule.
Febrile neutropenia (ANC <1.0 × 10^9/L, with a single temperature of ≥38.3°C or a sustained temperature of ≥38°C for more than 1 hour)	1. Interrupt nanatinostat/valganciclovir dosing. 2. Resume nanatinostat/valganciclovir at the same doses when ANC ≥1.0 × 10^9/L. 3. Use of growth factors (G-CSF, GM-CSF) are permitted per the ASCO 2015 clinical practice guidelines (Smith 2015).	Withhold until resolution to Grade 0 or 1.
QTc prolongation	**For QTc interval >480 msec and <500 msec:** 1. Check magnesium and potassium levels and correct any abnormalities. 2. If possible, stop any medications that may prolong the QTc interval. 3. Decrease nanatinostat to the next lowest nanatinostat dose level. 4. Resume nanatinostat/valganciclovir at the initial dose in the next cycle provided that the QTc interval improves to ≤470 msec at the start of that cycle. Otherwise continue nanatinostat at the next lowest nanatinostat dose level.	Maintain dose and schedule.

NCI CTCAE v5.0 Toxicity Grade	Recommended Dose Modifications for Nanatinostat and Valganciclovir	Recommended Dose Modifications for Pembrolizumab
	For QTc interval >500 msec: 1. Check magnesium and potassium levels and correct any abnormalities. 2. Interrupt nanatinostat/valganciclovir dosing and stop any medications that may prolong the QTc interval. 3. If the QTc interval improves to ≤470 msec just prior to the start of the next cycle, resume nanatinostat/valganciclovir at the initial dose. 4. If no other cause of QTc prolongation is identified, decrease dose of nanatinostat to the next lowest nanatinostat dose level. Otherwise continue to hold nanatinostat/valganciclovir for as long as necessary.	
Other study drug-related Grade 3/4 non-hematologic toxicity or Grade 3/4 clinically significant laboratory abnormalities	**Grade 4 non-hematologic AE**: 1. Discontinue nanatinostat/valganciclovir dosing. 2. Following resolution of the toxicity to ≤Grade 1 or to the patient's baseline value, if the Investigator considers it to be in the patient's best interest to resume therapy, this may be permitted at a lower dose level following discussion with Sponsor's Medical Monitor. **Grade 3 non-hematologic AE**: 1. Resume nanatinostat/valganciclovir at the same dose when toxicity resolves to ≤Grade 1.	See Table 8.
Treatment-related Grade 5 toxicity	1. Pause further enrollment in the study pending a Safety Monitoring Committee assessment.	Pause further enrollment in the study pending a Safety Monitoring Committee assessment.

Dose levels for Phase 1b are defined in Table 4.
AE = adverse event; ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; CTCAE = Common Terminology Criteria for Adverse Events; G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte macrophage-colony stimulating factor; NCI = National Cancer Institute; PO = orally; QD = once daily.

Table 8: Pembrolizumab Recommended Dose Modifications for Immune-Mediated Adverse Reactions

Adverse Reaction	Severity	Pembrolizumab Dose Modification
Pneumonitis	Grade 2	Withhold[1]
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold[1]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to >3 and up to 8 × ULN or total bilirubin increases to more than 1.5 and up to 3 × ULN	Withhold[1]
	AST or ALT increases to more than 8 × ULN or Total bilirubin increases to more than 3 × ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[2]	Baseline AST or ALT is more than 1 and up to 3 × ULN and increases to more than 5 and up to 10 × ULN or Baseline AST or ALT is more than 3 and up to 5 × ULN and increases to more than 8 and up to 10 × ULN	Withhold[1]
	AST or ALT increases to more than 10 × ULN or Total bilirubin increases to more than 3 × ULN	Permanently discontinue

Adverse Reaction	Severity	Pembrolizumab Dose Modification
Endocrinopathies	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with renal dysfunction	Grade 2 or 3 increased creatinine	Withhold[1]. Follow guidelines for valganciclovir dose reduction in Table 7. Resume in patients with complete or partial resolution (Grades 0 to 1) after valganciclovir dose adjustment and/or corticosteroid taper
	Grade 4 increased creatinine	Permanently discontinue
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold[1]
	Confirmed SJS, TEN or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[1]
	Grade 3 or 4	Permanently discontinue
Infusion-related reactions	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue

Source: Keytruda [pembrolizumab] Prescribing Information, 2023
[1]Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper
[2]If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue KEYTRUDA based on recommendations for hepatitis with no liver involvement.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; DRESS = Drug Rash with Eosinophilia and Systemic Symptoms; SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal

Patients should be monitored until resolution of the toxicity. During a dose interruption, study days and procedures will continue to accrue until the end of the current cycle (see Schedule of Events in Section 6). If the dose interruption extends beyond the end of the cycle, the subsequent Cycle Day 1 will not begin until dosing has resumed. If the dose is held for more than 14 days, the Investigator should consult with the Sponsor's Medical Monitor before dosing resumes.

If a patient has multiple dose interruptions for study drug toxicity or has had to interrupt for more than 14 days, a dose reduction may be considered. Re-escalation of study drug dose may only be performed after approval by the Sponsor's Medical Monitor.

5.6.1. Criteria for Suspension of Study Drug Treatment Due to Treatment-Related Toxicities

In the event of the following treatment-related toxicities, no additional patients should be enrolled until further review and assessment by the Safety Monitoring Committee:

- Death
- Grade 4 QTc prolongation (Torsade de Pointes)
- Occurring in ≥2 patients:
  - Grade 4 acute renal failure
  - Grade 4 multi-organ failure

5.6.2. Dose Modifications for Patients with Renal Impairment

Patients who develop an elevated creatinine while on study should have their dose of valganciclovir adjusted per Table 9.

An estimated creatinine clearance in adults is calculated from serum creatinine by the following formulas:

For serum creatinine measured in mg/dL:

For males = $\frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (\text{serum creatinine [mg/dL]})}$ = XX mL/min

For females = $\frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (\text{serum creatinine [mg/dL]})}$ = XX mL/min × 0.85

For serum creatinine measured in μmol/L:

For males = $\frac{(140 - \text{age [years]}) \times (\text{body weight [kg]}) \times 1.23}{\text{Serum creatinine (μmol/L)}}$ = XX mL/min

For females = $\frac{(140 - \text{age [years]}) \times (\text{body weight [kg]}) \times 1.23}{\text{Serum creatinine (μmol/L)}}$ = XX mL/min × 0.85

For patients already receiving a dose of valganciclovir lower than that recommended in Table 9, the Investigator should discuss the amount of dose reduction with the Sponsor's Medical Monitor.

Table 9: Valganciclovir Dose Adjustments for Patients with Renal Impairment

Creatinine Clearance (mL/minute)	Valganciclovir Dose (daily)	Valganciclovir Dose (twice daily)
≥60	900 mg once daily	900 mg twice daily
40–59	450 mg once daily	450 mg twice daily
25–39	450 mg every 2 days	450 mg once daily
10–24	450 mg twice weekly	450 mg every 2 days
<10 (on hemodialysis)	Not recommended (discuss with Medical Monitor)	Not recommended (discuss with Medical Monitor)

5.6.3. Missed or Vomited Doses

For dose levels 1 to 3, if a scheduled dose of nanatinostat or valganciclovir is missed, the patient should take the missed dose(s) as soon as possible during the same day if within 8 hours of the missed dose. For dose levels 4 to 13, or if more than 8 hours has passed, the planned dosing schedule will be resumed the following day without a change in the daily dose or schedule; do not make up missed or vomited doses.

If a scheduled dose of nanatinostat or valganciclovir is vomited, the patient should contact the site for consideration of anti-nausea medication and dosing should resume with the next

scheduled dose. No replacement dose should be given. If the situation persists, the site should consult with the Sponsor's Medical Monitor.

The prescribing information for pembrolizumab should be followed for any missed doses (Keytruda [pembrolizumab] Prescribing Information, 2023).

5.7. Prior and Concomitant Medications

Prior and concomitant medications include all vitamins, herbal remedies, over-the-counter, and prescription medications.

No other anticancer therapies (including chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted while the patient is receiving treatment with nanatinostat, valganciclovir, and pembrolizumab. Patients are not allowed to participate concurrently in any other therapeutic study.

If a patient takes an exclusionary medication while on study, the event will be deemed a protocol deviation and continuation of that patient in the study will be decided by the Sponsor's Medical Monitor.

5.7.1. Supportive Care Guidelines and Permitted Concomitant Medications

During the treatment period, medications required to treat AEs or manage cancer symptoms, and supportive care agents, such as antiemetics, antidiarrheal agents, and pain medications are allowed, except if specifically prohibited (Section 5.7.4). Patients may continue to use concomitant medications previously prescribed to treat non-cancer-related conditions provided that, in the Investigator's judgment, they will not interfere with the study outcomes.

Patients should receive appropriate supportive care measures deemed necessary by the treating Investigator including the following:

- Nausea and vomiting: If nausea and vomiting occur, consideration should be given to using prophylactic antiemetic therapy in subsequent cycles according to local institutional practice. Liberal oral fluid intake should be maintained if possible.
- Diarrhea: All patients experiencing diarrhea should be advised to drink liberal quantities of clear fluids. If this is not possible, IV fluid and electrolyte replacement therapy should be utilized.
- Neutropenia (See Section 5.7.1.2).

5.7.1.1. Pembrolizumab Infusion-Related Reactions

Pembrolizumab has been reported to cause infusion-related reactions varying in severity from hypersensitivity to anaphylaxis in 0.2% of patients. Patients should be monitored for the signs and symptoms of infusion-related reactions (including rigors, chills, wheezing, pruritis, flushing, rash, hypoxemia, hypotension, and fever). Table 10 provides infusion-related reaction treatment guidelines. For additional details, refer to the current prescribing information for pembrolizumab (Keytruda [pembrolizumab] Prescribing Information, 2023).

Table 10: Pembrolizumab Infusion-Related Reaction Treatment Guidelines

Severity (CTCAE Grade)	Action
Grade 1 or 2	**Interrupt or slow the rate of the infusion**. Increase the monitoring of vital signs until the patient is deemed medically stable in the opinion of the Investigator. The use of additional supportive therapies (IV fluid, antihistamines, NSAIDs, acetaminophen, narcotics) may be considered. For grade 2 reactions, patients may be pre-medicated prior to the next pembrolizumab infusion with acetaminophen 500-1000 mg oral (or an equivalent antipyretic) and diphenhydramine 50 mg oral (or an equivalent antihistamine).
Grade 3 or 4	**Stop the infusion and permanently discontinue pembrolizumab**. Monitor symptoms. Increase the monitoring of vital signs until the patient is deemed medically stable in the opinion of the Investigator. Additional appropriate supportive therapies may include IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, corticosteroids, and epinephrine. Hospitalization may be indicated.

Source: Keytruda [pembrolizumab] Prescribing Information, 2023
CTCAE = Common Terminology Criteria for Adverse Events; IV=intravenous; NSAID=nonsteroidal anti-inflammatory drug.

5.7.1.2. Hematopoietic Growth Factors

The prophylactic use of hematopoietic growth factors is prohibited unless the patient experiences an AE. Granulocyte colony-stimulating factor (G-CSF) agents may be administered in response to Grade ≥3 neutropenia (Table 7). The American Society of Clinical Oncology (ASCO) clinical practice guidelines should be followed (Smith 2015). Hematopoietic growth factors may not be used within 21 days of screening.

5.7.2. Concomitant Therapy Requiring Caution and/or Action

5.7.2.1. Corticosteroids

Patients may receive topical or inhaled corticosteroids while on study, or prednisone ≤10 mg per day (or the equivalent). The use of systemic corticosteroids is discouraged because the potential anti-tumor effect may confound the interpretation of study drug-related activity. Patients who develop severe conditions requiring systemic corticosteroid therapy may be treated as such and are not required to discontinue participation in the study.

5.7.2.2. Proton Pump Inhibitors

The effect of gastric pH on nanatinostat absorption is not known. If possible, proton pump inhibitors and H_2 antagonists should be excluded from patient use. If these medications must be given, do not administer proton pump inhibitors, H_2 antagonists, or antacids within 2 hours prior to or within 4 hours after nanatinostat administration.

5.7.2.3. Concomitant Therapies to be Used with Caution with Nanatinostat

A study with recombinant human CYP450 suggests that nanatinostat is a direct inhibitor of CYP3A4 isoform. In vitro studies indicated that nanatinostat is not metabolized by or induces the

activity of CYP3A4. A potential for drug interactions between nanatinostat and drugs that are substrates of CYP3A4 is low, but cannot be ruled out (see Appendix 1, Table 1). Please refer to the IB for a detailed description.

Select ARTs (saquinavir, tipranavir, darunavir, and idinavir) that are metabolized by CYP3A4 should be administered with caution. Coadministration of these ARTs may result in an increase in their systemic exposures. Caution is recommended during the coadministration of these drugs with nanatinostat (particularly saquinavir and indinavir due to their narrow therapeutic index), as well as other CYP3A substrates relevant to the study population (cyclosporine, sirolimus, tacrolimus).

As combined (estrogen-progesterone containing) oral contraceptives are metabolized by CYP3A4, caution is also recommended during the coadministration of these drugs with nanatinostat. Although the potential for drug interactions and risk of venous thromboembolism is low, the use of an alternative method of contraception is recommended.

Transporter studies indicate nanatinostat is likely a substrate of multidrug resistance 1 (MDR1) and BCRP transporters, but not an inhibitor of these transporters. Therefore, the use of strong MDR1/P-gp and BCRP inhibitors should be approached with caution (see Appendix 1, Table 2).

5.7.3. Concomitant Therapies to be Used with Caution with Valganciclovir

Drug-drug interaction studies with ganciclovir and valganciclovir were conducted in patients with normal renal function. Therefore, with concomitant administration of valganciclovir and other renally excreted drugs, patients with impaired renal function may have increased concentrations of ganciclovir and/or the co-administered drug. Such patients should be closely monitored for toxicity of ganciclovir and the co-administered drug. Established and other potentially significant drug interactions conducted with ganciclovir are listed in Appendix 2.

Patients receiving concomitant immunosuppressive agents such as cyclosporine, mycophenolate mofetil, sirolimus, and tacrolimus may be at risk for increased hematologic and/or renal toxicity.

Coadministration of the antiretroviral agent didanosine may result in an increase in its concentration and patients should be monitored closely for toxicity (eg, pancreatitis). In patients who are receiving a concomitant medication considered to pose a risk of significant drug interaction with valganciclovir, additional monitoring should be conducted as outlined in Appendix 2.

5.7.4. Prohibited Therapies

Patients are prohibited from receiving the following therapies during the screening and treatment phases of this study:

- Anti-cancer systemic chemotherapy or biologic therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than nanatinostat, valganciclovir and pembrolizumab.
- Radiation therapy.
- Tenofovir (unless the patient can be switched to an alternative ART).

- Live vaccines within 30 days prior to the first dose of investigational treatment and while participating in the study.
- Medications with a known risk of prolonging the QTc interval/TdP (Class Ia [disopyramide, quinidine, procainamide] and Class III [sotalol, dofetilide, ibutilide] antiarrhythmic agents) (Drew 2010). If, during the course of this study, the concomitant administration of drugs with a known potential to cause TdP is required and cannot be avoided, study drug administration must be interrupted until an assessment of the potential safety risk has been performed.
- Corticosteroids for any reason other than those outlined in Section 5.7.2.1.

5.8. Patient Numbering & Treatment Assignment

5.8.1. Patient Numbering

At the time of consent, patients will be assigned a 7-digit identification number consisting of a 4-digit site number (eg, 1001) followed by a 3-digit patient number (eg, 101). Patient numbers will be assigned sequentially at each site starting with 101 (eg, 1001-101, 1001-102, 1001-103, etc.) for patients enrolled in the Phase 1b portion of the study and starting with 201 (eg, 1001-201, 1001-202, 1001-203, etc.) for patients enrolled in Phase 2.

5.8.2. Treatment Assignment (Including Randomization)

Patients with EBV^+ RM-NPC will be enrolled in groups of 3 to 6 in the Phase 1b escalating nanatinostat dose groups 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 as shown in Figure 3.

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 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 group. An early safety analysis after the first 6 patients are randomized to this treatment group and followed for at least 2 cycles (7 weeks) of treatment will be performed as described in Section 5.5.3.3.

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.

5.8.3. Treatment Blinding

This is an open-label study; therefore, treatment assignments will not be blinded.

5.9. Study Drug Preparation and Dispensation

5.9.1. Study Drug Packaging and Labelling

The study treatment will be released upon receipt of all requested essential documents based on federal, state, and local regulations. Each bottle of study drug will have either a booklet or panel label describing the contents based on regulatory requirements and a place for the pharmacist to record the patient number. Additional information is described in Section 5.1 (nanatinostat), Section 5.2 (valganciclovir), and Section 5.3 (pembrolizumab).

5.9.2. Drug Supply and Storage

Drug supply and storage is described in Section 5.1 (nanatinostat), Section 5.2 (valganciclovir) and Section 5.3 (pembrolizumab). Additional information is provided in the Study Pharmacy Manual.

5.9.3. Study Drug Compliance and Accountability

5.9.3.1. Study Drug Compliance

Patient compliance with oral study drugs will be assessed by the Investigator and/or study personnel at each patient visit, and information provided by the patient and/or caregiver will be captured in the eCRF. This information must be captured in the source documents at each patient visit. Paper diaries will be utilized to record doses and collect tablet counts.

5.9.3.2. Study Drug Accountability

The Investigator or their representative will account for all study drugs supplied by the Sponsor. The Investigator shall maintain adequate records of the disposition of study drug, including

dates, quantity, lot numbers, and use by patients. Drug accountability will be reviewed during monitoring visits and at the completion of the study.

5.9.4. Study Drug Handling and Disposal

Upon completion of the study, all remaining study treatment at the sites will be accounted for and returned to the Sponsor, or their designee, via a traceable method (US Postal Service, FedEx, etc.) or disposed following institution's Standard Operating Procedures (SOPs), if instructed by the Sponsor.

6. SCHEDULE OF EVENTS

Scheduled study visits, assessments, and dosing of each study drug will occur according to the Schedule of Events provided in Table 11. Every effort should be made to follow the schedule outlined in this table. Allowed visit windows are specified as follows:

1. Screening assessments must occur within 28 days or 21 days of Cycle 1 Day 1:
    a. Vital signs, ECOG performance status, and physical exam should be performed within 28 days of start of study drug (Cycle 1 Day 1).
    b. Specified laboratory and radiologic assessments should be performed within 21 days prior to the start of study drug (Cycle 1 Day 1).
2. Radiologic assessments must be performed as indicated in Table 11. A visit window of ±7 days is allowed. Even if study treatment doses are held for a patient, radiologic assessments should stay on schedule.
3. All other assessments have a general ±3-day window for completion with the exception of safety follow-up assessments that have a ±5-day window and the long-term follow-up assessments that have a ±7-day window.
4. A creatinine clearance determination should be performed monthly, and in case of a creatinine elevation while on-study.

Table 11: Schedule of Events

	Screening[a]		Cycle 1 (28 days)				Cycle 2 (21 days)		Cycle 3+ (21 days)	EOT[b]	Safety Follow-up[c]		Long-Term Follow-up[d]	
Day(s) of Cycle[e]	**-28 to -1**	**-21 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**1**		**30 Days (±5 Days) After Last Dose**	**90 Days (±5 Days) After Last Dose**	**Without PD (q12 weeks ±7 days)**	**With PD (q12 weeks ±7 days)**
Study Day			**1**	**8**	**15**	**22**	**29**	**36**	**50+**					
Study Week			**1**	**2**	**3**	**4**	**5**	**6**	**8+**					
Obtain informed consent	X													
Enrollment/ Randomization			X											
Patient history														
Complete medical history	X													
Demography	X													
Prior antineoplastic therapies	X													
Inclusion/exclusion criteria	X													
Prior and concomitant medications	X		X	X	X	X	X	X	X	X	X[f]	X[f]		
Physical examination	X		X				X		X	X				
Weight	X		X				X		X	X				
Height	X													
ECOG performance status	X		X							X				
Vital signs[g]	X		X				X		X	X				
Laboratory assessments														
Hematology[h]		X	X	X	X	X	X	X	X	X				
Chemistry[i]		X	X	X	X	X	X	X	X	X				
Thyroid function tests[j]			X				X[qcycle2]							
Creatinine clearance (Cockcroft-Gault estimation)[k]		X	X				X		X	X				
Coagulation[h]		X								X				
Urinalysis[l]		X												
Hepatitis serology[m]	X													
Serum pregnancy test[n]		X												
Serum or urine pregnancy test[n]			X				X		X	X	X		X[0-6mo]	X[0-6mo]

	Screening[a]		Cycle 1 (28 days)				Cycle 2 (21 days)		Cycle 3+ (21 days)	EOT[b]	Safety Follow-up[c]		Long-Term Follow-up[d]	
Day(s) of Cycle[e]	**-28 to -1**	**-21 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**1**		**30 Days (±5 Days) After Last Dose**	**90 Days (±5 Days) After Last Dose**	**Without PD (q12 weeks ±7 days)**	**With PD (q12 weeks ±7 days)**
Study Day			**1**	**8**	**15**	**22**	**29**	**36**	**50+**					
Study Week			**1**	**2**	**3**	**4**	**5**	**6**	**8+**					
Disease assessments														
Brain CT or MRI[o]		X												
Tumor evaluation per RECIST v1.1 CT/MRI with contrast enhancement[o]		X							X[q6wks, wk26+ q12wks]	X			X[q12wks]	
Safety assessments														
12-lead ECG	X[p]		X[p]				X[p]			X[p]				
Adverse events	X		X	X	X	X	X	X	X	X	X	X[q]		
CMV[r]	X		X		X		X		X	X				
HIV[r]	X		X		X		X		X	X				
EBV DNA levels[r]	X		X	X	X	X	X		X	X	X		X	
Pharmacokinetics														
PK sampling[s]			X				X							
Biomarkers[t]														
Immunophenotype and functions[u]			X						X[qcycle3]	X				
Histone acetylation[v]			X											
Plasma biomarker analysis			X				X		X	X				
Tumor Biopsy														
Archival FFPE tumor specimen[w]	X													
De novo tumor biopsy[x]	X				X									
On-Study Biopsy (optional with disease progression or relapse)[y]			X											
Nanatinostat/valganciclovir dispensing/return			X[z]				X		X	X				
Pembrolizumab dosing (Phase 2 only)				X			X		X					

	Screening[a]		Cycle 1 (28 days)				Cycle 2 (21 days)		Cycle 3+ (21 days)	EOT[b]	Safety Follow-up[c]		Long-Term Follow-up[d]	
Day(s) of Cycle[e]	**-28 to -1**	**-21 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**1**		**30 Days (±5 Days) After Last Dose**	**90 Days (±5 Days) After Last Dose**	**Without PD (q12 weeks ±7 days)**	**With PD (q12 weeks ±7 days)**
Study Day			**1**	**8**	**15**	**22**	**29**	**36**	**50+**					
Study Week			**1**	**2**	**3**	**4**	**5**	**6**	**8+**					
Anti-neoplastic therapies since discontinuation of study treatment and response[aa]										X			X	
Survival contact[aa]														X

AE = adverse event; CR = complete response; CT = computed tomography; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; FFPE = formalin-fixed paraffin embedded; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetic; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; TSH = thyroid stimulating hormone

a. **Screening** – The screening visit may be conducted over multiple days in the 28 days prior to Cycle 1 Day 1 or conducted as a single visit within 21 days of Cycle 1 Day 1.
b. **EOT visit** – At the time patients discontinue study treatment, a visit should be scheduled as soon as possible and within 14 days after the last dose of study treatment.
c. **Safety Follow-up** – Assessments will occur 30 and 90 days after the last dose of study treatment for all patients. Visits at 30 days after last dose will be conducted in person to complete assessments. The safety follow-up assessments at 90 days after last dose may be completed by phone or in person. In situations for which the patient has declined further testing, follow-up via phone call, e-mail, medical records, clinic visits, or public records such as government census or death records will be performed to collect as much information as possible. The first Long-Term Follow-up visit may coincide with the 90-day Safety follow-up assessments.
d. **Long-term Follow-up** – Patients who discontinue treatment for reasons other than disease progression will have tumor and plasma EBV DNA level assessments every 12 weeks (3 months) ± 7 days for up to 1 year from the date of the last dose of study treatment, disease progression, the initiation of subsequent anti-cancer therapies, or end of the study, whichever occurs first. Scans performed during the Follow-up period should be performed on the same schedule with the same imaging modality as previously used. All patients enrolled in the study will be followed for survival every 12 weeks (3 months) according to Section 3.1.3.2 until withdrawal of consent, death, lost to follow-up, completion of 3 years of follow-up, completion of 1 year after the last patient discontinues treatment, or the study is terminated by the Sponsor, whichever occurs first. For females of childbearing potential, long-term follow-up visits must be completed in person for the first 6 months following the last dose of study drugs to perform pregnancy testing.
e. **Visit windows** – There is a ±3-day window allowable for each clinic visit following Cycle Day 1. The Safety Follow-up visit has a ±5-day allowable window, and Long-term Follow-up has a ±7-day allowable window. For disease assessments after Cycle Day 1, a ±7-day window is allowable.
f. During Safety Follow-up, only concomitant medications used to treat AEs and any new antineoplastic therapies will be collected.
g. **Vital signs** - Vital signs include heart rate, blood pressure, and temperature. For patients enrolled in Phase 1b dose levels 1-7 requiring serial PK draws and ECGs, vital signs should be collected following ECGs and prior to the PK blood draws on Cycle 1 Day 1 and Cycle 2 Day 1 at the following timepoints: pre-dose, just prior to the first dose of nanatinostat and valganciclovir, and post-dose at 1-, 2-, 4-, and 6-hours (±15 minutes). For patients enrolled in dose levels 8-13 and Phase 2 requiring serial PK draws and ECGs, vital signs should be collected following ECGs and prior to the PK blood draws on Cycle 2 Day 1 at the following timepoints: pre-dose, just prior to the first dose of nanatinostat and valganciclovir, and post-dose at 1-, 2-, 3-, 4-, 5-, and 6-hours (±15 minutes). At time points requiring ECGs, vital signs, and PK blood draws, assessments should be performed in as short of timeframe as possible and in this order: ECG, vital signs, then blood draw.
h. **Hematology and coagulation** – Hematology includes complete blood count to include white blood cells (WBCs) with differential, hemoglobin (Hgb), and platelets. Coagulation includes prothrombin time (PT) or International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT).
i. **Chemistry** – Chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose (non-fasting), calcium, phosphate, magnesium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, alkaline phosphatase (ALP), albumin, and uric acid.

j. **Free T3, free T4 and TSH** will be performed at baseline (Cycle 1 Day 1 pre-dose for all Phase 2 patients). Subsequently, TSH should be assessed every 2 cycles starting at Cycle 2 Day 1.

k. **Creatinine clearance (Cockcroft-Gault estimation)** – The Cockcroft-Gault formula will be used to calculate estimated creatinine clearance (CrCl), and should be performed at screening, monthly, and repeated locally in case of creatinine elevations while on study:

- Males: CrCl (mL/min) = (140 – age) × (weight [kg]) / 72 × (serum creatinine [mg/dL]); for females, the formula is multiplied by 0.85.
- By SI units, CrCl (mL/min) = (140 – age) × (weight [kg]) × 1.23 / (serum creatinine [µmol/L]); for females, the formula is multiplied by 0.85.

Valganciclovir dose will be adjusted based on CrCl as described in Section 5.6.2 for patients with creatinine elevations/impaired renal function.

l. **Urinalysis** will be performed locally at each site.

m. **Hepatitis screening** – Hepatitis B virus (HBV) surface antigen (Ag), HBV core and surface antibody (Ab), HBV DNA polymerase chain reaction (PCR; only for patients with positive HBV core Ab or surface Ag), hepatitis C virus (HCV) Ab (any subject positive for HCV Ab will be evaluated by qPCR).

n. **Pregnancy testing** – Pregnancy testing is only required for females of childbearing potential and will be performed locally at each site. Serum test must be performed during screening. Serum or urine tests are to be performed at the beginning of each cycle, at EOT, and at the 30-day Safety Follow-up visit. Pregnancy tests will be conducted during Long-term Follow-up visits until 6 months following last dose of study drug.

o. **Tumor evaluation** per RECIST v1.1 CT/MRI will be conducted at screening, Week 8, and every 6 weeks for the first 26 weeks (6 months), then every 12 weeks (±7 days) up to 1 year from the date of the last dose of study treatment, disease progression, the initiation of subsequent anti-cancer therapies, withdrawal of consent, lost to follow-up, or end of the study, whichever occurs first. Copies of all scans and redacted radiology reports are to be submitted according to vendor / Sponsor requirements in a timely manner. A scan to confirm an unconfirmed PR or unconfirmed CR ≥4 weeks later may also be performed.

The same imaging modality used at screening **must** be used throughout the study for each patient.

For patients who discontinue due to relapse/progression, the EOT visit imaging assessment is not needed if the last scan was within 4 weeks of the EOT visit.

For patients who discontinue treatment without relapse/disease progression, CT scan assessments will continue every 12 weeks for up to 1 year from the date of the last dose of study drug during the follow-up period until disease progression, start of new anti-cancer therapy, or end of study, whichever occurs first.

p. **12-Lead ECG** – All ECGs will be performed in triplicate. Average corrected QT interval using Fridericia's method (QTcF) is to be calculated to confirm eligibility. ECGs will be performed in triplicate as follows: 2 ECGs will be performed in triplicate pre-dose within 1 hour of dosing at least 15 minutes apart. For Phase 1b (dose levels 1-7), post-dose ECGs will be performed prior to and as close as possible to PK blood draws at 1-, 2-, 4-, and 6-hours post-dose (±15 minutes) on Cycle 1 Day 1. For Phase 1b (dose levels 8-13) and Phase 2, one set of triplicate ECGs will be performed on Cycle 1 Day 1 at 2 hours post-dose and on Cycle 2 Day 1 prior to and as close as possible to the PK blood draws at 1-, 2-, 3-, 4-(pre-dose of second divided dose), 5-, and 6-hours post-dose (±15 minutes). Detailed instruction on ECGs is provided in Section 7.4.2.5.

q. For patients in Phase 2 who are receiving nanatinostat, valganciclovir, and pembrolizumab, all AEs will be collected for up to and including 90 days after the last dose of study treatment or until the start of a new antineoplastic therapy, whichever is first; for all other patients, only serious adverse events (SAEs) will be collected during this safety follow-up time period.

r. **EBV DNA, CMV, HIV levels** – Plasma samples will be collected to investigate circulating EBV DNA, CMV, and HIV (HIV^+ patients only). EBV DNA levels will be utilized for safety and biomarker analysis. For patients in Follow-up: If no relapse/disease progression, then patients will continue to have EBV DNA levels monitored every 12 weeks for up to 1 year from the date of the last dose of study drug during the follow-up period, until disease progression, start of new anti-cancer treatment, or end of study, whichever occurs first.

s. **PK sample collection** – For Phase 1b (dose levels 1-7), PK will be collected on Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose and 1-, 2-, 4-, 6-, and 8-hours post-dose (±15 minutes). For Phase 1b (dose levels 8-13) and Phase 2, PK will be collected on Cycle 2 Day 1 at pre-dose, and 1-, 2-, 3-, 4- (pre-dose of second divided dose), 5-, 6-, and 8-hours post-dose (±15 minutes). For patients receiving divided or split daily dosing, the 4-hour PK time point samples should be collected prior to administration of the second dose of nanatinostat or nanatinostat and valganciclovir (ie, at approximately lunch time) and the 8-hour PK time point should be collected prior to administration of the second dose of valganciclovir (ie, at approximately dinner time; dose levels 6 and 7 only). At time points requiring ECG, vital signs, and PK blood draw, assessments should be performed in as short of timeframe as possible and in this order: ECG, vital signs, then blood draw.

t. **Exploratory biomarkers** – Blood draws for exploratory biomarkers should be taken prior to the patient taking study medication on that day.

u. **Immunophenotype and immune function** – Peripheral blood mononuclear cells (PBMCs) will be collected pre-dose and every 3 cycles starting at Cycle 3 Day 1 (Day 1 of Cycles 3, 6, 9, 12, etc.) and at End of Treatment. Cycle 1 Day 1 pre-dose sample may be collected during screening within 21 days of Cycle 1 Day 1.

v. **Histone acetylation** – PBMCs for histone acetylation will be collected pre-dose and at 3 hours (±15 minutes) post-dose.

w. **Archival Formalin-Fixed Paraffin-Embedded (FFPE) tumor specimen** – Mandatory for all patients. Eligibility will be based on local pathology review; confirmation of diagnosis by central pathology laboratory is not required for entry or initiation of treatment. A FFPE tumor block and/or 10 unstained slides of a representative tumor specimen or lymph node must be confirmed to be available at the time of screening and must be submitted to the central pathology laboratory within 8 weeks after Cycle 1 Day 1. If an archival tumor sample taken within 2 years prior to screening is not available, a de novo biopsy may be required.

x. Tumor specimens must meet the criteria described in Section 7.2.4. **De novo study biopsies –** Optional. Matched pre- and on-study tumor biopsies may be obtained pre-dose within 28 days of Cycle 1 Day 1 and on Cycle 1 Day 15; these specimens will be used for exploratory evaluation and will be provided to the central pathology laboratory, along with a frozen tissue specimen, if available. On-study biopsies for exploratory evaluation will be performed at the discretion of the Investigator when the disease site is accessible for biopsy and the patient is a candidate for tumor biopsy according to local practice guidelines.

y. **On-study biopsy** – Optional. FFPE tumor specimens collected at relapse or disease progression should be provided to the central pathology laboratory, along with a frozen tissue specimen, if available.

z. **Drug dispensing** – Depending on cohort assignment and dose schedule, additional bottles of study drug may be dispensed mid-cycle as needed.

aa. **Subsequent anti-neoplastic therapies and response** – Patients will be contacted by telephone call, e-mail, medical records, clinic visits, or public records such as government census or death records for assessment of additional therapy, response status, and survival every 12 weeks (3 months) until withdrawal of consent, death, lost to follow-up, completion of 3 years of follow-up, completion of 1 year after the last patient discontinues treatment, or the study is terminated by the Sponsor, whichever occurs first.

7. Enrollment and Study Procedures

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is provided in the Schedule of Events included in Table 11.

7.1. Informed Consent

The Investigator will provide for the protection of the patients following all applicable Good Clinical Practice (GCP) regulations. The informed consent form (ICF) must be reviewed and approved by the Sponsor and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) before the informed consent process may begin.

Prior to performing any study-specific screening or study-related procedures for any potential patient to be enrolled, the patient must be given or must complete the following:

- Be informed of all pertinent aspects of the study and all elements of informed consent
- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB/IEC approved Informed Consent Form

Study personnel must obtain documented consent from each potential patient prior to entering in a clinical study. Consent must be documented by obtaining the dated signature of both the patient and the person conducting the consent discussion on the consent form. If local law does not allow written consent, then oral consent, attested to by the dated signature of an impartial witness (someone not involved with the conduct of the study), is the required alternative.

If the patient is illiterate, an impartial witness must be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (ie, study staff personnel). If the patient is legally incompetent (ie, mentally incapacitated), the written consent of a legal guardian or legal representative must be obtained. Depending on local law or review committee requirements such consent may also need to be signed by an impartial witness.

The information from the consent form should be translated and communicated to the patient in language understandable to the patient. When the study patient population includes non-English speaking people, a certified translated consent form or an appropriate equivalent will be provided to the patient.

The initial informed consent form and any subsequent revised written informed consent form must receive approval and/or favorable opinion by the IRB/IEC in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information should be documented.

A copy of the signed ICF will be provided to the patient. The Investigator will retain all original versions of signed ICFs.

After informed consent is provided, patients who successfully complete all screening assessments and study entry criteria may be enrolled in the study. The period for completing screening assessments is 28 days.

An optional supplemental consent for future use of blood and tissue samples for research purposes (biobanking) may be proposed to patients based on local regulatory requirements. The assessments to be conducted on these samples are described as exploratory endpoints in the protocol.

Rescreening of patients is only allowed once per patient if the patient is not registered as entering the treatment phase (Cycle 1 Day 1). In this case, a new patient number will be assigned, and the patient will be identified with this number throughout their participation in the study.

7.2. Screening Period

Selected screening procedures are highlighted below. A summary of all screening assessments to be performed is provided in the Schedule of Events (Table 11).

7.2.1. Demographic Information

Standard demographic parameter information including age, gender, and race/ethnicity (recorded in accordance with local regulations) will be collected at the screening visit.

7.2.2. Physical Examinations

Physical examinations will be performed as specified in the Schedule of Events (Table 11). Documentation of the physical examination will be included in the source documentation at the investigational site. Any changes from the screening physical examination findings that meet the definition of an AE must be recorded on the AE eCRF.

7.2.3. Medical History

All relevant cancer-related history over the patient's lifetime should be recorded, including:

- Initial diagnosis
- Prior antineoplastic therapies (including surgery and radiotherapy) and dates
- Responses to prior antineoplastic therapies

The non-cancer-related medical history should include any ongoing medical conditions and symptoms and should also include the toxicity grade NCI CTCAE Version 5.0.

7.2.4. Tumor Specimen

An FFPE tumor block or 10 unstained slides of a representative tumor specimen obtained ≤2 years prior to screening must be available and submitted to the central pathology laboratory within 8 weeks after Cycle 1 Day 1. For available tumor specimens >2 years old, the Sponsor's Medical Monitor should be consulted to discuss eligibility.

The specimen must be representative of the current disease. If archival tumor tissue (tumor block or unstained slides) was not available prior to enrollment, a newly obtained tumor biopsy (excisional or core) may be required prior to enrollment. If a new biopsy is obtained to satisfy

eligibility, an FFPE tumor sample should be provided to the central pathology lab. De-identified pathology reports associated with these tissues are also required and must be sent to the central pathology laboratory with the tissue and/or slides.

The process for submitting archived tissue and procedures for central pathology review is provided in a separate Study Manual.

7.2.5. Baseline Disease Assessments

Any imaging assessments already completed during the regular work-up of the patient within 21 days prior to Cycle 1 Day 1, including before signing the main study ICF, can be considered as the baseline images if all imaging requirements for the study are met.

The imaging modality used for evaluation at screening must be consistently used throughout the study for each patient (CT with contrast or MRI). If positron emission tomography (PET) is used, a contrast-enhanced CT scan must be included.

7.2.6. Eligibility Determination and Patient Registration

Investigative sites will submit patient registration materials for Sponsor's Medical Monitor approval prior to the enrollment of the patient in the trial. Details on this process will be included in the Study Manual.

Once all screening procedures are complete, an eligibility checklist must be completed by the Investigator or designee and provided to the Sponsor's Medical Monitor with limited exceptions at least 72 hours prior to planned enrollment for review. Eligibility will be reviewed and approved by the Sponsor Chief Medical Officer or designee (eg, Sponsor's Medical Monitor) prior to patient enrollment.

7.2.6.1. Screen Failures

Patients who sign an ICF but are later deemed to be ineligible for enrollment before taking any study medication will be considered screen failures. The eCRF completion requirement for screen failures is outlined in the eCRF Completion Guidelines.

7.3. Treatment Period

Patients will be treated until discontinuation of study treatment as described in Section 7.3.3.

7.3.1. Treatment Cycles

Patients will receive nanatinostat at the assigned dose once or as a divided dose twice daily on Days 1 to 4 per week or Days 1 to 7 per week and valganciclovir 900 mg orally once daily, twice daily (for 21 days, with a subsequent dose reduction to 900 mg daily), or 450 mg orally twice daily continuously for 21-day treatment cycles (excluding Cycle 1, which is 28 days).

Pembrolizumab (200 mg IV) will be administered every 3 weeks starting on Cycle 1 Day 8.

7.3.2. Unscheduled Visit(s)

Unscheduled visits will be recorded in the eCRF. The specific tests and evaluations performed during an unscheduled visit will be determined by the Investigator.

7.3.3. Discontinuation of Study Treatment

Patients will continue study treatment until disease progression, unacceptable toxicity, start of new anti-neoplastic therapy, withdrawal of consent by the patient, patient is lost to follow-up, or discontinuation from the study due to any other reason (eg, Sponsor terminates the study). Maximum treatment duration with pembrolizumab is 24 months.

In case a patient voluntarily discontinues from study treatment, the Investigator must make every effort to determine the primary reason for the decision and record this information in the eCRF.

If a patient withdraws consent for participation in the study, all data collected up to the point of withdrawal must be maintained in the database and included in subsequent analyses, as appropriate. A patient may withdraw from the interventional portion of the study, but agree to continue follow-up of associated clinical outcome information in which case this information would be collected and maintained in the clinical trial database.

Patients who discontinue treatment without relapse/disease progression will continue to follow the CT scan assessment schedule until disease progression, start of new anti-neoplastic therapy, withdrawal of consent, completion of one year of follow-up, lost to follow-up, or end of study (see Table 11), whichever comes first.

Patients may be withdrawn permanently from the study if any of the following occur:

- Adverse event
- Progressive disease or relapse per RECIST v1.1 or iRECIST (for patients receiving pembrolizumab only)
- Lost to follow-up
- Physician decision
- Pregnancy
- Withdrawal of consent
- Study terminated by Sponsor
- Any protocol deviation for which continuing participation in the study would result in a significant risk to the patient's safety

7.3.4. End of Treatment

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible and within 14 days after the last dose of study drug, at which time all assessments listed for the End of Treatment (EOT) visit will be performed. The EOT visit will be recorded in the eCRF with the date and reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for follow-up safety evaluations 30 and 90 days following the last dose of study drug(s).

The assessments to be performed at EOT are listed in the Schedule of Events provided in Table 11.

7.3.5. Safety Follow-up Visit

All patients must complete safety follow-up assessments at 30 (± 5) and 90 (± 5) days following the final administration of study treatment. If a patient withdraws consent after the EOT visit but prior to the 30-day safety evaluation, safety information should be collected on the patient up to the date of consent withdrawal. The 90-day safety follow-up assessments may coincide with the first Long-Term Follow-up visit.

For each safety follow-up assessment, the following should be collected:

- 30-day Safety Follow-up:
  - AEs
  - Prior/concomitant meds for AEs
  - Pregnancy testing (for women of childbearing potential)
  - EBV DNA levels
  - Any antineoplastic therapies
- 90-day Safety Follow-up:
  - AEs (for the Phase 2 patients receiving pembrolizumab)
  - SAEs (for all patients)
  - Prior/concomitant meds for AEs
  - Any antineoplastic therapies

AE information will be collected following the last dose of study treatment through the appropriate safety follow-up period described above or until the start of a new antineoplastic therapy, whichever occurs first.

In addition to AEs, all concomitant medications given to a patient because of an AE during this period will be recorded on the Prior and Concomitant medication eCRF page.

All new anti-cancer therapies given to a patient within 90 days after the last dose of study treatment must be recorded in the eCRF. 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 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.

7.3.6. Long-term Follow-up Visits

The first Long-Term Follow-up visit may coincide with the 90-day safety follow-up assessment.

Patients who discontinue treatment for reasons other than disease progression will have tumor imaging and plasma EBV DNA level assessments every 12 weeks (3 months) ±7 days as detailed in Table 11, for up to 1 year following the last dose of study drug treatment, until disease progression, the start of subsequent anti-cancer therapies, withdrawal of consent, lost to follow up, or end of study, whichever occurs first. Scans performed during the Follow-up period should be performed on the same schedule with the same imaging modality as previously used throughout the study.

Survival Follow-up: All patients enrolled in the study will be followed for survival every 12 weeks (3 months) by phone call, e-mail, medical records, clinic visits, or public records, such as government census or death records, until the patient is lost to follow-up, death, withdraws consent, 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. Newly started anti-neoplastic therapies during this follow-up period must be recorded on the "Antineoplastic therapies since discontinuation" eCRF page.

7.3.7. Lost to Follow-up

Patients who do not complete scheduled visits and who are unable to be contacted following at least 3 documented attempts (one of which is contact by certified/registered mail) will be considered lost to follow-up.

7.4. Assessments During the Treatment Phase

Study treatment will start on Cycle 1 Day 1. Serial assessments of safety and efficacy will be performed as outlined in the Schedule of Events provided in Table 11. On scheduled visit days, the use of the central laboratory is preferred for all protocol-specified laboratory analyses; however, additional local laboratory assessments may be performed, as applicable, per site policy or for unscheduled visit days. Clinical decisions and dose modifications can be based on local laboratory results.

7.4.1. Efficacy Assessments

7.4.1.1. Baseline Evaluation

The following radiologic assessments are to be performed in the screening period (within 21 days prior to the start of treatment):

1. **For all patients:** CT with contrast or MRI of the head to rule out CNS involvement.
2. **For NPC patients:** CT with contrast or MRI of the nasopharynx, neck, chest, abdomen, and pelvis. If PET is used, a contrast-enhanced CT scan must be included.
3. **For non-NPC patients:** CT with contrast or MRI of the chest, abdomen, and pelvis.

7.4.1.2. Tumor Response Assessments

Tumor responses will be assessed by the Investigator per RECIST v1.1 (MRI or CT with contrast) and iRECIST (for patients receiving pembrolizumab). The CT scans should be performed with contrast unless contraindicated for medical reasons, in which case MRI should be used.

Although RECIST v1.1 will be the primary measure for assessment of tumor response and disease progression for efficacy endpoints, iRECIST guidelines should be used for treatment decision making for patients receiving pembrolizumab, including confirmation of unconfirmed progressive disease by RECIST v1.1 with additional imaging within 4 to 6 weeks (Appendix 3).

Investigator-determined response assessments at each assessment time point will be entered into the appropriate eCRF. Copies of all scans and redacted radiology reports are to be submitted according to vendor / Sponsor requirements in a timely manner.

All MRI or CT scan assessments will be determined from date of first dose and will follow the counting of calendar days and not the dosing cycles. It is critical that the same imaging modality used at screening is used throughout the study for each subject. The scans will be performed as follows:

- At Week 8 and then every 6 weeks (±7 days) for the first 26 weeks (6 months), and every 12 weeks thereafter for up to 1 year after permanent discontinuation of study treatment, until disease progression, the start of new anti-cancer treatment, withdrawal of consent, lost to follow-up, or the end of the study, whichever occurs first. A scan to confirm an unconfirmed PR or unconfirmed CR ≥4 weeks later may also be performed.
- At the EOT visit (unless the previous scan is within 4 weeks of the EOT visit).

If local regulatory authorities mandate less frequent imaging, the minimum frequency must be every 12 weeks.

All patients will be followed for disease progression or relapse using the schedule described in the Schedule of Events provided in Table 11. This includes patients who discontinue the protocol-specified treatments or the study early for any reason without documented evidence of progressive disease or relapse.

The radiologic assessments (MRI or CT with contrast) are considered the primary method of response assessment.

Patients who relapse or progress will continue to be followed for OS, all subsequent anti-neoplastic therapy, and response, including disease progression/relapse to subsequent anti-neoplastic therapy.

For a patient receiving pembrolizumab deemed clinically stable at the time of initial progression by RECIST v1.1, Investigators may elect to keep the patient on treatment using the iRECIST guidelines to assist with patient management (Appendix 3). Tumor imaging should be repeated within 4 to 6 weeks to confirm disease progression using iRECIST. Patients who have confirmed disease progression per iRECIST will discontinue treatment unless continued treatment is approved by the Sponsor.

7.4.2. Safety and Tolerability Assessments

Study assessments of safety include AEs, clinical laboratory tests, ECGs, vital signs, physical examinations, and ECOG status.

Safety data will be collected from the signing of the ICF up to and including 90 days post-last dose of study treatment according to the Schedule of Events in Table 11.

Adverse event monitoring and collection, in addition to other safety considerations, are summarized in Section 8. Laboratory assessments, vital signs, ECGs, physical examinations, and ECOG performance status are described in the subsequent sections below.

Tolerability will be assessed by the incidence of AEs leading to dose modifications or study drug discontinuation.

7.4.2.1. Laboratory Evaluations

7.4.2.2. Clinical Laboratory (Safety) Testing

Laboratory tests will be collected and analyzed in an accredited central or local/site laboratory in accordance with quality standards.

On scheduled visit days, the use of the central laboratory is preferred for the analysis of all indicated safety laboratory analyses; however, local laboratory assessments may be performed, as applicable, per site policy or for unscheduled visit days. Clinical decisions and dose modifications can be based on local laboratory results.

The required hematology, serum chemistry, urinalysis, serology, and other parameters to be collected at the time points described in the Schedule of Events (Table 11) are listed in Table 12. These tests may also be performed when clinically indicated (eg, patients who are hepatitis B core antibody positive should have HBV DNA PCR monitoring according to local guidelines). In addition, the investigative sites will provide archived and/or newly obtained tumor samples at baseline, and at Cycle 1 Day 15 and/or at the time of relapse or with disease progression, as applicable.

Viral levels (EBV, CMV, and HIV [for HIV^+ patients only]) will also be monitored to assess for viral reactivation.

Table 12: Required Laboratory Tests

Laboratory Test Category	Laboratory Tests	
Hematology	Hemoglobin, platelets, WBC with differential (absolute neutrophils, absolute monocytes, absolute eosinophils, absolute lymphocytes, absolute basophils),	
Coagulation	PT or INR, aPTT	
Serum Chemistry	AST (SGOT)	Bicarbonate
	ALT (SGPT)	BUN
	Albumin	Creatinine
	Total bilirubin	Glucose (non-fasting)
	Sodium	Chloride
	Potassium	Calcium
	Magnesium	Phosphate
	Total protein	Uric acid
	ALP	Thyroid function tests (TSH, free T3, free T4)
Urinalysis	Macroscopic panel (dipstick)	
Viral	HBV surface Ag	HBV DNA PCR[1]
	HBV core and surface Ab	HCV Ab[2]
	EBV DNA, CMV, HIV levels	
Pregnancy	Only for females of childbearing potential. Serum test must be performed during screening. Serum or urine tests are to be performed as described in the Schedule of Events. Pregnancy tests will be performed locally at each site.	

[1]HBV DNA PCR only for patients with positive HBV core Ab or surface Ag.
[2]Any patient positive for HCV Ab will be evaluated by quantitative PCR.
Ab = antibody; Ag = antigen; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CMV=cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PCR = polymerase chain reaction; PT = prothrombin time; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid stimulating hormone; WBC = white blood cell.

7.4.2.3. Pregnancy Testing

Pregnancy testing is only required for females of childbearing potential. A serum test must be performed during screening. Serum or urine tests are to be performed at the beginning of each cycle, at EOT, at the 30-day Safety Follow-up visit, and for up to 6 months post-last dose of study treatment. Pregnancy tests will be performed locally at each site.

7.4.2.4. Vital Signs

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. For Phase 1b dose levels 1 through 7, vital signs should be collected just prior to the first dose of valganciclovir and nanatinostat, and in concert with and just prior to PK blood draws on Cycle 1 Day 1 and Cycle 2 Day 1 through the 6-hour post-dose time point. For Phase 1b dose levels 8 through 13 and Phase 2, vital signs should be collected just prior to the first dose of valganciclovir and nanatinostat, and in concert with and just prior to PK blood draws on Cycle 2 Day 1 through the 6-hour post-dose timepoint as shown in Table 11. On other indicated visit days, vital signs will be collected once (prior to dosing of study treatment, if administered in clinic).

Investigators are to report any clinically significant abnormal findings as AEs.

7.4.2.5. Cardiac Assessments: Electrocardiograms (ECGs)

All 12-lead ECGs will be conducted in triplicate. Average QTcF will be calculated to confirm eligibility. ECG tracings will be provided to a central laboratory, instructions are provided in the Study Manual.

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. Average QTcF will be calculated to confirm eligibility. Careful skin preparation is essential to assure high quality ECGs. All ECGs should be collected using the same ECG machines and performed in as calm an environment as possible, not immediately following stressful procedures (ie, biopsies, etc.), with minimal distractions (talking, TV, etc.). Prior to each ECG, the patient should 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, 2 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 (maximum plasma concentration [C_{max}];1 and 2 hours), 4 hours, and 6 hours. If possible, patients should not consume additional food between dosing and the last ECG time point.

One set of triplicate 12-lead ECGs will be performed on Cycle 1, Day 1 at 2-hours post-dose for Phase 1b dose levels 8 through 13 and Phase 2. When performed in concert with serial PK collection on Cycle 2 Day 1 for these patients, 2 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 (C_{max}; 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.

All ECGs will be independently reviewed by a central laboratory. Instructions for the collection and transmission of ECGs to the central ECG laboratory will be provided in the Study Manual.

Clinically significant abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page. All eligibility and patient management decisions should be based on the local reading of the ECG.

7.4.2.6. Physical Examination

A physical examination should be conducted at screening, the beginning of each cycle, at the EOT visit, and any additional times deemed necessary by the Investigator.

7.4.2.7. Height and Weight

Height and weight will be measured at screening (Day -28 to Day -1) and weight will subsequently be measured on Day 1 of each cycle and at the EOT visit.

7.4.2.8. ECOG Performance Status

The ECOG performance status according to Table 13 (Oken 1982) will be assessed at the screening visit (Day -28 to Day -1), on Cycle 1 Day 1, and at the EOT visit.

Table 13: ECOG Performance Status

Grade	ECOG status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

7.4.3. Pharmacokinetics

The scheduled time points for the PK evaluations (assessments of nanatinostat, its metabolites, and ganciclovir [the active hydrolytic product of valganciclovir]) are outlined in the Schedule of Events in Table 11. Pharmacokinetic parameters to be evaluated include t_{max}, C_{max}, and AUC. Details for collection, shipment, and storage are provided in the Lab Manual.

7.4.4. Exploratory Biomarker Assessments

7.4.4.1. Rationale for Biomarker Assessments

The exploratory biomarker analyses outlined in this study are intended to foster an understanding of how baseline expression of certain pharmacodynamic markers may impact the activity of combination therapy with nanatinostat, valganciclovir, and pembrolizumab, and how pharmacodynamic markers such as plasma EBV DNA levels may correlate with clinical efficacy. Potential predictive markers will be studied to identify patients with optimal responses to nanatinostat and valganciclovir. The impact of study drug administration on B-cell/T-cell/NK cell/myeloid cell populations will be evaluated over time. Although on-study biopsies will be performed at the discretion of the Investigator, it is anticipated that at least 10 consenting patients per arm in Phase 2 will have on-study tumor biopsies (timing: within 28 days prior to Cycle 1 Day 1, Cycle 1 Day 15, and at relapse or with disease progression).

The specific study procedures to be conducted for each patient enrolled in the study are presented in the Schedule of Events in Table 11. Cells from peripheral blood or tumor tissue will be sent to a central laboratory selected by the study Sponsor for analysis of viral DNA levels, gene expression, phenotypic alterations in B-cells/T-cells/NK cells/myeloid cells and mutation profile.

Details on the collection procedure and timing for each procedure are described in Table 14 and will be provided in the Study Manual. The sample collection information must be entered on the appropriate sample collection log eCRF page(s) and requisition form(s).

Table 14: Biomarker Sample Collection Plan

Sample Type	Visit/Time Point	Analyses	Purpose
Archival FFPE tumor sample (if an archival tumor sample taken within 2 years prior to screening is not available, a newly obtained tumor biopsy [excisional or core] may be required)	Screening	• IHC: PD-1, PD-L1 and other immune checkpoint molecules • TIL counts: CD3, CD4, CD8 • EBV-associated genes/proteins: EBER, BZLF-1/ZTA, LMP-1, BGLF-4/PK, BXLF-1/TK, BRLF-1/Rta, etc. • Tumor Associated gene expression profiles	Identify possible predictive markers
On-study tumor biopsy (Optional)	• Up to 28 days prior to Cycle 1 Day 1 • Cycle 1 Day 15 • At relapse or with disease progression	EBV-associated genes/proteins, TIL counts, PD-L1 and other immune checkpoint molecules; markers related to resistance	Identify potential PD or resistance markers
Plasma	• Screening • Cycle 1 and 2 Days 1, 8, 15, and Day 1 of each subsequent cycle • Every 3 months in follow-up until disease progression	• EBV DNA levels (EBV viral load by q-PCR) • Analysis of tumor-associated genes (eg, BGLF4, p53, MVC, KRAS, etc)	Pharmacodynamic effect (on- and off treatment)
PBMC (whole blood)	• Pre-dose Cycle 1 Day 1 (may be collected during Screening) and 3 hours post-nanatinostat administration. • Every 3 cycles starting at Cycle 3 Day 1 (Day 1 of Cycles 3, 6, 9, 12, etc.) and at End of Treatment.	• Histone H3 acetylation (prior to and 3 hours post-nanatinostat administration, Cycle 1 Day 1 only) • RNA expression of selected immunological genes • Flow cytometry for immune cell markers • Flow cytometry for identification of circulating tumor cells and single cell RNAseq	Pharmacodynamic effect (on-treatment)

EBER = Epstein-Barr encoded RNA; EBV = Epstein-Barr virus; FFPE = formalin-fixed paraffin-embedded; IHC = immunohistochemistry; PBMC = peripheral blood mononuclear cell; PD-1 = programmed cell death-1; PD-L1 = programmed death-ligand 1; qPCR = quantitative polymerase chain reaction; TIL = tumor-infiltrating lymphocyte

7.4.4.2. Pharmacodynamic Assessments in Blood

For pharmacodynamic assessment of acetylation of histone H3 in PBMCs, pre- and on-treatment samples will be collected as indicated in the Schedule of Events provided in Table 11. These assessments are mandatory for all patients.

7.4.4.3. Additional Biomarker Assessments

If the patient agrees, any remaining tumor or blood samples and residual PK samples may be stored for up to 15 years and further analyzed to address pertinent scientific questions related to

EBV^+ solid tumors. A decision to perform additional biomarker-related analyses would be based on outcome data from this study or from new reported discoveries, as well as reagent and assay availability.

8. ADDITIONAL SAFETY CONSIDERATIONS

8.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any untoward medical event that occurs to a patient following the start of administration of the study drugs, whether or not considered study drug related. An AE can, therefore, be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom or disease temporally associated with the use of a drug, whether or not considered related to the drug. For example, it may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the Adverse Events eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

If an overdose occurs, whether accidental or intentional, and is associated with an AE, the AE should be recorded on the Adverse Events eCRF and will be reported consistent with instructions in Section 8.8. All overdoses, with or without an associated AE, will be recorded on the dosing eCRF.

All patients will be monitored for AEs during the study. Assessments may include monitoring any or all of the following parameters: the patient's clinical symptoms, laboratory, pathologic, radiologic, or surgical findings, physical examination findings, or other appropriate tests and procedures. All AEs reported during the study should be monitored until resolution, or until the event has stabilized or reached a new baseline (all follow up results are to be reported to the sponsor or designee). During a dose interruption, study days and procedures will continue to accrue until the end of the current cycle (see Schedule of Events in Section 6).

All AEs will be recorded by the Investigator from the time the patient signs the informed consent. Adverse events and SAEs will be recorded on the Adverse Events eCRF and in the patient's source documents. All SAEs must be reported to the pharmacovigilance clinical research organization within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

If the Investigator becomes aware of an SAE after the study-specified safety follow-up period and considers the event related to study drug, the event will be reported within 24 hours according to the procedures detailed in Section 8.2.1. Pre-existing conditions are not considered an AE unless the condition worsens by at least one Grade following the start of administration of the study treatment.

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

nanatinostat, valganciclovir, and pembrolizumab, all AEs will be recorded from the signing of the ICF and continue for up to and including 90 days after the last dose of study treatment or until a new anticancer treatment is started, whichever is first.

8.1.1. Clarification in Reporting of Deaths

Fatal events regardless of causality will be reported within 24 hours of the Investigator's knowledge through the safety follow period or until a new anticancer treatment is started, whichever is first. Death is an outcome of an adverse event and not an adverse event in itself. All reports of death should include an adverse event term for the cause of death (if known).

8.1.2. Clarification in Reporting of Disease Progression as an Adverse Event

Disease progression is expected in this study population, and thus disease progression should not be reported as an adverse event/serious adverse event term. If clinical disease progression is identified, the specific clinical event that identifies the disease progression should be reported as the adverse event for standard adverse event reporting. Death due to disease progression should be reported in the clinical database on the designated eCRF.

8.1.3. Laboratory Test Abnormalities

An abnormal laboratory value is an AE if the abnormality:

- Results in discontinuation from the study, or
- Requires treatment, modification or interruption of study treatment, or any other therapeutic intervention, or
- Is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion (Section 8.2) need to be documented as an SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome (eg, hyperuricemia with tumor lysis syndrome), only the diagnosis or syndrome should be recorded on the Adverse Events eCRF. If the abnormality is not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

8.2. Serious Adverse Event

An SAE is defined as one of the following:

- Is fatal or life-threatening
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in a persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant (ie, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above)

Events **not considered** to be SAEs are hospitalizations for the following:

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the condition under investigation and has not worsened since signing the informed consent.
- Social reasons and respite care in the absence of any deterioration in the patient's condition.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.

Note that treatment on an emergency outpatient basis that does not result in admission to hospital and involves an event not fulfilling any of the SAE definitions above is not an SAE.

8.2.1. Reporting of Serious Adverse Events

All SAEs must be reported to the Sponsor within 24 hours of the Investigator becoming aware of the SAE.

To report a SAE, sites will complete an SAE Report Form and submit the report to:

PRA Health Sciences / ICON Pharmacovigilance e-mail at CHOSafety@iconplc.com (North/South America) or MHGSafety@iconplc.com (Europe/Asia/Pacific/Africa)

or

Fax to +888-772-6919 or 1-434-951-3482 (North/South America)

+44-1792-525-720 (Europe/Asia/Pacific/Africa)

The Investigator should discuss with the Sponsor's Medical Monitor any SAEs for which the issue of seriousness is unclear or questioned. Contact information for the Sponsor's Medical Monitor is listed in Table 15.

Table 15: Sponsor's Medical Monitor

Region	Phone	E-mail
All	+1 858-337-6079	DCohen@Viracta.com

SAEs must be reported by each site to their appropriate IRB/IEC in accordance with the timeframes and procedures required by their IRB Policy.

The Sponsor will report SAEs to the US FDA and any other relevant regulatory authorities.

SAEs will be recorded from the signing of the ICF up to and including 90 days after permanent study discontinuation or until the start of a new antineoplastic therapy, whichever occurs first.

8.3. Severity of the Event

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event. All AEs will be assessed by the Investigator using NCI CTCAE Version 5.0.

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious", which is based on patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory obligations.

8.4. Relationship to Study Drugs

The Investigator will use his/her best medical judgment to determine the relationship of an AE to each study drug included in the protocol-defined study treatment.

The relationship of an AE or SAE to study drugs will be classified using the following 3 categories:

- Definitely related
- Possibly related
- Unrelated

To be classified as "definitely related," an AE should occur in a timeframe relative to administration of study drug(s) that suggests a strong causal relationship between the study drug(s) and the AE. In addition, there should be no other reasonable explanations for the AE, such as underlying disease or other concurrent conditions.

To be classified as "unrelated," an AE should occur in a timeframe relative to administration of study drug(s) that suggests a causal relationship between the study drug(s) and the AE is very unlikely. In addition, there should be a reasonable explanation for the AE, such as underlying disease or other concurrent condition.

To be classified as "possibly related," an AE should not fall clearly into 1 of the above 2 categories. This would include, for example, an AE that does not seem to occur in close temporal proximity to administration of study drug(s), but also has no other reasonable explanation.

8.5. Expectedness

For regulatory reporting, the Sponsor will determine the expectedness of events suspected of being related to nanatinostat and/or valganciclovir based on the effective version of the IB. The expectedness of events suspected of being related to pembrolizumab will be based upon the approved prescribing information.

The Sponsor or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with country-specific requirements (eg, 21 Code of Federal Regulations [CFR] 312.32[c], Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use [ENTR/CT3], or other applicable requirement).

8.6. Reporting Adverse Events

For all patients, excluding those in Phase 2 receiving nanatinostat, valganciclovir, and pembrolizumab, any AEs which occur from the signing of the 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, will be recorded.

For patients in Phase 2 who are receiving nanatinostat, valganciclovir, and pembrolizumab, all 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.

Unanticipated problems that require reporting to IRB might include the following:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure.
- A single occurrence, or more often small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population.
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem.
- An AE that is described or addressed in the IB, protocol, or ICF, but occurs at a specificity or severity that is inconsistent with prior observations.
- An SAE that is described or addressed in the IB, protocol, or ICF, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence.
- Any other AE or safety finding that would cause the Sponsor to modify the IB, study protocol, or ICF, or would prompt other action by the IRB to ensure the protection of human subjects.

8.7. Reporting of Pregnancy

8.7.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient are considered immediately reportable events. A positive urine pregnancy test will be followed by a serum test for confirmation. Study treatment is to be discontinued immediately and patients instructed to return any unused portion of the study treatment to the Investigator. Female patients will be asked to consent to data collection until the outcome of a pregnancy, should a pregnancy occur during the study.

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Drug Safety immediately (within 24 hours) using the Pregnancy Initial Report Form provided by the Sponsor (Section 8.2.1). The female patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female patient until completion of the pregnancy and must notify Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form.

If the outcome of the pregnancy is abnormal (eg, spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the seriousness criteria, it must be reported as an SAE to Drug Safety within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in-utero exposure to the study treatment should also be reported to Drug Safety within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

Pregnancies may also be reported to the IRB/IEC per their requirements.

8.7.2. Male Patients

Female partners of male patients participating in the study are recommended to use 2 forms of birth control including at least one form of highly effective and one effective barrier method (defined in Section 4.2, inclusion criterion 14c) while their partner is treated on study and for 6 months after the last administration of study drug. If a female partner of a male patient taking study treatment becomes pregnant, the male patient should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. Pregnant female partners will be requested to consent to be followed as described in Section 8.7.1.

8.8. Reporting of Overdose

An overdose is defined as any accidental or intentional use of the study drug in an amount higher than the protocol-defined dose.

If an overdose occurs, whether accidental or intentional, and is associated with an AE, the AE (not the overdose) should be recorded on the Adverse Event eCRF. If an overdose occurs, with or without an AE, the additional doses taken will be recorded on the dosing eCRF. Adverse events associated with overdose, misuse, abuse, or medication error should be reported using the procedures detailed in Reporting of Serious Adverse Events (Section 8.2) even if the AEs do not meet seriousness criteria.

8.9. Emergency Measures

In the event of an emergency, standard emergency procedures will be employed. The Investigator is to be consulted and informed immediately.

The Investigator will provide all the necessary emergency equipment and specially trained trial site personnel to handle emergency events during this study.

The investigational site is responsible for ensuring 24-hour emergency availability.

All cases of emergency must immediately be reported to the Sponsor's medical monitor and to the clinical project manager and will be noted in the eCRF.

8.10. Unanticipated Problems

An AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human patients and reported to the IRB/IEC, only if it is unexpected, serious, and would have implications for the conduct of the study (eg, requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or IB).

Therefore, any incident, experience, or outcome that meets all of the following criteria could be reported by the Investigator to the IRB/IEC as an unanticipated problem:

- Unexpected given the following:
  a. The research procedures that are described in the protocol-related documents; and
  b. The characteristics of the subject population being studied.
- Related or possibly related to participation in the research, and
- Suggests that the research places subjects or others at a greater risk of harm than is previously known or recognized.

9. STATISTICAL ANALYSES

9.1. Overview

The objective of the statistical analysis is to evaluate the efficacy and safety of the coadministration of nanatinostat and valganciclovir, with or without pembrolizumab, in patients with relapsed/refractory EBV^+ solid tumors without available therapies. All data will be summarized by dosing regimen, disease subtype, and overall.

9.2. Statistical and Analytical Plans

A statistical analysis plan (SAP) will present the detailed statistical methods and analyses for this study.

9.3. Definition of Analysis Populations

The following patient populations will be assessed:

1. **Safety Analysis population:** All patients who receive at least one dose of study treatment (nanatinostat, valganciclovir, or pembrolizumab). The safety analysis population will be used for all listings and all demographic and baseline summaries.
2. **Full Analysis Set:** 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.
3. **Modified Intent-to-Treat (mITT) population:** The mITT population is defined as all RM-NPC patients who have received at least one dose of study treatment (nanatinostat,

valganciclovir, or pembrolizumab), have a confirmed diagnosis of EBV^+ by central pathology review, met all inclusion criteria, and have baseline (screening) and at least one post-baseline tumor assessment for efficacy.

4. **PK population:** All treated patients with at least one available PK parameter of interest.

9.4. Sample Size and Power Considerations

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 tumor patients.

The reported ORR for PD-1 inhibitors in RM-NPC patients has ranged from 20% to 30%. 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).

9.5. Baseline Characteristics and Subject Disposition

Demographic and baseline (last non-missing observation prior to treatment) disease characteristics will be summarized by dosing regimen for the Safety population. Patients' age, height, weight, and continuous baseline characteristics will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, maximum), while age classification (≤65 or >65 years), gender, ethnicity, histology, and other categorical variables will be provided using frequency tabulations (count, percent) by dosing regimen. Medical history data (coded by Medical Dictionary for Regulatory Activities [MedDRA] dictionary) will be provided in data listings.

Patient disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of patients enrolled by site will be provided. Major protocol deviations will be summarized using frequency tabulations for the Full Analysis Set population. Corresponding patient listings will be provided as well.

9.6. Efficacy Analysis

Efficacy analyses will be performed on the Full Analysis Set and the mITT population.

As described in Section 7.4.1.2, tumor responses for efficacy analyses will be assessed using the Investigator per RECIST v1.1 (MRI or CT with contrast) and will involve all known or suspected disease sites.

9.6.1. Primary Efficacy Endpoint Analysis

For Phase 2, the primary efficacy endpoint is the determination of ORR, defined as the percentage of patients with a CR or PR within the first 26 weeks (6 months) of treatment as

assessed by the Investigator using RECIST v1.1. ORR will be summarized by dosing regimen with 95% CI obtained by Clopper-Pearson Exact methods and stratified by prior anti-PD-1 treatment exposure.

9.6.2. Secondary Efficacy Endpoints Analysis

Secondary efficacy endpoints will include DOR, disease control rate (DCR), PFS, and OS:

- **Duration of response** (DOR): defined as the interval from date of first observed CR or PR to the date of documented disease progression or death due to any cause, whichever occurs first. All patients who have not progressed will be censored at the last non-missing tumor assessment. Estimates of median DOR with 95% CI will be determined by dosing regimen using Kaplan-Meier methods.
- **Disease control rate** (DCR): defined as the percentage of patients having a CR, PR, or stable disease at any time during treatment, as assessed by the Investigator using RECIST v1.1. DCR will be summarized by dosing regimen with 95% CI obtained by Clopper-Pearson Exact methods.
- **Progression-free survival** (PFS): defined as the interval from the start of study drug treatment to the date of first documented disease progression or death from any cause, whichever occurs first. Responding patients and patients who are lost to follow-up will be censored at their last tumor assessment date. Estimates of median PFS with 95% CI will be determined by dosing regimen using Kaplan-Meier methods. The 95% CI around the PFS and OS rates at 12 months (56 weeks) will also be presented.
- **Overall survival** (OS): defined as the interval from the start of study drug treatment to date of death for any reason. Surviving patients and patients who are lost to follow-up will be censored at their contact date. Estimates of median OS with 95% CI will be determined by dosing regimen using Kaplan-Meier methods.

9.6.3. Exploratory Endpoints

All exploratory endpoints will be summarized by dosing regimen and overall.

9.7. Safety Analysis

Safety analysis will be based on all patients in the Safety population and will be summarized overall, by dosing regimen, and by any other relevant subgroup (eg, solid tumor type).

Study medication exposure will be summarized for each patient and tabulated by dosing regimen including duration of study medication, total dose taken, and dose reductions.

Adverse events, vital sign measurements, clinical laboratory measurements, and concomitant medications will be summarized overall and by dosing regimen. Tabulations and listings of values for dose holds, modifications, or discontinuations; vital signs; and laboratory safety evaluations will be presented.

Adverse events will be coded according to MedDRA and classified using the NCI CTCAE v5.0. The incidence rates of AEs will be tabulated by System Organ Class and Preferred Term. Subsets of AEs to be summarized include SAEs, events of all CTCAE grade severities, suspected

treatment-related AEs, and events that resulted in withdrawal of study medication. The most severe grade of each preferred term for a patient will be utilized for summaries of AEs by NCI CTCAE grade. All AEs with corresponding attributes will be displayed in a by-patient listing. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE Grade 3 or higher, suspected treatment-related events, all deaths, and SAEs will also be displayed in by-patient listings separately.

Clinical laboratory results will be summarized descriptively by dosing regimen, which will also include a display of change from baseline. Laboratory values outside of the normal ranges will be identified. Clinically significant hematologic and non-hematologic laboratory abnormalities that meet Grade 3 or Grade 4 criteria according to the CTCAE will be listed and summarized. Graphical display of selective lab parameters over the course of study will be provided.

Vital sign measurements will be listed for each patient at each visit. Descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized by dosing regimen.

9.8. Interim Analysis

No interim analysis is planned.

10. STUDY COMMITTEES AND COMMUNICATIONS

A Safety Monitoring Committee comprising of the study lead Investigators and the Sponsor Safety Team will monitor the safety of treatment throughout the study.

11. LABORATORY REQUIREMENTS

All study-related laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patients' study data is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests must be submitted to the Sponsor prior to initiating the study. This document should be returned along with the Form FDA 1572 or Statement of Investigator. The Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

12. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

The Investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All study-related information will be recorded on source documents. All required data will be recorded in the eCRFs. All eCRF data must be submitted to the Sponsor throughout and at the end of the study.

If an Investigator retires, relocates, or otherwise withdraws from conducting the study, the Investigator must notify the Sponsor. If an Investigator changes during the course of the study, the Sponsor and any local regulatory authorities, as applicable, must first approve the change of Investigator and the new Investigator must provide the Sponsor the documentation listed below.

Before initiating the study, the Investigator must provide copies of the following documents to the Sponsor:

- Fully executed and signed Form FDA 1572 or Statement of Investigator, where appropriate.
- Fully executed clinical trial agreement.
- Current curriculum vitae (also applies to all sub-Investigators listed on the Form FDA 1572).
- Current medical license (online verification is also acceptable) of the Investigator (also applies to all sub-Investigators listed on the Form FDA 1572).
- Financial disclosure (also applies to all sub-Investigators listed on the Form FDA 1572).
- Investigator-signed protocol signature page.
- Investigator-signed acknowledgement of receipt of the current nanatinostat IB.
- IRB approval letter for the protocol and informed consent including written assurance of continuing approval (at least annually). A copy of the annual progress report submitted to the IRB/IEC must also be provided.
- IRB-approved ICF.
- Where applicable, a list of the IRB/IEC members or a Federal-Wide Assurance/ Department of Health and Human Services (FWA/DHHS) number.
- Additional documents as necessary per local requirements.

The Sponsor personnel or representatives may visit the study site, if necessary, before initiation of the study to review information with study site personnel about protocol requirements pertaining to the study drug, CRFs, monitoring, SAE reporting, and other relevant information.

12.1. Ethics

12.1.1. Ethics Committee

Before initiating the study, the Investigator will obtain confirmation from the ethics committee (EC) that the EC is properly constituted and compliant with all requirements and local regulations.

The Investigator will provide the EC with all appropriate material, such as the protocol, current nanatinostat IB, site specific informed consent form, and other written information provided to the patients. The study will not be initiated until the Investigator obtains appropriate EC approval in writing for the protocol and informed consent document, and copies are received by the Sponsor.

EC approval will be obtained for any substantial protocol amendments and informed consent revisions before implementing the changes. The Investigator will provide appropriate reports on the progress of the study to the EC, per local requirements, and to the Sponsor or designee in accordance with applicable local regulations.

12.2. Ethical Conduct of the Study

The Investigator will ensure that this study is conducted in full conformity with regulations for the protection of human patients of research codified in the following:

- US CFR applicable to clinical studies: 45 CFR Part 46; 21 CFR Parts 11, 50, 54, 56, 312
- International Council for Harmonisation (ICH) Guideline E6
- Declaration of Helsinki
- Applicable national and local legal and regulatory requirements

The Investigator will also be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

12.2.1. Patient Information and Informed Consent

The Principal Investigator(s) at each investigative site will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient, and/or a signed original as required by local regulations.

12.2.2. Maintaining Patient Confidentiality

The Principal Investigator and designees, employees, and agents involved with this study will comply with relevant local, state, federal, and regional laws, as applicable, relating to the confidentiality, privacy, and security of patient's health information. Data generated during this study or disclosed by the Sponsor to the Investigator will only be used as appropriate for the

execution, analysis, review, and reporting of this study. Such information shall not be used for any other purposes and will remain confidential.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study patient's contact information will be securely stored at each investigative site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study patient research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the Sponsor. This will not include the patient's contact or identifying information. Rather, individual patients and their research data will be identified by a unique study identification number. The study data entry and study management systems used by investigative sites and by the Sponsor will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor. Though the results of the study may be presented in reports, published in scientific journals, or presented at medical meetings, patient names will never be used.

To ensure patient safety and in adherence with regulatory guidelines, personal medical information may be reviewed by representatives of the Sponsor, the IRB/IEC, or regulatory authorities. This personal information will not be reused or disclosed to any other person or entity, or for other research.

12.2.3. Use of Research Samples and Data

The Sponsor will be responsible for all stored samples generated during this study. Some samples will be stored with specific vendors as appropriate (eg, PK samples). Samples and data will be stored using codes assigned by the clinical data system. Data will be kept in password-protected computers.

With the patient's approval, as approved by local IRBs, and in compliance with local regulations, de-identified biological samples will be stored by the Sponsor. These samples may be analyzed during the study or stored for future research following study completion. These samples, and the data obtained from the analysis, will be shared with other researchers, some of whom may be outside of this study.

During the conduct of the study, an individual patient can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent regarding biosample storage will not be possible after the study is completed.

Data generated from patients and collected for this study will be analyzed and stored by the Sponsor or its designee. If a patient withdraws consent, no additional data or samples will be collected from the patient. Survival information may be collected as outlined in Section 3.1.3.2. After the study is completed, the de-identified, archived data will be maintained by the Sponsor and may be made available for use by other researchers including those outside of the study.

12.3. Data Handling and Recordkeeping

12.3.1. Data Collection Responsibilities and Access to Source Data

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Each participating site will maintain appropriate medical and research records for this study, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of the Sponsor and/or its designee and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

This study will utilize a 21 CFR Part 11-compliant data capture system provided by the Sponsor or its designee for the purposes of data collection. Specific instructions on the system used for data collection will be provided in the Study Manual. Clinical data will be entered directly from the source documents.

12.3.2. Retention of Records

All essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product or for 25 years whichever is longer. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

12.3.3. Study Monitoring

Before an investigational site can enter a patient into the study, the Sponsor or its designee will qualify the investigational study site, which will include:

- Determining the adequacy of the facilities.
- Discussing with the Investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or its designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed.

- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor or its designee.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been reported, and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff need information or advice.

The clinical monitoring plan will outline the nature and frequency of site monitoring. Remote monitoring may be performed, which may include accessing and viewing medical records from a location outside of the study center, as allowed by national law.

12.3.4. Audits and Inspections

Authorized representatives of the Sponsor or its designee, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification.
The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any applicable regulatory requirements. Remote audits or inspections may be performed, which may include accessing and viewing medical records from a location outside of the study center, as allowed by national law. The Investigator should contact the Sponsor or its designee immediately if contacted by a regulatory agency regarding an inspection.

12.3.5. Quality Control and Quality Assurance

The Sponsor or designee performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients in this study, Sponsor personnel and the Investigator review the protocol, the current IB, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study. During these site visits, information recorded in the eCRFs is verified against source documents.

Quality control procedures will be implemented against data collected centrally. Missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Applicable procedures will follow written SOPs in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor or its designee, and inspection by local and regulatory authorities.

12.4. Investigational Product Accountability

The Investigator must maintain accurate records (including dates, quantities, and bottle identification numbers) of all study drug supplies received. All records must be made available to the Sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

Current ICH GCP guidelines require the Investigator to ensure that study drug deliveries from the Sponsor are received by a responsible person (eg, pharmacist).

Drug inventory and accountability records for the study treatment will be kept by the Investigator/pharmacist. Study treatment accountability throughout the study must be documented.

12.5. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.6. Compensation for Injury and Insurance

In the event of a side effect or injury, appropriate medical care as determined by the Investigator or designated alternate will be provided.

If bodily injury is sustained, resulting directly from the use of the study drug or by required study procedures, the Sponsor will reimburse the study site for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury that is not covered by the patient's medical or hospital insurance, provided that the injury is the following:

- Not caused by the patient's pre-existing medical condition or underlying disease,
- Not due to a negligent or wrongful act or omission by the study doctor and study staff,
- Not caused by the study doctor or study staff's failure to follow the study protocol, other written instructions provided by the Sponsor, applicable laws or regulations, and
- Not requiring treatment that would have occurred as standard care if the patient was not taking part in the study.

No other compensation of any type will be provided by the Sponsor. Financial compensation for lost wages, disability, or discomfort due to the study participation or procedures is not available.

12.7. Study Termination and Site Closure

If the Sponsor elects to terminate the study prematurely, it will provide appropriate notification to the Investigators, IRBs/ECs, and FDA and other relevant regulatory authorities, as applicable. The notification will include instructions for handling patients still on study drug, data collection procedures, and requirements for study close-down. If required by applicable regulations, the Investigator must inform the ethics board promptly and provide the reason for the suspension or termination.

If the Sponsor elects to terminate or suspend this study prior to completion, it will discuss the feasibility of continued administration of nanatinostat/valganciclovir with or without pembrolizumab with each participating Investigator for those patients that appear to be benefitting from nanatinostat/valganciclovir with or without pembrolizumab.

The Sponsor will also cooperate with participating sites in terms of collecting outstanding study data sufficiently to allow for the generation of a study manuscript.

If an Investigator suspends or terminates the study, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide a detailed written explanation. The Investigator will also return all nanatinostat/valganciclovir/pembrolizumab containers, as well as any other study materials, to the Sponsor or designee, or will destroy the materials at the investigative site. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to the following:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

The study will be considered complete when all patients complete study follow-up.

12.8. Use of Study Information and Publication

The Sponsor intends that the data from this study will be presented and published following completion of data analysis. This study will be registered in a publicly accessible database such as clinicaltrials.gov. by the Sponsor in keeping with the policy of the International Committee of Medical Journal Editors (ICMJE). Once completed, the results of the study will be posted on these publicly accessible databases as required by law.

The results of the study may be published or presented by the Investigator(s) following review and agreement by the Sponsor. Each Investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the Sponsors prior to submission. Any publication or presentation of ancillary reports or local site outcome data must wait until the primary clinical publication is “in press.” The Sponsor reserves the right to withhold the presentation of confidential or proprietary information.

Authorship will be based upon the principles outlined in the ICJME guidelines (ICMJE 2018). In addition, as a guideline, to ensure representation of centers making substantial contributions to this study, centers enrolling at least 5% of the study population will be invited to suggest an investigator for publication co-authorship. Other contributors not meeting authorship criteria will be acknowledged individually should they agree. Data derived from the study are the exclusive property of the Sponsor.

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14. APPENDICES

Appendix 1. Concomitant Therapies to be Used Cautiously with Nanatinostat

Appendix 1, Table 1: Examples of Sensitive Substrates of CYP3A

Enzyme	Therapeutic
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

Appendix 1, Table 2: Examples of Strong Inhibitors of P-gp and BCRP Transporters

Enzyme	Therapeutic
P-gp	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP	curcumin, cyclosporine A, eltrombopag

Appendix 2. Established and Other Potentially Significant Drug Interactions with Ganciclovir

Concomitant Drug	Change in Concentration of Ganciclovir or Concomitant Drug	Increased Monitoring Required	Clinical Comment
Imipenem-cilastatin	Unknown	If required, only administer as inpatient with close monitoring for seizure activity	Risk of generalized seizures
Cyclosporine or amphotericin B	Unknown	Monitor serum creatinine at least twice weekly for first week, followed by monitoring every week thereafter	Risk of renal toxicity
Mycophenolate Mofetil (MMF)	No change in levels of ganciclovir or MMF in patients with normal renal function	Monitor serum creatinine and complete blood count (CBC) at least twice weekly for first week, followed by monitoring every week thereafter	Risk for hematological and renal toxicity
Other drugs associated with myelosuppression or nephrotoxicity [a]	Unknown	Monitor serum creatinine and CBC at least twice weekly for first week, followed by monitoring every week thereafter	Risk for increased hematological and renal toxicity
Didanosine	No change in ganciclovir Increased didanosine	Serum amylase weekly for first month on combination, monthly thereafter	Monitor closely for didanosine toxicity (eg, pancreatitis)
Probenecid	Increased ganciclovir	Monitor CBC at least twice weekly for first week, followed by monitoring every week thereafter	May require dose reduction of valganciclovir

CBC = complete blood count.
[a] Includes adriamycin, dapsone, doxorubicin, flucytosine, hydroxyurea, pentamidine, tacrolimus, trimethoprim/sulfamethoxazole, vinblastine, vincristine, and zidovudine.
Adapted from Valcyte [valganciclovir] Prescribing Information, 2021.

Appendix 3. Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to RECIST version 1.1.

Method

Computed tomography (CT) or magnetic resonance imaging (MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

Computed tomography and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Definitions of Measurable/Non-Measurable Lesions

Measurable lesions

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) OR
- 10 mm by caliper measurement in clinical examination (lesions that cannot be accurately measured by calipers should be recorded as non-measurable) OR
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At both baseline and follow-up, only the short axis will be measured and followed.

Non-measurable lesions

All other lesions, including small lesions (longest diameter of <10 mm or pathological lymph nodes of ≥10 to <15 mm in the short axis) as well as truly non-measurable lesions, are defined as non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic

involvement of skin or lung, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Definitions of Target/Non-Target Lesions

Target lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions in total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and should be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, and in addition, should be those that lend themselves to reproducible repeated measurements. The sum of the diameters (longest diameter for non-nodal lesions, short axis for nodal lesions) of all target lesions will be calculated and reported as the baseline sum diameter. If lymph nodes are included, only the short axis is added to the sum.

Non-target lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or, in rare cases, 'unequivocal progression'.

Post-Baseline Assessment

At every planned follow-up scan visit as described in the protocol after baseline, the investigator will assess the target lesions selected at baseline quantitatively, assess the non-target lesions selected at baseline qualitatively, and search for new lesions. The lesion assessments are then combined into an assessment of the entire subject at that visit (called the visit response or the overall response).

Definition of Target Lesion Response

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target lesions) must have reduction in the short axis to <10 mm.

Partial response: At least a 30% decrease in the target lesion sum diameter versus the baseline sum diameter.

Progressive disease (PD): At least a 20% increase in the target lesion sum diameter versus the smallest sum diameter obtained during the study (this includes the baseline sum if that is the smallest sum diameter obtained during the study). In addition to the relative increase of 20%, the sum diameter must also show an absolute increase of at least 5 mm.

Stable disease (SD): Neither sufficient decrease to qualify as partial response nor sufficient increase to qualify as PD.

Definition of Non-Target Lesion Response

CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (< 10 mm in the short axis).

Non-CR/non-PD: Persistence of 1 or more non-target lesions or tumor marker levels maintained above normal limits.

PD: Unequivocal progression of existing non-target lesions or the appearance of 1 or more new lesions.

Overall Response

The following table shows the criteria for the assessment of overall response at each time point for subjects who have measurable lesions at baseline.

Evaluation of Overall Response at Each Time Point

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/not evaluated	No	PR
SD	Non-PD/not evaluated	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Source: RECIST version 1.1 criteria.
Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Best Overall Response

Best overall response (BOR) in this study is defined as the BOR across all time points, eg, a subject who has SD at first assessment, partial response at second assessment, and PD at last assessment has a best overall assessment of PR. If SD is assessed as the BOR, it must also meet the SD criteria at least once after study entry at 6 weeks or longer from baseline. If SD is the best time point response and the minimum time requirement is not met, the subject's best response will depend on subsequent assessments eg, a subject who has SD at first assessment and PD at second assessment and does not meet the minimum duration for SD, will have a best overall assessment of PD. The same subject lost to follow-up after the first SD assessment would be considered unevaluable.

Appendix 4. Immunologic Response Evaluation Criteria in Solid Tumors

(Source: Seymour 2017)

Immunologic Response Evaluation Criteria in Solid Tumors (iRECIST) is based on RECIST v1.1, but adapted to account for the tumor response seen with immunotherapeutic drugs. When feasible, Investigators are encouraged to keep patients on treatment until progression is confirmed by the Investigator, working with local radiology, according to the rules in this section. This allowance to continue treatment beyond the initial radiologic progressive disease (PD) factors in the observation that some patients may have a transient increase in tumor burden after starting immunotherapy and then experience subsequent disease response.

A summary of the adaptations is provided here, with additional detail in the iRECIST publications (Seymour 2017). iRECIST should be used by the Investigator to assess tumor response and progression for the purpose of treatment decisions. These data will be captured in the clinical database.

Assessment at Screening and Prior to RECIST v1.1 Progression

Until radiographic progression based on RECIST v1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST v1.1 Progression

In patients who have an assessment of radiologic PD per RECIST v1.1, the Investigator will decide whether to continue a patient on study treatment until repeat imaging is obtained (using iRECIST to guide treatment decisions). This decision would be based upon the patient's overall clinical condition meeting the criteria for clinical stability defined by the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care
- Absence of rapid progression of disease

Any patient deemed clinically unstable should be discontinued from study treatment and tumor imaging would not be repeated for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the patient may continue to receive study treatment, and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment.

iRECIST defines new response categories, including immune unconfirmed progressive disease (iUPD;unconfirmed PD) and immune confirmed progressive disease (iCPD;confirmed PD). For the purposes of iRECIST assessment, the first visit showing progression per RECIST v.1.1 criteria will be assigned an overall response of iUPD.

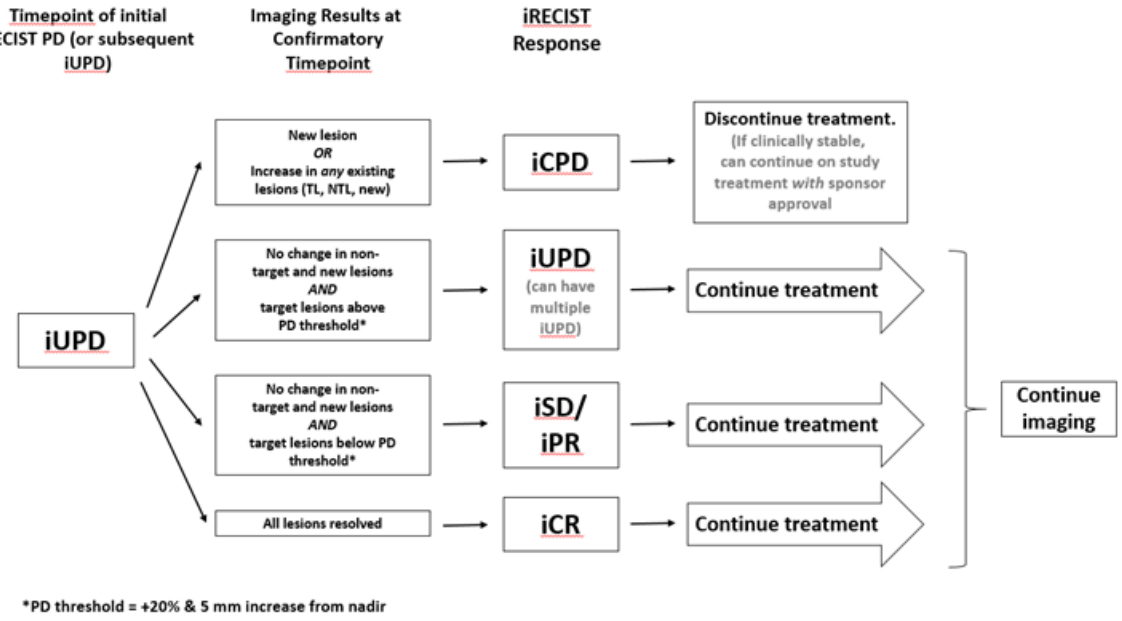
At this visit, the initial target and nontarget lesions identified at baseline will be assessed as usual, with collection of lesion measurements on the target lesion eCRF and tumor states on the nontarget lesion eCRF.

For data collection per iRECIST, the **main difference is in the assessment of new lesions**, which are classified as measurable or nonmeasurable, using the same size criteria as for baseline lesion assessment in RECIST v1.1 (at least 10 mm in long axis [or 15 mm in short axis for nodal lesions]). From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as "new lesions – target." The sum of diameters of these lesions will be calculated but kept distinct from the sum of diameters of target lesions identified at baseline. All other new lesions will be followed qualitatively as "new lesions – nontarget."

Assessment at the Confirmatory Imaging (4-8 Weeks After Assessment of RECIST PD)

Confirmatory imaging should be performed at least 4 weeks, but no longer than 8 weeks following initial iUPD assessment. On the confirmatory imaging, the outcomes of tumor evaluation by iRECIST can be (1) confirmation of progression (with an overall response of iCPD), (2) persistence of unconfirmed progression (with an overall response of iUPD), (3) disease stability (iSD), or (4) response (immune partial response [iPR]/immune complete response [iCR]) as illustrated in Figure 1.

Appendix 4, Figure 1: Assessment of Tumor Response Using iRECIST



iCPD =immune confirmed progressive disease; iCR = immune complete response; iPR = immune partial response; iSD = immune stable disease; iUPD = immune unconfirmed progressive disease; NTL = nontarget lesion; PD = progressive disease; TL = target lesion

iRECIST Criteria for Confirmation of Progression

Progression is considered as confirmed, with an overall response of iCPD, if ANY of the following occurs:

- Worsening of any of the individual component responses (target lesion, nontarget lesion, or new lesion) that were the basis for the initial overall iUPD determination:

  - Target lesions: worsening is a further increase in the sum of diameters of ≥5 mm, compared with any prior iUPD timepoint.
  - Nontarget lesions: worsening is any significant growth in lesions overall, compared with a prior iUPD timepoint; this does not have to meet the "unequivocal" standard of RECIST v1.1
  - New lesions: worsening is any of the following:
    - An increase in the measurable new lesion sum of diameters by ≥5 mm from a prior iUPD timepoint.
    - Visible growth of non-measurable new nontarget lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST v1.1

Persistence of iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if the following is observed:

- No worsening of existing tumor burden (target, nontarget, and new lesions) as described above occurs AND
- The target lesion sum of diameters (target lesions identified at baseline) remains above the RECIST-defined threshold for target lesion progression.

The second factor would be applicable only in cases where the target lesion increases at the initial assessment of iUPD met the criteria for progression (≥20% and ≥5 mm increase from nadir). Cases where initial iUPD was based upon progression of nontarget lesions or identification of new lesions, but target lesion change does not meet PD criteria would be covered by the section below on Resolution of iUPD.

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which the iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, according to the following:

- No worsening of existing tumor burden (nontarget and new lesion) AND
- The target lesion sum of diameters (target lesions identified at baseline) is not above the RECIST-defined threshold for target lesion progression.

The response is classified as iSD or iPR (depending upon the sum of diameters of the target lesions), or iCR if all lesions resolve. iCR, iPR, and iSD can all be assigned after iUPD has been documented, as long as iCPD was not confirmed. Following a determination of iSD, iPR, or iCR, the next visit that shows radiographic progression, whenever it occurs, is again classified as

iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the patient continues to be clinically stable, then study treatment may continue following the regular imaging schedule. If PD is confirmed, then patients should be discontinued from study treatment.

If an iCPD as defined above, but the patient is achieving a clinically meaningful benefit, and no further increase in the tumor burden is seen at the confirmatory tumor imaging, then an exception to continue study treatment may be considered following consultation with the Sponsor. If study treatment is continued, then tumor imaging should continue to be performed.

Determination of Progression after Assessment of iSD/iPR/iCR

After achieving a response of iSD/iPR/iCR, subsequent iUPD is indicated by any of the following:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir). The nadir is always the smallest sum of diameters observed throughout the entire study.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
  - If nontarget lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time.
  - Additional new lesions appear.
  - Previously identified measurable new lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum.
  - Previously identified non-measurable new lesions show any significant growth.

If any of the factors above indicate iUPD, the iUPD evaluation process is repeated, similar to the first occurrence of iUPD. iUPD must be confirmed before iCPD can occur.